Session 12D

Process Validation – Critical Steps

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Learning Objectives

• Validation Vs Verification
• Process Validation Vs Design Validation
• Why and when to perform Validation?
• Types of validation
• Performing a process validation
• Re-validation requirements
• Summary
Process Validation

• Verification Vs Validation:
  – Verification means conformation by examination and provision of objective evidence that specified requirements have been fulfilled
  – Validation means conformation by examination and objective evidence that the particular requirements for a specific intended use can be consistently fulfilled
Process Validation (cont’d)

• Process Validation Vs Design Validation:

  – *Process validation* means establishing by objective evidence that a process consistently produces a product meeting its predetermined specification

  – *Design Validation* means the design has been developed from Customer Requirements, and reviewed by a team of identified fully competent stakeholders to ensure that the proposed device design conforms to user needs and intended use
Why Validation?

- Manufacture must prove with a high degree of assurance that the product can be manufactured according to the quality attributes before a batch is placed on the market.
When to validate a process?

- Is it possible to verify the process?
  - Yes: Is the verification sufficient and cost effective?
    - Yes: Process Verification
    - No: Is redesign possible?
      - Yes: Redesign Process
      - No: Validate the Process

- No: Validate the Process

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## Process Validation

### Comparison of Validation Requirements

<table>
<thead>
<tr>
<th>FAD Requirements</th>
<th>ISO 13485 Requirements</th>
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<tr>
<td>Where the results of a process cannot be fully verified by subsequent inspection and test, the process shall be validated with a high degree of assurance and approved according to established procedures. The validation activities and results, including the date and signature of the individual(s) approving the validation and where appropriate the major equipment validated, shall be documented.</td>
<td>The organization shall validate any processes for production and service provision where the resulting output cannot be verified by subsequent monitoring or measurement. This includes any processes where deficiencies become apparent only after the product is in use or the service has been delivered.</td>
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What Processes should be Validation?

• **GHTF Guidance:**
  – Sterilization processes
  – Clean room ambient conditions
  – Aseptic filling process
  – Sterile packaging sealing processes
  – Lyophilization (freeze-drying) process
  – Heat-treating processes
  – Plating processes
  – Plastic injection molding processes
Types of Validation

1. Prospective Validation

   Validation conducted prior to the distribution.

   Normally a Prospective validation is performed on any new pieces of equipment used in the design or manufacturing of a medical product.

2. Concurrent Validation

   A subset of prospective validation conducted with the intention of ultimately distributing product manufactured during the validation study.
Types of Validation (cont’d)

3. Retrospective Validation

– Validation of a process for a product already in distribution based upon accumulated production, testing and control data

– Where no equipment qualification has been performed, or where the equipment qualification is inadequate, than a Retrospective validation should be performed.
Process Requirements

Standards

Operators

Inputs

Procedures

Equipment

Outputs
Process Requirements (cont’d)

- Inputs
- Standards
- Procedures
- Operators
- Equipment

Outputs

IQ → PQ → Process

OQ
Process Validation

• Validation requirements (QSR):
  1. Installation Qualification (IQ)
     • Process equipment consistently operates within established limits and tolerances
  2. Operational Qualification (OQ,) (Process performance)
     • The process is effective and reproducible
  3. Performance Qualification (PQ)
     • The finished product produced by a specific process meets all release requirements for functionality and safety
How to perform Process Validation

- Determine what process to validate (IQ, OQ, PQ)
- Write a validation protocol
- Conduct the protocol and collect the data
- Analyze the data
- Improve the process, as warranted based on the data analysis
- Prepare a report
- Keep the documentation as a quality record
How to Perform Process Validation (cont’d)

- Validation Steps:
  - Written Protocol
    - Scope of the validation plan
    - Develop a check list based on the requirements
      - Equipment
      - Test description
      - Acceptance criteria
      - Change control
      - Responsibilities …..
Process Validation

• Validation Steps (Cont’d):
  - Written Protocol
    • Put the instructions into the protocol
    • Put the data collection table and data collection analysis methods into the protocol
    • Test the protocol using simulated data
Process Validation (cont’d)

• Validation Steps (cont’d):
  - Data Collection and recording results
    • Think about how you will collect the data
    • Leave plenty of room to write in the results (use pen)
    • Consider mistake proofing and data analysis when creating the form
  - Written Report
    • The validation should produce a written report
    • We can add the data and draw conclusion
    • The completed version becomes the quality record
Installation Qualification-IQ (21 CFR §820.70(g))

**Equipment:**

Each manufacturer shall ensure that all equipment used in the manufacturing process meets specified requirements and is appropriately designed, constructed, placed and installed to facilitate maintenance, adjustment, cleaning, and use.
Process Validation (cont’d)

Installation Qualification-IQ (21 CFR §820.70(g))

• **Maintenance schedule:**

  Each manufacturer shall establish and maintain schedule for the adjustment, cleaning, and other maintenance of equipment to ensure that manufacturing specifications are met. Maintenance activities, including the date and individual(s) perforating the maintenance activities, shall be documented.
Process Validation (cont’d)

Installation Qualification-IQ (21 CFR §820.70(g))

• Inspection:

Each manufacturer shall conduct periodic inspections in accordance with established procedures to ensure adherence to applicable equipment maintenance schedule. The inspections, including the date and individual(s) conducting the inspections, shall be documented.
Installation Qualification-IQ (21 CFR §820.70(g))

- **Adjustment:**
  Each manufacturer shall ensure that any inherent limitations or allowable tolerances are visibly posted on or near equipment requiring periodic adjustment or are readily available to personnel performing these adjustments.

- **OSHA Requirements:**
  Each manufacturer shall meet OSHA’s standards:
  - Machine Guarding
  - Lock Out – Tag Out
Operational Qualification (OQ)

Purpose:

To ensure that all process outputs and results comply with predefined specifications and requirements. The process design is stable, capable and suitable for reproducibly manufacturing commercial batches.

21 CFR §820.30(h) Design transfer

Each manufacturer shall establish and maintain procedures to ensure that the device design is correctly transferred into production specification.
Process Validation (cont’d)

• Operational Qualification (OQ)
  - QSR Guide for Process performance:
    • Establishing documented evidence that the process is effective and reproducible
  - GHTF Guidance for Operational qualification:
    • Establishing objective evidence process control limits and action levels which results in product that meets all predetermined requirements
Operational Qualification (OQ)

- To ensure that the process is robust,
  - Determine and understand the process variations
  - Detect these process variations and assess their extent
  - Understand the influence on the process and the product
  - Control such variations
Process Validation (cont’d)

• **Operational Qualification (OQ)**
  
  - To ensure that the process is robust:
    
    • Have defined production specifications
    
    • Implement the specifications on the production equipment that passed IQ
    
    • Set control limits and action limits on the process to ensure that the process is reproducible
    
    • Challenge the process by using “worst case” conditions
    
    • Trained and qualified human resource
    
    • Verified and approved raw materials
Process Validation (cont’d)

• **Performance Qualification (PQ)**
  - QSR Guide for Product performance qualification:
    • Establishing documented evidence through appropriate testing that the finished product produced by a specified process(es) meets all release requirements for *functionality* and safety.

- GHTF Guidance for Performance qualification (PQ):
  • Establishing by objective evidence that the process, under anticipated conditions, consistently produces a product which meets all predetermined requirements.
Process Validation (cont’d)

• Performance Qualification (PQ)

To ensure that the product meets all the requirements:

• The process parameters have to be determined
• To demonstrate the robustness, conduct challenge tests
• Run the process under normal conditions over time to ensure that everything works as expected
• Set action limits to make sure the process continues to operate as designed
• The action limits might be on both input process parameters and output
Process Validation (cont’d)

• Tools and techniques:
  • Acceptance sampling plan
  • Process capability study
  • Control charts
  • DOE
  • FMEA
  • FTA (Fault tree analysis)
  • Precision and Accuracy study
Process Validation (cont’d)

• The need for re-validation should be determined based on the criticality of the application of the equipment being qualified.

• Unexpected process changes can occur, even in a well-developed process. The manufacturer may use quantitative, statistical methods whenever feasible.

• A re-validation may not be as extensive as the Prospective and Retrospective validation.
Process Validation (cont’d)

• CFR- §820.75(c) When changes or process deviations occur, the manufacturer shall review and evaluate the process and perform revalidation where appropriate. These activities shall be documented.

• QSR expects an investigation into any deviation. Keep records of the investigation. If you don’t revalidate, record the rationale for the decision and identify the person who made the decision.
Summary

• ISO 13485 and FDA requires Validation when product cannot be verified by subsequent measurement
• Prospective, Concurrent and Retrospective Validation
• Installation, (IQ), Operational (OQ) and Performance Qualification
• OSHA requirements should be addressed
• Quality records includes, Validation protocol, data collection and written report
• Re-validation may require (CFR- §820.75) when changes or process deviations occur
• Validation requires documented evidence
Questions?

Thank You!
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