

STATE OF MICHIGAN



JAMES J. BLANCHARD, Governor

DEPARTMENT OF PUBLIC HEALTH

3500 N. LOGAN
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→ October 10, 1990

Gerald Quinnan, Jr, M.D.
Acting Director
Center for Biologics Evaluation
and Research
Food and Drug Administration
8800 Rockville Pike
Bethesda, MD 20892

*Received HFB-100 on 10/22/90 → forwarded to HFB-120
for review purposes, action needed.
M. Dulaney*

→ HFB-122

Dear Dr. Quinnan:

The following comments are offered in response to the observations listed on Form FDA 483 which was presented to us by Messrs. Heintzelman and Rouse at the conclusion of their inspection on September 12 and 13, 1990.

Observation 1: Reagents quarantined in the GMP quarantine area of Bldg. were stored directly on the floor and underneath a showerhead.

Comment: This showerhead has been removed and the pipe has been capped-off. Pallets and a shelf have been placed in the GMP quarantine area and no reagents are now stored directly on the floor.

Observation 2: Bioassay incubator room/closed () had stoppers, gowns, pipets, pipet tips, test tubes, test tube racks, antiquated equipment, mops, sponges, drying autoclave gowns, and a pair of pants stored along with sterility test samples.

Comment: Extraneous materials have been removed and workers have been instructed to use this room as an incubator only.

Observation 3: Bioassay incubator room/closet () had test tubes, stirrer, power supply, unidentified boxes, and a paper electrophoresis unit stored along with sterility test samples.

Comment: Extraneous materials have been removed and workers have been instructed to not use this room as a storage area.



Observation 4:

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Comment:

Growth of _____ was recorded, however, on worksheets used by workers testing this lot of media. Workers have been instructed to accurately transcribe and verify test information from worksheets to records.

Observation 5:

Procedure for dispensing M-endo plates appears inadequate to prevent contamination in that we observed an employee enter the room dressed in "street" clothes to retrieve a coffee cup.

Comment:

The employee involved has been remedially instructed in the proper use of this room. Standard operating procedures for the use of this room are being reviewed and will be modified as warranted.

Observation 6:

Procedures used to determine Exp. Dates of GMP chemicals are inconsistent in that chemicals are given in-house exp. dates in excess of chemical manufacturer's exp. date, i.e. lot of TSB used in production of media for Q.C. was expired. This practice of extended exp. dates was observed in multiple bldgs.

Comment:

The current written policy for GMP chemicals does not address manufacturer's expiration dating. A survey of all GMP chemicals will be conducted and this policy subsequently revised to achieve consistency between MDPH expiration dating and that of the manufacturer.

Observation 7:

Exp. dates for GMP items were not consistent in that it was difficult to determine whether the listed date was the receiving date or the exp. date.

Comment:

The difficulty described in this observation in the tetanus production facility arose from the discontinued practice of labeling GMP reagents with the date the reagent was released from GMP quarantine. GMP labels now in use bear an expiration date for each reagent. All containers of reagents labeled with the no longer used label have been removed from the GMP storage area of the tetanus production facility.

Observation 8:

Buffer solutions used in the production of diphtheria and tetanus toxoids (_____ had expired one year previously and were still in use.

Comment:

Review of production records for diphtheria and tetanus confirmed that neither of these buffers were used in production beyond their expiration dating. The containers of these solutions have been removed from the production area.

Observation 9: Aseptic processing corridor had numerous dead flies resting upon light fixtures. One fixture cover was observed to have a hole in it.

Comment: A work order has been submitted to repair the defective fixture cover. Because the light fixtures and top side of fixture covers are outside of the clean room environment and because these fixtures are sealed with silicone caulking, we believe it is best to remove flies only during shutdown of the facility or repair of an individual fixture. The source of flies in the plenum above the facility is being investigated.

Observation 10: Anthrax production facility (fermenter room) utilizes an exhaust fan which vents directly outside. The inspectors observed wind blowing directly into the fermenter room through the fan vent.

Comment:

Observation 11: Anthrax prod. fac. was observed to be in a state of general disrepair in that there was: (A) Paint peeling from the walls (B) Exposed light fixtures (C) Cracked ceiling (D) Exposed raceways (E) Dirt & filth & dust on overhead pipes (F) Cluttered work space.

Comment: Since the inspection, the anthrax production facility has received a thorough cleaning. While some dust was present on overhead pipes, no dirt and filth were found. Due to the present urgent need for anthrax vaccine, the structural defects listed in this observation cannot be immediately addressed. As soon as emergency production is completed, improvements to the facility will be made.

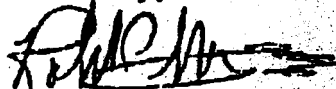
Observation 12: Anthrax Seed Sample Data worksheet for FAV-001 has _____ and XI limits specified that are not met within prod. and are different for each of the individual sub-lots, i.e. #25, #21, #26 and #27 used to formulate the final bulk.

Comment: Anthrax seed sample data worksheets have been revised, specifying only those criteria pertinent to the monitoring of the acceptability of seed culture growth.

Observation 13: Anthrax prod. records are inconsistent in that procedures used to formulate Lot #21 are different from those used to formulate Lots #25, 26 & 27 in that media is autoclaved for sterilization for Lot #21 and filtered for sterilization for Lots #25, 26 & 27.

Comment: The approved licensed procedure for sterilization of _____ for production states that the medium is brought to _____ then quickly cooled to _____. It is our belief that this procedure does not insure effective sterilization of the medium. We have therefore added a _____ filtration step immediately preceding the heating step. Our review of the records of sublots 21, 25, 26 and 27 indicates that these steps were consistent for all of the sublots. Sterilization procedures for the seed and production media are not identical and this may have led to confusion during the inspectors' review of these records.

Sincerely,



Robert C. Myers, DVM, Chief
Division of Biologic Products
Bureau of Laboratory and
Epidemiological Services

RCM:ds