PDA
Parenteral Drug Association
India Chapter

The Quality Edifice and Sterility Assurance of Parenterals

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Sessions:

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1. **Investigations- The ABC of expectations**
2. **Environmental Monitoring- Need for preventive controls & verification possibilities**
3. **Understanding Risks for predictive controls**
4. Uncovering nuances of FDA's draft guidance on 'Circumstances that Constitute Delaying, Denying, Limiting, Or Refusing a Drug Inspection.
5. Manual Aseptic Processing- The Crossroads
6. Sterility Assurance Packages- Essentials and Expectations

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Case 3

Understanding Risks for Predictive Controls

Case study:

Crucial self audits and Internal audit- how to turn them around

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AGENDA

- Recent audit observations
- Firm's response to observations
- FDA expectations on observations and response
- Role of self/internal audits
- Design of self/internal audits

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Welcome to a deep-dive with Case # 1-15

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CASE 1: Recent audit observations

Topic/area	Observation
Vendor qualification program and incoming material release system (Sterile gloves)	Visible holes, flaking, cracking, and/or discoloration were observed in the gloves purporting to be sterile
	Damaged or incomplete packages were found in many glove packages examined for package integrity
	These gloves, purporting to be sterile, are worn by aseptic manufacturing operators in the filling suites
	The cardboard boxes used to ship and store these gloves were also found to be damaged. Crushed insects were found on one of the glove's outer package inside the shipping box
	These defective gloves are especially concerning in part because they were used to perform manipulations directly over empty vials. Investigators observed at least 20 line interventions using these gloves. Design concerns of the RABS – positioning over the sterile empty vials

CASE 1- Recent audit observations (continued)

Topic/area	Observation
Vendor qualification program and incoming material release system (Sterile gloves)	**Response given by firm:** Discontinue using the current supplier and qualify new glove suppliers
	FDA comments on firm's response: Provide the type of tests (methods) and physical examination to be conducted to qualify new glove suppliers, the acceptance criteria of the tests/examination of the gloves and primary packaging, criteria for rejection of vendor and investigation performed
	Procedures to examine gloves prior to use: Procedures in place to verify the integrity of the gloves prior to use. Standard operating procedures (SOPs) lack specific instructions to operators on how to perform examination of glove integrity prior to use. In addition, investigators interviewed employees and verified that glove integrity checks had not been performed. Production records also did not reflect that glove verification activities have carried out prior to production.

CASE 2: Recent audit observations

Topic/area	Observation
Improper data recording	The investigator noticed that during an inspection of the packaging area a production employee had recorded the final packed quantity of the batch , even though the quantity was not yet known because the operator had not yet weighed the batch.
	Immediately after observing the incident, the investigator requested a copy of page 6 of the batch record and was given a photocopy. A full batch record provided later that day did not include the original page 6. Instead it included a new version of page 6
	The investigator observed at least two examples when a manufacturing step was recorded in the batch record before it occurred: 1) The production operator had already recorded the start time as 12:15 PM , although it was still 11:00 AM when investigator noticed this situation. 2) At approximately 11:00 AM on the same date, a production officer had already recorded the API details in the batch production record, although the step had not yet occurred.

CASE 3: Recent audit observations

Topic/area	Observation
Inadequate media fill studies	Significant number of media fill vials were rejected without justification
	176 vials were rejected for "Other Rejections." locations at which these "Other" vials were rejected and the reason for rejection were not documented
	FDA comments: No amount of successful media fills can be used to validate poor aseptic design, operations, controls, and practices. Sterility assurance requires a holistic approach in every aspect of the aseptic operations. Firm should conduct a careful risk assessment of aseptic operation with the aim of achieving a high degree of sterility assurance

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CASE 4: Recent audit observations

Topic/area	Observation
Microbial monitoring	Firm did not adequately assess contamination risk to determine the worst-case locations and timing for active viable air monitoring sites. Active air samples are collected during idle conditions, each of which are located at the backside of the filling machine and are not representative of the conditions during production. Sampling was not conducted under dynamic conditions.
	Active air sampling is deficient. The microbiologist sprays the ------, followed by wiping with a cloth. The media plate is loaded onto the air sampler later. There is no assurance that residual -------does not impact the detection of contaminants.
	Inspection found that there is no assurance that personnel monitoring (finger dabs), with periodic use of the ------- to disinfect the gloves, is conducted at a time that allows accurate recovery and counts of contaminants.
	FDA expectations: Provide an enlarged diagram of the locations of air sampling (viable and non-viable), plan to perform active air sampling under dynamic conditions, and the modified SOP on how personnel monitoring is conducted to address concerns.

CASE 5: Recent audit observations

Topic/area	Observation
Contamination or mix -ups	Firm failed to perform operations within specifically defined areas of adequate size and to have separate or defined areas of such other control systems necessary to prevent contamination or mix -ups . Firm did not disinfect the conveyor after storage outside the ISO-5 area; this conveyor is used to transport filled and partially stoppered vials
	Inspection found that the same "mop" is used throughout the production of a batch and is even stored outside the ISO-5 area before re-use. This "mop" is used to disinfect the RABS and equipment surfaces inside the RABS during setup and manufacturing activities. The repeated use of the same "mop" poses a significant risk of cross-contamination to the open vials with microbial and/or particulate matter from the cloth mop
	Firm allows RABS to be opened during processing. Opening of the RABS during processing should be a rare event and used only for narrowly defined situations, not for routine interventions
	Firm did not use a sporicidal disinfectant for cleaning inside of the Class 100 (ISO 5) filling areas

CASE 6: Recent audit observations

Topic/area	Observation
Inadequate laboratory controls (Stability)	Inspection revealed many examples where you failed to exercise proper controls in evaluating the stability of your drug products Review of three month stability samples currently under analysis, revealed an inconsistency in the number of vials removed from the stability chamber: 32 vials had been removed but only a total of 2 vials for room temperature and accelerated conditions were tested. Firm has not accounted for the disposition of the remaining 30 vials. Additionally, examination of three-month stability samples currently under analysis found that one vial had been substituted and tested in place of the other conditions
	No explanation was provided regarding the missing vials in all cases.

CASE 7: Recent audit observations

Topic/area	Observation
Computer or related systems	Firm failed to exercise appropriate controls over computer or related systems to assure that only authorized personnel institute changes in master production and control records or other records (21 CFR 211.68(b)). The firm's HPLC instruments do not have restrictions in place to prevent any change or deletion of analytical raw data. Additionally, there is no audit trail in place to determine any previous deletion of raw data.
	Firm's response: Discontinued usage of systems at inspection site and other sites , and will assess previous use of the these systems
	FDA comments on firm's response: please submit an assessment of the integrity of the data from the systems only for lots of finished product still within expiry as of the

CASE 8: Recent audit observations

Topic/area	Observation
Facility maintenance	firm failed to maintain the buildings used in the manufacture, processing, packing, or holding of a drug product in a clean and sanitary condition (21 CFR 211.56(a) inspection of finished drug product cold storage (2- 8°C) room found water damage and the presence of mold growth on finished product shipping containers, and observed pools of water on the floor.
	Firm's response: corrective actions to clean and control the temperature and humidity of the cold room
	FDA comments on firm's response: address the presence of mold spores in the cold room. Our investigators will evaluate these corrections during our next inspection

CASE 9: Recent audit observations

Topic/area	Observation
Documentation review	Firm's quality control unit failed to review and approve all drug product production and control records to determine compliance with all established, approved written procedures before a batch is released or distributed (21 CFR 211.192). Firm's quality unit failed to adequately review and approve your firm's production and control records. There is no assurance that the quality unit fully reviewed and approved all batch-related documentation prior to release of finished product to the U.S. market. Firm distributed the lots to the U.S. market without adequate review
	FDA expectations: Provide corrective actions to improve quality unit's release and approval processes. Additionally, provide evidence of a retrospective documentation review of all drug products distributed to the U.S. within the last three years to determine those products' compliance with all established written procedures. Identify any information gaps in the records, and ensure any deviations and atypical events are investigated. Provide completion dates for all

CASE 10: Recent audit observations

Topic/area	Observation
Calibration /validation	Firm failed to routinely calibrate, inspect, or check according to a written program designed to assure proper performance and to maintain adequate written records of calibration checks and inspections of automatic, mechanical, electronic equipment, or other types of equipment, including computers, used in the manufacture, processing, packing, and holding of a drug product (21 CFR 211.68(a)).
	Firm failed to establish a validation program for the computer software used for production, inventory, lot number generation, and laboratory test methods used for raw material, bulk, and finished product test release. Firm also uses the program to assist your quality unit for product, document and component control
	FDA expectations: Provide validation plan/protocol for the system. Include timelines and a schedule of all corrections

CASE 11: Recent audit observations

Topic/area	Observation
Improper data recording	The investigator noticed that during an inspection of the packaging area a production employee had recorded the final packed quantity of the batch , even though the quantity was not yet known because the operator had not yet weighed the batch.
	Immediately after observing the incident, the investigator requested a copy of page 6 of the batch record and was given a photocopy. A full batch record provided later that day did not include the original page 6. Instead it included a new version of page 6
	The investigator observed at least two examples when a manufacturing step was recorded in the batch record before it occurred: i. The production operator had already recorded the start time as 12:15 PM , although it was still 11:00 AM when investigator noticed this situation. ii. at approximately 11:00 AM on the same date, a production officer had already recorded the API details in the batch production record, although the step had not yet occurred.

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CASE 12: Recent audit observations

Topic/area	Observation
Improper data recording	investigator noticed that a QC analyst was performing a Loss on Drying (LOD) analysis and had recorded the completion time and total time in the usage log book for the LOD oven usage logbook although the step was not yet completed
	investigator also found that weights for three samples were recorded on blank pieces of paper and not directly onto the test data sheets
	Firms response to observation: Firms response to this observation stated that a new SOP has been created to address this issue and that training on this SOP has occurred
	FDA comments on observation: Response did not address the extent of this practice, the impact on the quality of the product and why laboratory management failed to detect this practice. Response also provided no actions to improve oversight by quality unit (e.g., independence, authority, resources). The above practices observed during the inspection raise concerns regarding the reliability and accuracy of the data generated at firm, including any other inappropriate data-related practices permitted by the firm when an inspection is not in progress.

CASE 13: Recent audit observations

Topic/area	Observation
Power failure	The inspection revealed that more than 100 power outages occurred in a year. The investigator was told that when a power failure occurs, the backup generator does not turn on automatically, but rather needs to be manually started by an employee. In each instance, firm failed to conduct an investigation into the power outage's impact on quality of product(s) being manufactured at the time. The inspection documented that, despite the fact that firm has an uninterrupted power supply used by the QC laboratories, power failures have impacted the QC stability chambers. However, in each case, no investigation was conducted to determine the impact of the power loss on the samples kept within the chambers. Moreover, quality managers stated to investigator that no procedure for this type of investigation exists at the facility
	FDA comments on firm's response: Provide an assessment of the validity of the data generated during the documented power outages. Provide a report documenting the power outages experienced since the date of response and a summary of the resulting investigations with the product impact performed

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CASE 14: Recent audit observations

Topic/area	Observation
Equipment failures	Deviations pertaining to laboratory equipment failures were not investigated. During the review of the service report log books for HPLC and GC units, the investigator found many instances of servicing due to instrument problems that were not documented as deviations.
	Firm's response: Response stated that the SOP has been changed to require deviations only for instances in which servicing was required to repair a problem with the instrument
	FDA comments on firm's response: Response failed to address why no deviation was filed and investigated for the instances in which instrument problems were the cause of system maintenance. As a general laboratory practice, any equipment malfunction that may have an impact on quality control testing should be appropriately recorded and investigated

CASE 15: Recent audit observations

Topic/area	Observation
Analytical methods	Inspection documented that there is no raw data for the related substance preparation testing and there is no raw data for the standard and sample preparation for the residual solvent testing of the same lots. Analysts informed the investigator that no raw data for standard and sample preparations are kept in the records.
	Firm's response: Your response states that your firm will begin maintaining the raw data used for the assays cited on the Form FDA-483
	FDA comments on firm's response: The firm makes no commitment to perform a laboratory-wide audit to determine whether other assays conducted in your laboratory also require procedural or administrative changes to maintain all raw data generated during performance

CASE 15: Recent audit observations

Topic/area	Observation
Electronic signatures	Firm failed to have adequate procedures for the use of computerized systems used in the QC laboratory. At the time of the inspections, QC laboratory personnel shared the same username and password for the operating systems and analytical software on each workstation in the QC laboratory. In addition, no computer lock mechanism had been configured to prevent unauthorized access to the operating system. The investigator noticed that the current QC computer users are able to delete data acquired. In addition, the investigator found that there is no audit trail or trace in the operating system to document deletions.

Design of self audits

What do these observations tell us, and what are the lessons for our organization?

Now we know what this tells us… What do we do about it in our own organizations?

Design of self audits

Does it initiate a self audit, if yes what will be the process?

1. Will it be same as our typical self audits
2. If not, what is the difference

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Design of self audits

This brings us to next set of questions:

- Do we need to have specific objectives for self audits.
- If yes, what are those..
- How are they articulated
- Who articulates them
- Where does it get documented
- How does it get communicated
- Lastly who are the stake holders and how are they brought on board.

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Design of self audits

How is the process of self audit executed?

- How do we select the self audit team?
- Who is an SME? How are they selected?
- Is the audit conducted in the same manner as a regulatory audit?
- If not, what is the difference?
- What is the role of an auditee department?
- What is the role of an auditor? SME?

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Design of self audits

What defines closure?

- Do we need a quantified output at the end of self audit?
- How is it different than regular “run of the mill” observations from any regular audit?
- How is close out measured?
- What defines success of an audit?
- Who decides the success? Accountability?
- What is the role of “auditor” and “auditee” in achieving closure?
- How are lessons learnt articulated, communicated, and to whom ?
- How are the “lessons learnt” getting institutionalized, and how is it reviewed?

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