BIOPROCESS AUDIT SITUATIONS & FINDINGS – CASE STUDY

DCVMN, Hyderabad – INDIA

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dcvmn
Developing Countries Vaccine Manufacturers Network

Introduction

Case

Fermenter / Reactor/Vessels possible audit findings.

Instructions to the group

1. Read the FDA Warning Letter provided. Use the flipchart and complete the assigned item of the table based on the FDA auditor's findings and on the Pharmaceutical inspection co-operation scheme (PIC/S) PI 024-1 2005 - Aide-memoires: Inspection of Biotechnology Manufacturers.

2. Make a brief presentation to the class.

3. Simulate interviews showing one correct and one undesired audit situation.

4. Prepare a brief audit report based on the outcome of the point audited and present to the class.

FDA WARNING LETTER

The Food and Drug Administration (FDA) conducted an inspection of XXX at XXX. During the inspection, documented deviations from current good manufacturing practice (CGMP) in the manufacture of Influenza Virus Vaccine, including the bulk monovalent blend pools and trivalent bulk batches. These deviations from CGMP include the applicable requirements XXX that described a number of significant objectionable conditions relating to the facility's compliance with CGMP. The XXX sterility failure investigation conducted by the quality control unit failed to include and address the bulk sterility failure of the monovalent blend pool # YYY.

Your firm failed to establish and follow scientifically sound and appropriate specifications, standards, sampling plans, and test procedures designed to assure that drug products conform to appropriate standards of identity, strength, quality, and purity. [21 CFR 211.160]. For example,

made, is obstructed by the operators when making the connections.

FDA WARNING LETTER (Cont.)

1) Your firm failed to establish separate or defined areas or other control systems for aseptic processing operations to prevent contamination or mix-ups. [21 CFR 211.42(c) (10). For example, formulation rooms do not meet manufacturing needs and prevent contamination, due to the equipment configurations within the Class area, in that the airflow, above the critical area where multiple aseptic connections are made, is obstructed by the operators when making the connections.

FDA WARNING LETTER

2) Your firm failed to establish and follow written procedures to assure the cleaning and maintenance of equipment used in the manufacture, processing, packing, or holding of a drug product. [21 CFR 211.67(b). For example, cleaning validation for the clean-in-place (CIP) process Vessel which is utilized in the aseptic formulation of trivalent bulk influenza vaccine, did not include an assessment of the spray ball coverage for the vessel. The spray ball is used for cleaning product contact equipment. In addition, the study did not include swab sampling of the product transfer lines.

3) Appropriate validation studies have not been conducted for critical processes. For example, validation for the manual cleaning of the fermenter's connections.

4) There is no indication that prior to August 2004 there were periodic preventive maintenance programs or procedures to prevent malfunctions or contamination for the tanks and fermenters.

FDA WARNING LETTER

No adequate investigations into deviations performed, as required by applicable FDA regulations.
Please describe in detail how XXX will attain GMP compliance: with regard to deviation investigations by, among other things, taking into account other failures or discrepancies that may be related, and then using all of the relevant information to conduct a root cause analysis to ensure that adequate steps are taken for the evaluation of product impact, deviation investigations, and the implementation of effective corrective and preventive actions.

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Nonconformity	Major / Minor (justify)	Documentation to request
1. Fermenter with improper CIP design (no/inadequate/unvalidated spray ball, pump).		
2. Open system. Lot of flexible piping involved. Critical operation performed manually (e.g., critical valves in CIP-SIP). Use of culture bottle with no sterile sampling device).		
3. Critical services failures during production.		
4. Lack of integrity testing before / after process (including filters). Mechanical seals failure, loss of pressure and condensate. Media hold test failure.		
5. No data acquisition (SCADA) / trend analysis.		
6. Vessel inside and outside corrosion; quality of welding, material of construction.		
7. Dead legs with improper CIP-SIP.		
8. Lack of vendor documents and certifications including DQ, FAT.		
9. Lack of exhaust filter and incinerator		
10. Untrained / poorly trained operators		