Process Validation

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Learning Objectives

- Understand the Background and Definitions of Process Validation (PV)
- Recognize when Validation is Required
- Understand PV Regulatory Requirements
- Identify Guidance and Installation, Operational and Performance Qualifications
- Understand Requirements for Process Monitoring, Process Changes and When to Revalidate

References and Regulatory Requirements

21 Code of Federal Regulations (CFR) 820:
Quality System Regulation

21 CFR 820.75: Process Validation

Preamble to 1996 Quality System (QS) Regulation

Background: Regulatory Requirements

The Quality System Regulation,

21 CFR 820.75
http://www.ecfr.gov/cgi-bin/text-idx?SID=5f15fc6205369484e218941accf68eeb&mc=true&node=se21.8.820_175&rgn=div8

Background: Guidance

GHTF Guidance: Quality Management System Medical Devices – Process Validation Guidance; SG3; 2004

http://www.imdrf.org/docs/ghtf/final/sg3/technical-docs/ghtf-sg3-n99-10-2004-qms-process-guidance-04010.pdf

Linkage to Other Sections of the Quality System

- Design Controls: Using Risk Analysis and Identifying Essential Design Outputs
- Purchasing Controls: Selecting Suppliers on their ability to meet specified requirements
- Personnel: Training and Qualifications
- Production and Process Controls: Using software and software automated processes

Quality System Regulation: Definitions

Definitions 21 CFR 820.3 (aa)

***Verification**:* confirmation by examination and provision of objective evidence that specified requirements have been fulfilled.

Quality System Regulation: Definitions

Definitions 21 CFR 820.3 (z)

Validation: confirmation by examination and provision of objective evidence that the particular requirements for a specific intended use can be consistently fulfilled.

Quality System Regulation: Definitions

Definitions 21 CFR 820.3 (z)(1)

Process Validation: establishing by objective evidence that a process consistently produces a result or product meeting its predetermined specifications.

Regulatory Requirement

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.

21 CFR 820.75(a)

Examples: Is Validation Required?

1.) Sterile Package Sealing Processes?

Yes; limitations and destructive

2.) Dimensions of a Manual cutting process?

No; manual process, can be fully verified.

3.) Filling processes?

Maybe; need additional information

2004 GHTF QMS PV Guidance, also see Figure 1: Process validation decision tree and examples

When to Start? Earlier the Better

No specific requirement in design, but requirement under 21 CFR 820.80 is that process validation is completed prior to finished device release. Items to consider…

- When to initiate PV in the design process
- Translation of design output criteria into production parameters and specifications
- Addressing design, process and purchasing changes

Where to Start?
Master Validation Plans

Not a 21 CFR 820 requirement, but is recommended per GHTF Guidance. The plan should…

- Define the product and process flow
- Identify what needs to be validated
- Consider protocols and specifications
- Be documented and approved

Regulatory Requirement

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.

21 CFR 820.75 (a)

Regulatory Requirements: Personnel Performing Validation

- Each manufacturer shall ensure that validated processes are performed by qualified individual(s) .

  21 CFR 820.75(b)(1)

- Personnel who perform verification & validation activities shall be made aware of defects and errors that may be encountered as part of their job functions.

  21 CFR 820.25(b)(2)

Regulatory Requirement

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.

21 CFR 820.70(g)

Installation Qualification (IQ)

Simply put in guidance, is everything installed correctly.
Things to consider…

- Equipment design features
- Installation and Environmental Conditions
- Safety features
- Supplier documents, Calibration, preventative maintenance and spare parts.

http://www.imdrf.org/docs/ghtf/final/sg3/technical-docs/ghtf-sg3-n99-10-2004-qms-process-guidance-04010.pdf (Guidance - Definitions Pg. 5 & Section 5.3)

Operational Qualification

Challenge process parameters to assure the process will result in product that meets requirements. Things to consider…

- Process control limits
- Material specifications and handling
- Process change control and training
- Potential failure modes, action levels and worst case scenario
- Software V&V for intended use

http://www.imdrf.org/docs/ghtf/final/sg3/technical-docs/ghtf-sg3-n99-10-2004-qms-process-guidance-04010.pdf (Guidance - Definitions Pg. 5 & Section 5.4)

Determining Process Validation Parameters, Criteria and Limits

GHTF Guidance, Example: heat sealer

Design Output – a sealed pouched as measured by seal thickness and strength

PV Parameters,

1. Temperature
2. Pressure
3. Time

Performance Qualification (PQ)

Demonstrate the process will consistently produce acceptable product under normal operating conditions. Things to consider…

- Procedures and limits from OQ
- Acceptable product
- Actual manufacturing conditions
- Process repeatability and long term stability

http://www.imdrf.org/docs/ghtf/final/sg3/technical-docs/ghtf-sg3-n99-10-2004-qms-process-guidance-04010.pdf (Guidance - Definitions Pg. 5 & Section 5.5)

How Many Runs or Samples are Enough?

The requirement for testing from the first three production lots or batches has been deleted...

Comment #85 to Preamble to 1996 QS Regulation

The challenges should be repeated enough times to assure that the results are meaningful and consistent.

GHTF Guidance Section 5.5 PQ

Stable and Capable Process

Stable Process – produces a consistent level of performance, total variation is reduced and is more predictable.

Capable Process – When consistent performance is achieved the remaining variation must be made to fit within the upper and lower specification limits.

GHTF Guidance Annex A Statistical Methods and tools for process validation.

Regulatory Requirement

Each manufacturer shall establish and maintain procedures for monitoring and control of process parameters for validated processes to ensure that the specified requirements continue to be met.

21 CFR 820.75(b)

Process Validation Monitoring

Monitor and control process parameters for validated processes so the specified requirements continue to be met.

- Robustness of Process
- Statistical Process Control
- Use of Action Limits and Control Charts

Production and Process Changes

Establish and maintain procedures for changes to a specification, method, process or procedure. Such changes shall be verified or where appropriate validated according to 21 CFR 820.75 before implementation…Changes shall be approved in accordance with 21 CFR 820.40

21 CFR 820.70(b)

Regulatory Requirement: Revalidation

When changes or process deviations occur, the manufacturer shall review and evaluate the process and perform revalidation where appropriate. These activities shall be documented.

21 CFR 820.75(c)

Revalidation Continued

Examples of Reasons for Revalidation

- Change(s) in the actual process
- Negative trend(s) in quality indicators
- Change in product design that affects process
- Transfer of process to another facility
- Change of the application of the process

GHTF Guidance Section 6.4

Use of Historical Data

Data used from device history records such as batch records, control charts and testing and inspection data can be used. Also any validation type can use historical data.

Summary

- Manufacturers are legally obligated to meet the requirements for process validation in 21 CFR 820
- The GHTF Guidance is a useful educational tool for understanding how to validate a process
- Performing process validation activities ensures that the process output is predictable and predetermined
- The completion of appropriate process validation activities can help reduce waste, reduce cost and reduce the time it takes to get a medical device on to the market.

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