



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

• August 31, 1995

WARNING LETTER

Certified-Return Receipt Requested

Robert Myers, D.V.M.  
Responsible Head  
Michigan Department of Public Health  
3500 North Logan  
Lansing, Michigan 48909

Dear Dr. Myers:

During an inspection of the Michigan Department of Public Health, 3500 North Logan, Lansing, Michigan, conducted on April 28 to May 5, 1995, FDA inspectors Lyn D. Olson, Ph.D., Florence A. Kaltovich, Kelley L. Clark, and Scott D. Barlow documented significant deviations from Title 21, Code of Federal Regulations (21 CFR), Parts 600-610 and Part 211 with respect to the manufacture of your products as follows:

1. Failure to notify the Director, Center for Biologics Evaluation and Research (CBER), of proposed changes in location, equipment, responsible personnel, and manufacturing methods in accordance with 21 CFR 601.12(b) in that:
  - a. Beginning with the manufacture of Immune Globulin lot IG107, an open reaction tank has been used instead of a shaker tank as described in your Establishment License Application. As a result, mixing of the product and the size and arrangement of the clarifying filters have been modified.
  - b. New master cell banks for Rabies vaccine production were obtained and utilized for manufacturing.
2. Failure to assure that the cell lines used for manufacturing biological products are genetically stable and free of contaminants [21 CFR 610.18(c)] in that all tests necessary to characterize and qualify the new master cell banks have not been performed.

Organization and Personnel

1. Failure of the personnel engaged in the manufacture, processing, packaging, or holding of a drug product to be adequately trained in

current good manufacturing practice (CGMP) including the CGMP regulations and written procedures required by these regulations as they relate to the employee's functions [21 CFR 211.25]. Employees of the Divisions of General Services and Laboratory Services do not receive CGMP training on a continuous basis to assure they remain familiar with applicable CGMP requirements.

2. Failure of the quality control unit to have written procedures delineating its authority to approve or reject all components, drug product containers, closures, in-process material, labeling, and drug products, and to review production records to assure that either no errors have occurred or that they have been fully investigated [21 CFR 211.22].

#### Buildings and Facilities

1. Failure to provide separate or defined areas or such control system for the firm's manufacturing and processing operations to prevent contamination or mixups [21 CFR 211.42(c)] in that:
  - a. Access to the blood derivative manufacturing and rabies manufacturing buildings is not controlled.
  - b. There is no separate air lock for degowning in the rabies manufacture building.
  - c. Unlocked cold rooms are use to store
2. Failure to establish a system for monitoring environmental conditions [21 CFR 211.42(c)(10)(iv)] in that:
  - a. The bacterial vaccine gowning room is not monitored during periods of activity.
  - b. Monitoring is not performed during rabies vaccine manufacture.
3. Failure to maintain any building used in the manufacture, processing, packing, or holding of a drug product in a good state of repair [21 CFR 211.58] in that water from the cooling unit in cold room drips onto boxes of stored final product; the leak has not been fixed after several informal reports to maintenance.

#### Control of Components and Drug Product Containers and Closures

1. Failure to have written procedures describing in sufficient detail the receipt, identification, storage, handling, sampling, testing, and approval or rejection of components and drug product containers and closures [21 CFR 211.80(a)] in that SOP for receipt and release of raw material does not include the flow of raw material containers from receiving (building to the warehouse (building ), and Quality Control (building to prevent contamination or mixups.

2. Failure to open, sample, and reseal containers in a manner designed to prevent contamination of their contents and contamination of other components, drug product containers or closures [21 CFR 211.84(c)(2)] in that there is no sampling area for large containers of raw material.

#### Production and Process Control

1. Failure to establish and/or follow written procedures for production and process control 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 the quality control unit [21 CFR 211.100] in that:
  - a. Two employees were observed entering room to charge the fermenter without hair covers.
  - b. Expired medium lot 1635 was used in the manufacture of
  - c. There is no written procedure for the following:
    - 1) The qualification of new lots of media used during rabies and bacterial vaccine manufacture.
    - 2) The production of fraction II+III and fraction II+IIIw intermediates.
    - 3) The formulation of fraction II+III<sup>r</sup> rework lots and fraction V rework lots from plasma run lots.
    - 4) The formulation of albumin or immune globulin lots from fraction V and fraction II+IIIw rework lots.
    - 5) Sampling of large containers of raw materials.
2. Failure to establish 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 process [21 CFR 211.113(b)] in that:
  - a. There is no written procedure relating to sterile media fills.
  - b. There is no written procedure relating to the flow of personnel between room (hot laboratory) and the cell culture laboratory.

#### Packaging and Labeling Control

Failure to have written procedures describing in detail the receipt, identification, storage, handling, sampling, examination, and/or testing of labeling and packaging material [21 CFR 211.130(a)].

#### Holding and Distribution

Failure to have written procedures describing the distribution of drug

products including a system by which the distribution of each lot of drug product can be readily determined and whereby the oldest approved stock of drug product is distributed first [21 CFR 211.150] in that there is no written procedure for interstate distribution of Immune Globulin (Human) vaccine.

#### Laboratory Controls

1. 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:
  - a. Release of media used in the manufacture of rabies and diphtheria vaccines is based on satisfactory growth during production.
  - b. Endotoxin specifications for intermediate blood derived products after the drying run have not been established.
2. Failure to establish and/or follow written testing program designed to assess the stability characteristics of drug products [21 CFR 211.166(a)] in that:
  - a. There is no program in place for
  - b. There is no evidence that samples are randomly selected for final product testing for the Diphtheria and Tetanus Toxoids and Pertussis Vaccine, Adsorbed, (DTP) stability program.
3. Failure to follow the stability program for the rabies vaccine [21 CFR 211.166(a)] to assure valid estimates of stability in that:
  - a. The sample size collected and tested is inadequate.
  - b. Test intervals are inadequate.
  - c. The storage temperature is not always recorded.
  - d. Stability samples are removed prior testing.

#### Records and Reports

1. Failure to maintain adequate and complete batch production and control records for each batch of drug product produced [21 CFR 211.188(b)] in that:
  - a. The batch record for Immune Globulin (Human) lot IG106 did not contain the written deviation report describing changes in the procedure.
  - b. Batch records for diphtheria toxin lots DTN74 and DTN51 and tetanus toxin lots TT3448, TT3449, and TT3450 did not include all manufacturing procedures, equipment identification, and storage sites of in-process and final material.
  - c. The batch record for plasma run lot PR2811 did not include

the expiration date of the section for individual container weights was incomplete; the buffer was not prepared according to the specified procedure; and a difference between the documented centrifugation stop time on the tank record and the batch record was noted.

2. Failure to investigate and document the failure of a batch or components to meet specifications [21 CFR 211.192] in that since January 1995 at least one cell culture batch per month was contaminated, and no investigation has been done.
3. Failure to have complete laboratory records [21 CFR 211.194(a)] in that sterilization records for the autoclaves used by the Quality Control laboratory do not always include the sterilization time, person operating the autoclaves, and review signature.

The above identified deviations are not intended to be an all inclusive list of deficiencies at your facility. Federal agencies are advised of the issuance of all warning letters about drugs so that they may take this information into account when considering the awards of contracts. In accordance with 21 CFR 600.10(a), it is your responsibility, as Responsible Head, to exercise control of the establishment in all matters relating to compliance with all pertinent regulations. You are also responsible for the training of employees in manufacturing methods and for their being informed concerning the application of the regulations pertinent to their respective functions.

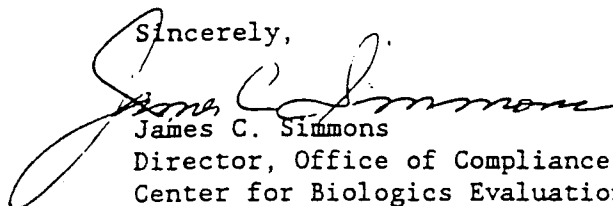
We acknowledge your June 9, 1995, response to the Form FDA 483 issued at the close of the inspection. We view the response to items 1, 2, 3, 6, 11, and 14 of the form FDA 483 as incomplete because it does not include supportive documentation indicating in detail how and when corrective actions will be taken and the approximate dates by which they will be completed. The kind of supportive documentation necessary includes, but is not limited to, appropriate license supplements, standard operating procedures, copies of revised master batch production records, training records, and monitoring data. In addition, you may refer to and need not repeat in detail the corrective actions mentioned during the April 12 and July 5, 1995, meetings with CBER in response to this Warning Letter.

You should notify this office in writing within 15 working days of receipt of this letter of any additional steps you have taken to correct the noted violations and to prevent their recurrence. If corrective action cannot be completed within 15 working days, state the reason for the delay and the time within which the corrections will be completed. Failure to promptly correct these deviations may result in regulatory action without further notice. These actions include license suspension and/or revocation, seizure, and/or injunction.

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Your reply should be sent to my attention in the Office of Compliance, Center for Biologics Evaluation and Research, 1401 Rockville Pike, Suite 200N, HFM-600, Rockville, Maryland, 20852.

Sincerely,

A handwritten signature in cursive script, appearing to read "James C. Simmons". The signature is written in black ink and is positioned to the left of the typed name and title.

James C. Simmons

Director, Office of Compliance

Center for Biologics Evaluation and Research