

- b. the validation of the sterilization-in-place cycle of the *lyophilizers* is incomplete in that temperature distribution studies have not been performed. (b)(4)
 - c. the lyophilization cycle validation is inadequate in that only one typhoid vaccine product lot was used to demonstrate cycle reproducibility.
 - d. the *blistering* *scanware* machine has not been validated. (b)(4)
3. Failure to routinely calibrate, inspect, or check automatic, mechanical, or electronic equipment used in the manufacture, processing, packaging, and holding of a drug product according to a written program designed to assure performance [21 CFR 211.68(a)] in that:
 - a. the thermocouples used to monitor the *depyrogenation* ovens temperature and the *autoclave* temperature have never been calibrated. (b)(4)
 - b. the chamber and surface of the lyophilizers *are* not periodically monitored for the presence of oil and thermal fluid. (b)(4)
 - c. the thermometers and hygrometers used to monitor temperature and humidity in building *have* not been calibrated since September 1995 and in Class *and* *filling* areas in building *have* never been calibrated. (b)(4)
4. Failure to clean, maintain, and sanitize equipment and utensils to prevent malfunction or contamination that would alter the safety, identity, strength, quality, or purity of the drug product [21 CFR 211.67(a)] in that:
 - a. the air vent filters used on the formulated bulk container, tetanus toxoid glass carboys, and *autoclave*; the HEPA filter used on the *depyrogenation* oven; and the *filter* used on the *lyophilizers* have not been integrity tested.
 - b. the effectiveness of the cleaning and sanitizing agents used during routine cleaning and sanitization of areas where live microorganisms are campaigned has not been established.
 - c. residue limits for *used* in the production areas as a fumigating agent have not been established. (b)(4)
5. Failure to maintain or follow written procedures for cleaning and maintenance of equipment including utensils, used in the manufacture, processing, packing, or holding of a

- a. there is no written procedure to describe the cleaning method used to clean tetanus toxoid purification tanks ~~in building~~ in building (b)(4)
 - b. periodic evaluation of the cleaning method used to clean multi product equipment, e.g., centrifuges, mix tanks, ~~fermentors~~ fermentors, and the transfer line into the lyophilization area is not performed. (b)(4)
6. Failure to maintain separate or defined areas or such control systems as necessary to prevent contamination during aseptic processing [21 CFR 211.42(c)(10)(iii) and 211.46(b)]. For example:
- a. sterile siliconized stoppers are placed inside the filling machine hopper located outside the Class ~~environment~~ i.e., a Class ~~environment~~ environment. (b)(4)
 - b. integrity tests, air velocity, and smoke studies have not been performed for the HEPA filters supplying air to the Class ~~filling~~ filling areas. (b)(4)
 - c. the inoculation of the ~~seed~~ subculture medium flask and the ~~fermentor~~ fermentor with the tetanus toxoid concentrate seed culture of *Clostridium tetani* is performed in an uncontrolled environment. (b)(4)
7. Failure to establish laboratory controls that include scientifically sound and appropriate specifications, standards, sampling plans, and test procedures designed to assure that components, drug products 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 the sterility test used on finished products had not been validated to assure that the antimicrobial properties of the Tetanus Toxoid Adsorbed affect the recovery of all possible contaminants.
8. Failure of the quality control unit to approve or reject all procedures or specifications impacting on the identity, strength, quality, and purity of drug products [21 CFR 211.22(c)] in that moisture specification for the Ty21a lyophilizate was changed from 1-3% to ~~without~~ without a complete product evaluation. (b)(4)
9. Failure of the quality control unit to approve or reject all components, drug product containers, closures, in-process materials, packaging material, labeling, and drug products [21 CFR 211.22(a)] in that viable and nonviable monitoring results obtained during filling operations are not reviewed as part of lot release.
10. Failure to thoroughly investigate any unexplained discrepancy or the failure of a batch to meet any of its specifications [21 CFR 211.192] in that no investigation was performed for the failure of Vivotif capsule lots 14611-01 and 14611-02 to meet viable cell count release specification.

11. Failure to establish and/or follow written procedures for the use of suitable rodenticides, insecticides, fungicides, fumigating agents, and cleaning and sanitizing agents and to prevent the contamination of equipment, components, drug product containers, closures, packaging, labeling material, or drug product [21 CFR 211.56(c)] in that product manufacturing areas are fumigated with formalin and the removal of residual formalin is not performed.
12. 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. There is no written procedure describing the HEPA filter testing that should be performed during filter replacement, i.e., efficiency, integrity, velocity.
 - b. There is no written procedure describing product filling parameters, e.g., volumes and speed for the *wavy* filling machine.
13. Failure of the quality control unit to review any complaint involving the possible failure of a drug product to meet any of its specification [21 CFR 211.198 and 211.22] in that there is no assurance that the adverse drug reaction reports from the United States are evaluated by quality control.
14. Failure to establish and/or maintain written procedures for the receipt, identification, storage, handling, sampling, examination, and/or testing of labeling and packaging material [21 CFR 211.122(a)] in that there is no procedure describing the specifications or requirements to be examined when product labels are modified.

(b)(4)

We acknowledge receipt of your October 22, 1997, written response which addresses the inspectional observations on the Form FDA 483 issued at the close of the inspection and we will respond to your letter under separate cover.

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. It is your responsibility to exercise control of the establishment in all matters relating to compliance with all pertinent regulations.

Please 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

Page 5 - Swiss Serum and Vaccine Institute Berne

deviations may result in regulatory action without further notice. These actions include license suspension and/or revocation, and seizure.

Your reply should be sent to me at the Office of Compliance, Attention: Division of Case Management, Center for Biologics Evaluation and Research, 1401 Rockville Pike, Suite 200N, HFM-600, Rockville, Maryland, 20852.

Sincerely,


for, James Simmons
Director Office of Compliance
Center for Biologics Evaluation and Research