

DATE: May 26, 1993

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SUBJECT: Annual Inspection of the Michigan Department of Public Health (MDPH), License # 0099, Trip DH-5, May 3, 1993

TO: Boyd Fogle, Director, Division of Inspections and Surveillance, HFM-650

THROUGH: William Fricke, M.D., Chief, Lab of Hemostasis, HFM-340 *ccf \**  
Donald Tankersley, Chief, Lab of Plasma Derivatives, HFM-345 *ccf*  
Joseph C. Fratantoni, M.D., Director, Division of Hematology, HFM-330  
Amy Scott, Chief, Branch I, Division of Establishment Licensing, HFM-206  
Susan Vargo, Ph.D., Acting Director, Division of Establishment Licensing, HFM-205

This was the regular, annual inspection of the Blood products production facilities of the Michigan Department of Public Health (MDPH), 3500 North Logan, Lansing MI 48909 License number 99, performed on May 4 through May 7, 1993. At approximately 9:00 a.m. we arrived at Michigan Department of Public Health and were met by Dr. George Burgoyne, Chief of Blood Derivatives, to whom the FDA form 482, Notice of Inspection, was issued (attachment 1).

#### I. Summary of Findings

The following observations were made on an FDA 483 (attachment 2) which was issued to Dr. Robert Meyer, Responsible Head at the exit interview.

1. In building , room the -30°C freezer contained several totes that were not secured with plastic cable locks,

e.g.,

2. Reaction tank number     in room number     in the fractionation area had an undated record of cleaning tag affixed.
3. In building number     in room     , the pH4 buffer, lot number     prepared on 4/22/93 did not bear an expiration date.
4. The -30°C cold storage area in room     contained a quarantined cage that was not secured.
5. In building     in room     several tanks (e.g.,     had no cleaning tags affixed.
6.     , part number     with a test date of 3/9/93 did not bear an expiration date.
7. In building     room     the animal area for mice, the last calibration for the temperature chart recorder was 7/90.
8.     GMP number     was labeled 7/27/93 as an expiration date, but the date in the log book record for GMP testing gave the expiration date as 7/28/93.
9. In building     , in the hall way outside of room     where cryoprecipitate is stored, the chart recorder was past due date for calibration.
10. In building     in room     instrument lacked calibration stickers, maintenance SOPs, or validation date, e.g., MDPH     , MDPH
11. The sterility suite in building     is inadequate for proper sterility testing, i.e., there is no separate sample staging area, no gowning area, and the area is not restricted to unwanted traffic.

12. In room        the aseptic filling suite, there is no volumetric sampling for viables (airborne bacteria).
13. There is no SOP for conducting a recall.
14. There are no time limits for production processes, e.g., the filtration step for albumin.
15. There is no validation of electronic calculations performed by scales used in the formulation of product e.g., the scale in room 106 used for weighing albumin powder.
16. There is no annual review of production batch records.
17. 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.

MDPH has been cited continually for many of these observations. The observations are not only numerous, but represent substantial noncompliance with applicable regulations and may affect the safety, purity, or potency of products manufactured at MDPH. We recommend that a regulatory letter be sent to Michigan, asking that MDPH assure that resources are appropriate to comply with the provisions of the current Good Manufacturing Practice regulations.

## II. History of Business and Firm's Training Program

Essentially, the firm's operations and personnel remain unchanged from the previous inspection. A training program is

## III. Facilities and Products

The Michigan Department of Public Health (MDPH) is located in Lansing, Michigan. The blood operations employ approximately people in the manufacture of albumin, immune globulin, and factor VIII. The normal operating hours are 8:00 am to 5:00 pm,

MDPH processes liters of plasma per year. This inspection reviewed the manufacturing and quality control procedures performed in building building building and building

At the beginning of the inspection, we requested batch records for the last three lots of albumin produced and the last lot of immune globulin. Various MDPH documents were reviewed and checked for correctness of calculations, conformance to specifications, discrepancies in lot numbers of components, and adherence to SOPs. The adverse reaction file from August 92 to the present was also requested and reviewed. The most recent complaint was dated 1-13-93 from Jeff Weathers of the American Red Cross and stated that there were reports from Red Cross affiliates that 1 stopper had been dislodged for lot HA1075 and that there were two reports of stopper dislodgement for lot HA1084.

SOPs for pyrogen testing, receiving and checking in plasma containers, autoclave loading for building plasma thawing, raw material sampling, albumin reprocessing, and GMP training were requested. At this point Mr. Eckenrode of production and Mr. Saad of quality assurance explained that MDPH had previously received Form FDA 483s with observations for lack of SOPs, but that SOPs were in the process of being generated (exhibit 1) and reviewed for all product related activities. The SOPs will be categorized by a

The inspection began at the procurement unit (shipping and receiving) where the records for the receipt of plasma and raw materials were reviewed. Although no computerized records are kept, it is possible to trace components from receipt to their destination.

Bags of plasma are pooled in room of building . We observed technicians opening plasma bags manually, using utility knives. The technicians wore rubber boots, cover suits, hairs covers, face masks with

face shields to protect eyes and rubber gloves.

The animal quarters were observed and appeared satisfactory. During discussions with Michigan personnel it was learned that MDPH is not accredited by AALAC (American Association for Accreditation of Laboratory Animal Care).

#### IV. Records Review

The SOP March 3, 1988 version was reviewed and appeared acceptable. The SOP for

March 3, 1993 version was reviewed and appeared acceptable.

The Water for Injection testing results for 9/1/92 through 3/26/93 for the points of use in building numbered were reviewed and appeared acceptable. On 1/6/93 a plate count of 13 was recorded, which according to the SOP for water testing generates a report,

This report was requested by the CBER inspectors and was provided by MDPH personnel. The report for 1/6/93 for Water for Injection point was generated according to SOP and the action appeared reasonable.

The environmental monitoring data during the aseptic fill of albumin lot HA1107 (albumin 25%) was reviewed. The environmental monitoring consists of rodac plates (contact plates), settling plates, and particulate monitoring performed with a which is recertified annually. The data for particulate monitoring showed class 10 conditions are maintained at the point of filling throughout most of the filling operation. A observation was made on Form FDA 483 (observation number 12) because of the lack of volumetric sampling for airborne viable particles during aseptic filling.

The batch record for immune globulin released by CBER on 11/16/92 was reviewed and appeared satisfactory. The batch record indicated that vials were filled, with 1565 total rejects. The rejects were because of:

80	filling and capping rejects
1393	foreign object rejects
6	faulty closure rejects
1	glass defect
17	short volume
66	samples
2	broken
1565	total vials
	total vials passed

During record review of quality control testing of albumin (Blood Derivative Product Checklist Bulk Product Specifications & Lot Release Specifications (exhibit 1)) for release it was observed that testing for \_\_\_\_\_ had been discontinued. The SOP for discontinuing testing appeared to be followed and the memorandum to the file (exhibit 3) was reviewed and appeared in order. It is noted that the last revision for Blood Derivative Product Checklist Bulk Product Specifications is 10/15/90 and that the memorandum (exhibit 3) is dated February 22, 1991, yet the Blood Derivative Product Checklist Bulk Product Specifications for lot \_\_\_\_\_, produced more than two years after the discontinuation of testing of \_\_\_\_\_ still has not been revised to show that those tests are not required. Additionally, the batch record for lot \_\_\_\_\_, on page 31, step 60, still reflects that samples for \_\_\_\_\_ quality control testing should be collected.

The batch record for Albumin lot \_\_\_\_\_ which was released by CBER March 31, 1993 was reviewed. During the course of this review of the batch record, an observation (number 14) was written on Form FDA 483 regarding the lack of time limits for filtration (see batch record for lot \_\_\_\_\_ "production record" page 25). Also, during the review of the batch record, it was noted that the calculations in the \_\_\_\_\_ albumin powder were off occasionally by a gram, e.g., for lot \_\_\_\_\_ the gross weight is 6246 grams, the tare weight is 418 grams, and the net weight is 5829 grams, a discrepancy of one additional gram. A CBER inspector speculated that the calculations were being determined by decimal figures that were not displayed on the calculating scale and that the displayed numbers were rounded off. This observation was written on the Form FDA 483 as number 15.

## V. Exit Interview

The Form FDA 483 was issued to Dr. Robert Myers.

The following MDPH personnel were present during the exit discussion:

Judy Boice	Vaccine Production
Gary Warren	Blood Derivatives
L. J. Charamello	Blood Derivatives
Bob Winter	General Services
Daryl Anderson	General Services
Louise Simon	Plasma Derivatives
Paul Makley	Blood
Chun N. Shih	Vaccine R & D
T. C. Yang	CC
Steve Kahr	Vaccine Production
H. Burgoyne	Vaccine Production
Doug Brown	Vaccine Production
Harry Fuatukis	Blood Derivatives
Jerome Eckenrode	Blood Derivatives
Richard Hoot	Vaccine Production
Nancy Summerton	Engineering
William Nummy	Blood Derivatives
Ann Stephens	Vaccine Production
F. M. Saad	CC
Bob Kirston	Animal Care
William Bursaw	Filling and Packaging
Jane Rhodes	Chief, General Services
Carolyn Copedoe	Chief Biochemistry

MDPH personnel were present as the items in the 483 were read and opened for discussion. During the discussion, Mr. Eckenrode pointed out that during a previous inspection FDA inspectors had indicated that changes had occurred in manufacturing that must be reported to FDA. Mr. Eckenrode stated that MDPH believed that the changes were within the parameters established by the method. The present FDA inspectors stated that any changes to manufacturing that have the potential to affect the safety, purity, or potency of a biologic must be submitted and approved by CBER prior to implementation. MDPH personnel acknowledged that this had not always happened in the past, and Mr. Eckenrode gave an

example where a change in processing was later found to affect the stability of albumin. Another example given by MDPH personnel in response to the 483 was that the individual responsible for calibration had retired a year ago, yet a replacement had not been hired to date.

In addition, MDPH personnel suggested that the lack of computers prevented a through record review. The FDA inspectors agreed that the lack of computers hindered the meaningful review of records associated with the manufacture of product at MDPH. The FDA inspectors noted that there was no formal trend analysis of sterility testing, no SOP for conducting recalls (see observation 13), inadequate determination of when calibration is due, and some forms and records are illegible and in need of revision.

MDPH personnel acknowledged that instruments used for end product testing, e.g., had no installation or operational qualification, and no maintenance SOPs. Also, in regards to observation number 15, MDPH personnel acknowledged that validation of the computers present had not occurred.

The FDA inspectors summed up the inspection by reading observation number 17, that it appeared that MDPH had insufficient personnel to assure compliance with cGMP 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. MDPH personnel did not dispute this observation, and in fact agreed with it.

**Attachments:**

Form FDA 482  
Form FDA 483

\_\_\_\_\_  
Daniel Kearns

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Bobby Mason

Eleanor Koo  
Eleanor Koo