



Memorandum

Date • August 1, 1994

From Edward A. Fitzgerald, Ph.D., Director, DPQC, OELPS (HFM-230)

Subject Annual Inspection of Michigan Department of Public Health, License No. 99

To Chief, Biological Product Inspections Branch, OC (HFM-655) *JK 9/25*

Through: Richard Daemer, Ph.D., DVP, OVRR (HFM-448) *RD*
Jerome A. Donlon, M.D., Ph.D., Director, OELPS (HFM-200)
Jerome A. Donlon (Director MDPH)

I. Summary of Findings

I performed the annual inspection of Michigan Department of Public Health (MDPH) for viral products on July 25-26, 1994. Their only active viral product is Rabies Vaccine Adsorbed (RVA). The preceding inspection of RVA was August 31-September 2, 1992 and seven items were noted on Form FD483. All items have been addressed by management and corrective actions carried out as indicated in the firm's letter to Dr. Zoon of November 12, 1992. Item No. 2 ("Many of the reagents used in manufacturing had a labeled warning, from the chemical manufacturer, stating they were not intended for drug manufacturing") has been difficult to fully correct. As noted in Dr. Heintzelman's report (page 3, part V.a.), MDPH did not feel they could purchase _____ without this disclaimer on the label. I checked the label from a current lot of _____ purchased from _____ and found that the label states "For laboratory use only, not for drug, household or other use". According to MDPH, this product is only sold by a limited number of manufacturers and all of them contain a similar disclaimer. Since _____ is used in the _____ it is an extremely important reagent in manufacture and could not be easily replaced. Also, during the inactivation cycle (_____), the _____ is completely hydrolyzed so that no detectable amount remains in the product. For these reasons, I did not feel this citation should be repeated. All other reagents checked during this inspection had no such disclaimer on their labeling.

I also checked the status of MDPH's response to Item No. 6 in the June, 1989 inspection ("That no validation data was available for removal of residual protein from filling equipment") since Dr. Heintzelman was not completely satisfied with the firm's response in 1992. I was told that new filling equipment has been ordered so that each product line will have its own dedicated filling heads, tubing, valves, etc. In addition, MDPH is preparing a validation protocol for removal of cleaning agents. The next inspector should check for the presence of this protocol.

The last CBER inspection of MDPH took place on May 31-June 3, 1994 for bacterial products. Mr. D. Kearns and Ms. D. Jansen left a FD483 with 15 observations. MDPH replied with a letter to Dr. Zoon dated June 10, 1994 (Exhibit 3). A number of these observations were of a general nature (Nos. 3, 4, 6, 8, 13 and 15). I checked to see if these had been addressed as stated in the above letter and found it necessary to repeat two of these observations (Nos. 6 and 15) during this inspection.

I noted six observations on Form FD483 (Exhibit 2) as follows:

1. That raw materials are stored in a warehouse (Bldg) that has not been approved by CBER, FDA.
2. That tissue culture roller bottles are not quarantined, tested and released as GMP material.
3. That no expiration date was assigned to rabies sublots produced as a component of Rabies Vaccine, Adsorbed.
4. The harvest of cell culture roller bottles used in production of Rabies Vaccine, Adsorbed is not performed consistently in accordance with the existing SOP.
5. Three expired lots of Rabies Vaccine, Adsorbed, were stored in the "In Process" refrigerator (Room : in Bldg
6. Temperature recording for incubator (Bldg was not complete in that it was not continuous and two weekdays were not recorded.

II. History of Business

Michigan State Department of Public Health is located at 3500 North Logan/Martin L. King Jr. Blvd., Lansing, Michigan. The normal operating hours are 8:00 am to 5:00 pm. MDPH is currently licensed for nine biological products for human use. Two of these, Tetanus Toxoid (adsorbed) and Diphtheria Toxoid (adsorbed), are not being actively produced. Rabies Vaccine Adsorbed is the only viral product currently manufactured. A map of the MDPH grounds is included as Exhibit 4.

The map indicates the location of building (Bldg , which is used as a warehouse for storage of raw materials. This building has not been approved by CBER and was cited by Mr. Kearns/Ms. Jansen on their inspection. In the reply to the FD483 from the above inspection (Exhibit 3, Observation No. 6), Dr. Myers stated that an ELA supplement would be submitted to CBER by June 20, 1994. Since no supplement had been prepared by the date of this inspection, I repeated the citation (Exhibit 2, Observation no. 1).

MDPH is currently involved in

. They are working with on combinations of

III. Persons Interviewed and Individual Responsibility

I arrived at MDPH at 8:40 am, July 25, 1994, and presented credentials and Form FD 482 (Exhibit 1) to Dr. Robert Myers, Responsible Head. Other persons who accompanied me during the inspection or provided relevant information in their areas of expertise were as follows:

Dr. Fathi M. Saad	Chief, Quality Control Section
Mr. Steve Kahn	Supervisor, Rabies Vaccine Production
Dr. T.C. Yang	Quality Control Section
Dr. Barbara Kintner	Supervisor, Animal Care Unit
Mr. William Bursaw	Supervisor, Filling and Packaging
Mr. George Baxter	Supervisor, Raw Material Receiving
Mr. Richard Hoort	Vaccine Production

There have been two significant personnel changes since Dr. Heintzelman's inspection. Both Mr. Douglas Brown (Rabies Production) and Mr. Joseph Poerio (Filling and Packaging) have retired. They have been replaced by Mr. Steve Kahn and Mr. William Bursaw respectively.

IV. Firm's Training Program

Dr. Myers reviewed the training records for all employees in the As indicated in the MDPH letter to Dr. Zoon of Nov. 12, 1992, Mr. William R. Nummy has been assigned to Dr. Myers office to Nummy was on leave during the inspection but I examined the employee records which included These records were satisfactory given that the program has only been operational for less than two years. I have also included a current list of SOPs for the Biologic Products Division (Exhibit 5).

V. Facilities and Manufacturing Operations

A. Manufacturing Records

I reviewed the complete manufacturing records for Rabies Virus Adsorbed lot Nos.

During the inspection, I observed that none of these sublots was assigned an expiration date (Exhibit 2, Observation No. 3). They are stored in Refrigerator No. after their release from quarantine and are usually used within 5-6 months. However, if the antigen-binding value is low (<3.0 units of antigen), a sublot could be held for an indefinite period of time. I found two sublots () that had been produced in April, 1993 and were still waiting to be pooled. I also observed one discrepancy between certain production records (Exhibits 6 and 7) and the SOP for the production of

(Exhibit 8). Both Mr. Kahn and Dr. Myers had indicated that the harvest of the roller bottles was occasionally performed differently depending on the condition of the cell sheet. If the cell sheet was confluent, the bottles were harvested normally by pooling the contents of each bottle and freezing at -85°C (Exhibit 8, Page 1, Section 1.3; Page 3 Section 1.0, Day 33). If the cell sheet is not confluent, the entire roller bottle is frozen. All roller bottles are later thawed and pooled in an attempt to harvest as much cell-associated virus as possible. This observation was listed as No. 4 on Form FDA 483 (Exhibit 2). All other records were satisfactory and in accordance with all applicable SOPs.

Dr. Myers discussed with me the labeling changes that were made for RVA when it began to distribute this product in June 1992. Copies of the package circular and transmittal forms are included as Exhibit 9.

B. Raw Materials

MDPH divides its incoming raw material into several categories. They consider

All material comes into Bldg where it is checked in and assigned a storage destination. All material to be stored at ambient temperature is sent to Bldg. This warehouse has quarantine areas along the wall where material is stored in locked cages until sampled, tested and released. The released material is moved to labeled, freestanding shelves in the center of the warehouse where the stock is rotated using a FIFO system. I observed that the tissue culture bottles used to support cells for production were held in Bldg but had not been handled as material (Exhibit 2, Observation No. 2), despite Dr. Myers response to the same observation during the Kearns/Jansen inspection (Exhibit 3, Observation No. 15). Material to be used in production that require refrigeration (e.g. cell culture media) or frozen storage (e.g. fetal bovine serum, trypsin) are held in Bldg in Rooms (2-8°C) and (-20°C) respectively until released. After release, they are sent directly to the production area in Bldg.

C. Rabies Vaccine Production

All production of through the final bulk stage is carried out in Bldg. Cell culture passage and media production is conducted in Room. All cultures and media are tested for sterility and media is stored at 2-8°C. Room is used for glassware washing and preparation. Released sublots (RSL) are also held here in Refrigerator No.

As mentioned previously (see Section VA.), none of these RSLs had been assigned an expiration date (Exhibit 2, Observation No. 3). The infection, incubation, harvest and inactivation of rabies virus is carried out in Room. Entrance to this room is strictly controlled by airlock and gowning procedures. A single freezer (-85°C) is used to store rabies seed virus as well as all production samples requiring low temperature storage. Although this freezer had a back-up, I suggested the addition of another small freezer so that all the seed virus would not be in the same unit. I observed the incubation of RSL Nos. as well as the preparation for inactivation of

previous harvest pools. Following inactivation and adsorption with aluminum phosphate, all RSLs must be sampled for residual live virus and quarantined while these samples are tested by the [redacted] Quarantined RSLs are held in Refrigerator No. [redacted]. All temperature charts for the refrigerators, freezers and incubators in Bldg [redacted] were checked and found to be satisfactory. Bldg [redacted] had just been re-certified by [redacted] in May 1994 for air pressure, filter integrity and viable/non-viable particulates.

D. Filling and Packaging

The Filling and Packaging area is located on the [redacted] floor of Bldg [redacted]. Mr. Bursaw and Dr. Saad explained the testing of the Water for Injection (WFI) system used in this area. Each WFI drop (point of use) is tested once each week for pH, conductivity, microbiological contamination and LAL. Each drop is tested monthly for all chemical and biological tests. The WFI storage tank is tested each day for all test parameters. MDPH is currently [redacted]

The filling suite is a class 100 area containing a [redacted] filling machine (Model [redacted]). Their environmental monitoring system uses [redacted] machine for non-viable particles and an [redacted] machine for viable particle sampling. All "in process" material is stored in Room [redacted] (2-8°C). I observed [redacted] Lot Nos. [redacted] stored in sealed bags awaiting release from Quality Control. Three expired lots of RVA (Lot Nos. [redacted]) were also stored in this refrigerator but no one could explain why they were here (Exhibit 2, Observation No. 5).

Labeling is performed in Room [redacted] and Albumin (25%) Lot No. [redacted] had just completed the labeling cycle. Label storage and reconciliation records for RVA Lot No. [redacted] were examined and found to be in good order. No other labeling or packaging was taking place at this time. In response to one observation made during the Kearns/Jansen inspection (Exhibit 3, Observation No. 4), a record system has been set up to document room temperature exposure of final product during labeling and an SOP has been drafted.

I also examined Cold Room No. [redacted] in Bldg [redacted] which had been mentioned in Dr. Heintzelman's EIR and listed as an observation in the Kearns/Jansen inspection (Exhibit 3, Observation No. 14). The room was crowded but all material had been segregated and labeled appropriately. There were several examples of material that could have been discarded (miscellaneous testing samples) or stored elsewhere (Tetanus antitoxin produced in 1965) and I suggested that they consider reorganizing this room.

E. Quality Control

The in vivo control testing for RVA (general safety test, NIH potency test, rabies virus inactivation curves) is performed in Bldg [redacted] under the supervision of Dr. Barbara Kintner. The in vitro testing (chemistry, sterility, cell culture) is performed in Bldg [redacted]. Dr. T.C. Yang explained the current tests being conducted for adventitious agents on samples from RVA Lot No. [redacted]. The incubator used for these tests (No. [redacted]) did not have a temperature chart recorder. Temperatures were recorded in a log book and there [redacted]

were several work days (e.g. July 19, July 25) on which no entries had been made (Exhibit 2, Observation No. 6). Sterility test media is prepared by the Division of Laboratory Services (Bldg) and the Growth Promoting Quality (GPQ) test is also performed there. I reviewed copies of the GPQ test records for the most current lots of Thioglycollate and Soybean Casein Digest media as well as bulk and final container sterility test records for RVA Lot No. No sterility testing was in progress because a contractor was performing the validation of the laminar flow hoods in the test area. I also reviewed the latest autoclave validation records for the two autoclaves (Nos used in the RVA production area (Bldg.

VI. Recall and Distribution/Adverse Experiences

I discussed the distribution of RVA with Dr. Myers and received copies of the distribution data through March 1994 including doses distributed by MDPH and (Exhibits 10 and 11). I also received a copy of the most recent SOP concerning recall of distributed product from the field (Exhibit 12). I reviewed the Adverse Experience File for RVA and found three reports listed since the 1992 inspection. One report concerned muscle spasms in one patient which were experienced one month after post-exposure prophylaxis and which resolved in 2-3 weeks. In the second report, one patient reported "throbbing in the left eye" after a 3-dose prophylactic series. The last report concerned a nodule, eventually identified as an angioliopoma, that was found near the RVA injection site. All reports seemed to be complete and were followed up in a timely manner. I also reviewed a copy of an SOP entitled "Postmarketing Reporting of Adverse Drug Experience to the FDA" and the latest Annual Periodic Adverse Experience Report for RVA submitted to FDA on May 18, 1994.

VII. Discussion with Management

Dr. Myers requested that other senior management personnel involved in biologics production be included in the exit discussion in addition to those involved in RVA production. Those attending the meeting were as follows:

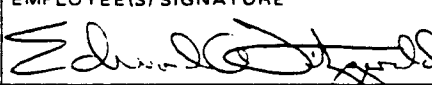
NAME	TITLE/AFFILIATION/DEPARTMENT
Robert C. Myers	Chief, Bio. Products Division
William Bursaw	Filling and Packaging Unit/Bio. Products Division
Karl Ebner	Vaccine Development R & D
Judith Boice	Vaccine Production
Jane Rhodes	General Services
J.W.Eckenrode	Blood Derivatives
Dick Hoort	Vaccine Production
F.M. Saad	Chief, Quality Control Section
Steve Kahn	Rabies Vaccine Production
Barbara Kintner	Animal Care
T.C. Yang	Bioassay Unit, Quality Control Section
Daryl Anderson	D.G.S., Physical Plant

Nancy Summerton
Graylon Copedge
William White
L.J. Charamella

Engineering - Bio Products Division
Biochemistry Unit
Athena Neuro Science, Inc.
Blood Derivatives

I discussed the observations on the FD 483 (Exhibit 2) and tried to re-emphasize some of the points made during Dr. Heintzelman's 1992 inspection and Mr. Kearns/Ms. Jansen's 1994 inspection, especially concerning Quality Control testing of raw materials. I said that, in my opinion, the facility and production methods (record keeping, SOPs, etc) were changing for the better, but that more needed to be done for full compliance with the GMP regulations.

I concluded the inspection at 3:00 pm on July 26, 1994.

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION		DISTRICT ADDRESS AND PHONE NUMBER	
NAME OF INDIVIDUAL TO WHOM REPORT ISSUED TO: DR Robert C Myers		PERIOD OF INSPECTION July 25-26, 1994	C. F. NUMBER
TITLE OF INDIVIDUAL RESPONSIBLE HEAD		TYPE ESTABLISHMENT INSPECTED BIOLOGICS MANUFACTURER	
FIRM NAME Michigan Dept of Public Health		NAME OF FIRM, BRANCH OR UNIT INSPECTED DIVISION OF Biologic Products	
STREET ADDRESS 3500 North Logan		STREET ADDRESS OF PREMISES INSPECTED _____	
CITY AND STATE (Zip Code) LANSING, Michigan 48909		CITY AND STATE (Zip Code) _____	
DURING AN INSPECTION OF YOUR FIRM (I) (WE) OBSERVED:			
<ol style="list-style-type: none"> 1. That Raw materials are stored in a warehouse (Bldg.) that has not been approved by CBER, FDA. 2. That tissue culture Roller bottles () are not quarantined, tested and RELEASED as GMP material. 3. That no expiration date was assigned to Rabies Sublots produced as a component of Rabies Vaccine, Adsorbed. 4. The harvest of cell culture Roller Bottles used in production of Rabies VACCINE, Adsorbed IS NOT PERFORMED CONSISTENTLY IN ACCORDANCE WITH THE EXISTING SOP 5. expired Lots of Rabies VACCINE, Adsorbed, were stored in the "IN PROCESS" REFRIGERATOR (Room) in Bldg. . 6. Temperature recording for incubator (Bldg.) is not complete in that it was NOT continuous (i.e.) two weeks were not RECORDED 			
SEE REVERSE OF THIS PAGE	EMPLOYEE(S) SIGNATURE 	EMPLOYEE(S) NAME AND TITLE (Print or Type) EDWARD A FITZGERALD DIRECTOR, DPQC, CBER	DATE ISSUED 7/26/94