Process Validation Guidance - SG3.N99-10

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1. Purpose and Scope

- **Purpose: to assist manufacturers in understanding process validation requirements**
- **Scope: applies to manufacturing processes, servicing and installation**

2. Definitions

2.4 Process Validation

Establishing by objective evidence that the process consistently produces a result or product meeting its predetermined requirements

2.6 Verification

Confirmation by examination and provision of objective evidence that the specified requirements have been fulfilled

3. Processes That Should Be Validated

3.1 Special Processes

- **Special processes are those for which the product cannot be fully verified**

- **National regulations may require process validation for special processes**

Example of a Special Process

- **Clinical or destructive testing is necessary to show the process produced the desired result or product**
- **Example: Testing all package seals destroys packages**

Example of a Special Process

- **Routine end-product testing:**
  - **does not examine all quality attributes**
  - **has insufficient sensitivity to verify the desired safety and efficacy**
- **Example: visual examination of weld does not detect voids**

3.3 Process Validation Decision

A. Is process output fully verifiable?

Yes

B. Is verification sufficient & cost effective?

Yes

C. Verify & control the process

3.3 Process Validation Decision

A. Is process output fully verifiable?

No

D. What is level of risk to patient?

Low

E. Accept risk. Verify and control process

or

F. Validate for business reasons

3.3 Process Validation Decision

A. Is process output fully verifiable?

No

D. What is level of risk to patient?

High

G. Validate to control risk

or

H. Redesign product and/or process and go back to “A”

3.3 Process Validation Decision

- **FDA requires process to be validated if process cannot be fully verified**
- **Option E, to accept risk, is not an option for U.S.-distributed devices!**

3.4 Examples of Processes That Should Be Validated

- **Sterilization processes**
- **Clean room ambient conditions**
- **Aseptic filling processes**
- **Sterile packaging sealing processes**
- **Lyophilization process**
- **Heat treating processes**
- **Plating processes**
- **Plastic injection molding processes**

3.4 Examples of Processes That May Be Verified

- **Manual cutting processes**
- **Testing for color, turbidity, total pH for solutions**
- **Visual inspection of printed circuit boards**
- **Manufacturing and testing of wiring harnesses**

4. Statistical Methods and Tools for Process Validation

Annex A

The Value of Statistical Tools

- **Nonconformities often occur because of:**
  - **Errors made**
  - **Excessive variation**
  - **Off target processes**

Errors

- **Mistake proofing methods can reduce errors**
  - **Make it impossible for error to occur**

    or
  - **Make it impossible for error to not be detected**
- **Perform challenge tests to show that mistake proofing methods work**

Excessive Variation & Off Target Processes

- **Capability study measures ability of process to consistently meet specifications**
- **Useful in dealing with excessive variation and off target processes**
- **Perform tests at nominal and worst case conditions**

Variation

- **All processes have some variation**
- **Use histogram to show variation**
- **Apply normal curve to histogram**
- **Normal curve is bell-shaped, and 99.73% of units fall within ± 3 standard deviations of average**

Unstable Process vs Stable Process

- **Unstable process is inconsistent and unpredictable**
- **Stable process is consistent and predictable, BUT is it capable?**

Stable AND Capable Process

- **Stable and capable process:**
  - **Is consistent**
  - **Is predictable**
  - **Has variation that falls within the upper and lower specification limits**

How to Reduce Variation

- **Identify key input variables that affect outputs (screening experiment)**
- **Understand effect of input on output (response surface study)**
- **Understand how inputs behave (capability study)**
- **Establish targets (robust design methods) and tolerances for inputs (tolerance analysis)**

Control Charts

- **Monitor results of changes in inputs**
- **Determine resulting variation in output**
- **Identify inherent variation of process**
- **Use to continuously monitor process and assure state of control**

Useful Statistical Tools

- **See Appendix A for descriptions of useful statistical tools**

5. Conduct of a Validation

Checklist for Validation Activity

- **Form multi-functional team**
- **Plan approach and define requirements**
- **Identify and describe process**

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Checklist for Validation Activity

- **Specify process parameters & desired output**
- **Decide on verification and/or validation**
- **Create master validation plan**
- **Select methods and tools for validation**

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Checklist for Validation Activity

- **Create validation protocols**
- **Perform IQ, OQ, PQ and document results**
- **Determine continuous process controls**
- **Control process continuously**

2.5 Process Validation Protocol

A document showing how validation will be conducted, including test parameters, product characteristics, manufacturing equipment, and decision points on what constitutes acceptable test results

Include in Protocol:

- **Process to be validated**
- **Device(s) to be manufactured with process**
- **Criteria for successful validation**
- **Length and duration of validation**
- **Shifts, operators, equipment to be used**
- **Utilities and quality**

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Include in Protocol:

- **Operators and operator qualifications**
- **Complete description of process**
- **Relevant specifications for product, components, manufacturing materials, etc.**
- **Special controls or conditions on preceding processes during validation**

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Include in Protocol:

- **Process parameters to be monitored and methods for controlling and monitoring**
- **Product characteristics to be monitored and methods**
- **Any subjective criteria for evaluating product**

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Include in Protocol:

- **Definition of non-conformance**
- **Statistical methods for data collection and analysis**
- **Consideration of maintenance and repairs of manufacturing equipment**
- **Criteria for revalidation**

2.1 Installation Qualification (IQ)

Establishing by objective evidence that all key aspects of the process equipment and ancillary system installation adhere to the manufacturer's approved specification and that the recommendations of the supplier of the equipment are suitably considered

2.2 Operational Qualification (OQ)

Establishing by objective evidence process control limits and action levels which result in product that meets all predetermined requirements

2.3 Performance Qualification (PQ)

Establishing by objective evidence that the process, under anticipated conditions, consistently produces a product which meets all predetermined requirements

For IQ, OQ and PQ

Determine:

- **What to verify/measure**
- **How to verify/measure**
- **How many to verify/measure (statistical significance)**
- **When to verify/measure**

For IQ, OQ and PQ

Define:

- **Acceptance/rejection criteria**
- **Required documentation**

5.3 Installation Qualification (IQ)

- **Key Objective: Is the equipment installed correctly?**
- **Important IQ considerations:**
  - **Equipment design**
  - **Installation conditions (wiring, utilities, functionality)**

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5.3 Installation Qualification (IQ)

Important IQ considerations:

- **Calibration, preventive maintenance, cleaning schedules**
- **Safety features**
- **Supplier documentation, prints, drawings, manuals**

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5.3 Installation Qualification (IQ)

Important IQ considerations:

- **Software documentation**
- **Spare parts list**
- **Environmental conditions**

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5.3 Installation Qualification (IQ)

- **Use equipment supplier qualification studies as:**
  - **Guides**
  - **To obtain basic data**
  - **To supplement installation qualification**
- **Supplier qualification studies usually are not sufficient to substitute for IQ**

5.4 Operational Qualification (OQ)

- **Key Objectives:**
  - **Develop and challenge process parameters**
  - **Establish action levels**
  - **Determine robustness of process**
  - **Determine ability to avoid approaching worst case conditions**

5.4 Operational Qualification (OQ)

OQ considerations:

- **Process control limits**
- **Software parameters**
- **Raw material specifications**
- **Process operating procedures**

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5.4 Operational Qualification (OQ)

OQ considerations:

- **Material handling requirements**
- **Process change control**
- **Training**
- **Short term stability and capability of process**

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5.4 Operational Qualification (OQ)

OQ considerations:

- **Potential failure modes, action levels and worst case conditions**
- **Use of statistically valid techniques to establish key process parameters and optimize process**

5.5 Performance Qualification (PQ)

- **Key objective: Demonstrate process will consistently produce acceptable product under normal operating conditions**
- **Challenge process to simulate conditions during actual manufacturing**
- **Include range of conditions defined by action levels allowed in written SOPs**

5.5 Performance Qualification (PQ)

- **Analyze process to determine normal range of variation for process output**
- **Analyze process and product data to identify variation due to controllable causes**
- **Eliminate controllable causes of variation**

5.5 Performance Qualification (PQ)

Controllable causes of variation include:

- **Temperature**
- **Humidity**
- **Variations in electrical supply**
- **Vibration**
- **Environmental contaminants**

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5.5 Performance Qualification (PQ)

Controllable causes of variation include:

- **Purity of process water**
- **Light**
- **Human factors (training, ergonomic factors, stress, etc.**
- **Variability of materials**
- **Wear and tear of equipment**

5.6 Final Report

- **Summarize and reference all protocols and results**
- **Provide conclusions regarding validation status of process**
- **Validation team and management should review and approve report**

6. Maintaining a State of Validation

6.1 Monitor and Control

- **Monitor trends to ensure process remains within established parameters**
- **Investigate causes of negative trends**
- **Take corrective action**
- **Consider need for revalidation**

6.2 Changes in Process and/or Product

- **Evaluate any changes in procedures, equipment, personnel, etc.**
- **Determine effect on process and consider need for and extent of revalidation**

6.3 Continued State of Control

- **Changes in raw materials and/or processes may be undetected or considered not significant**
- **Cumulative changes may affect process**
- **Consider periodic revalidation to account for cumulative changes**

6.4 Examples of Reasons for Revalidation

- **Process change affects quality or validation status**
- **Negative trend in quality indicators**
- **Product design change affects process**
- **Moving process to another facility**
- **Change in application of the process**

Revalidation

- **Evaluate need for revalidation**
- **Document evaluation**
- **Include:**
  - **Historical results from quality indicators**
  - **Product changes**
  - **Process changes**
  - **Changes in external requirements**

Revalidation

- **Revalidation may be less extensive than original validation**
- **Example 1: Purchase of new equipment**
  - **Repeat IQ**
  - **Most of OQ already established**
  - **Some PQ may need repeating**

Revalidation

Example 2: Change raw material supplier

- **IQ need not be repeated**
- **Repeat parts of OQ and PQ to fully understand interaction between new raw material and process**

7. Use of Historical Data for Validation

Use of Historical Data for Validation

Sources of historical data include:

- **Batch records**
- **Manufacturing log books**
- **Lot records**
- **Control charts**
- **Test and inspection results**
- **Customer feedback**
- **Field failure reports**
- **Service reports**
- **Audit reports**

Historical Data for Validation

- **Validation can be <u>partially</u> based on historical data**
- **Relying completely on historical data is not feasible if:**
  - **Appropriate data not collected**
  - **Manner of collection does not allow for adequate analysis**
  - **Data is pass/fail (usually not adequate)**

Historical Data for Validation

- **If data is adequate and representative, conduct analysis per written protocol**
- **Determine if process has:**
  - **Operated in state of control**
  - **Consistently produced product meeting predetermined requirements**
- **Document analysis**

Summary of Activities

Initial considerations:

- **Identify and describe process**
- **Decide on verification and/or validation**
- **Create master validation plan**

Summary of Activities

If decision is to validate:

- **Form multi-functional team**
- **Plan approach & define requirements**
- **Identify & describe processes**
- **Specify process parameters and output**
- **Create master validation plan**
- **Select methods and tools for validation**

more . . .

Summary of Activities

If decision is to validate:

- **Create validation protocols**
- **Perform IQ, OQ, PQ and document results**
- **Determine continuous process controls**
- **Prepare final report and secure management approval**
- **Control process continuously**

Summary of Activities

Maintaining a state of validation

- **Monitor and control process continuously**
- **Revalidate as appropriate**

The End