



Quality System Regulation Process Validation

**FDA Small Business
Regulatory Education for Industry (REdI)
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Learning Objectives

- Understand Background and Definitions
- Recognize when Validation is Required
- Know PV Regulatory Requirements
- Identify Installation, Operational and Performance Qualifications
- Be aware of Process Monitoring, Process Changes and when to Revalidate
- Review Compliance and WL Data

Background

- 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

- Preamble to QS Regulation

- 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 and Risk

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

Quality System Regulation

Definitions 21 CFR 820.3 (aa)

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

Quality System Regulation

Definitions 21 CFR 820.3 (z)

Validation means 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 21 CFR 820.3 (z)(1)

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

Regulatory Requirements

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)

Validation Required or Not

Sterile Package Sealing Processes?

Yes

Manual cutting processes?

No

Filling processes?

Maybe

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...

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

Where to Start?

Master Validation Plans

Not a specific 820 requirement, but is recommended per GHTF Guidance.

The plan should...

- I. Define the product and process flow
- II. Identify what needs to be validated
- III. Consider protocols and specifications
- IV. Be documented and approved

Regulatory Requirements

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)

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 Requirements

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/ghrf/final/sg3/technical-docs/ghrf-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...

- Determine process control limits
- Material specifications and handling
- Process change control and training
- Determine potential failure modes, action levels and worst case scenario
- Perform software V&V for intended use

<http://www.imdrf.org/docs/gh/final/sg3/technical-docs/gh/f-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 pouch as
measured by seal thickness and strength

PV Parameters, name three...

1. Temperature
2. Pressure
3. Time

Performance Qualification (PQ)

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

- Approved procedures and limits from OQ
- Acceptable product
- Simulate actual manufacturing conditions
- Is the process repeatable and stable long term

<http://www.imdrf.org/docs/ghrf/final/sg3/technical-docs/ghrf-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...

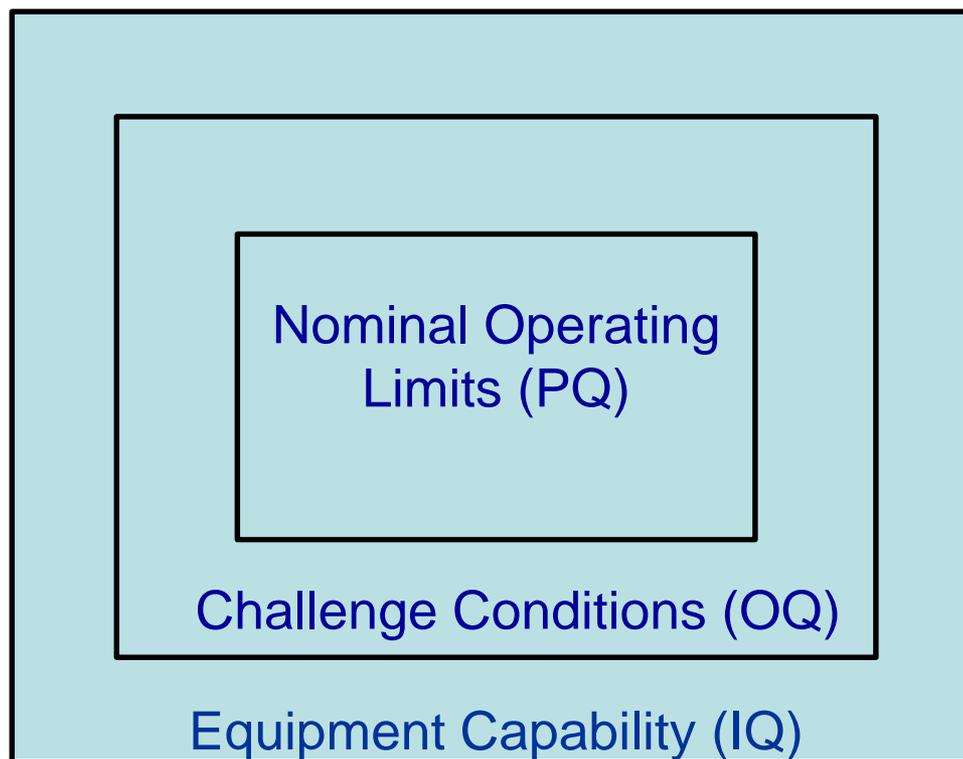
Preamble comment #85

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

GHTF Guidance Section 5.5 PQ

Process Characterization

By the end of IQ, OQ and PQ the following should be answered.



This will help you understand if your process is stable and capable.

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 Requirements

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.

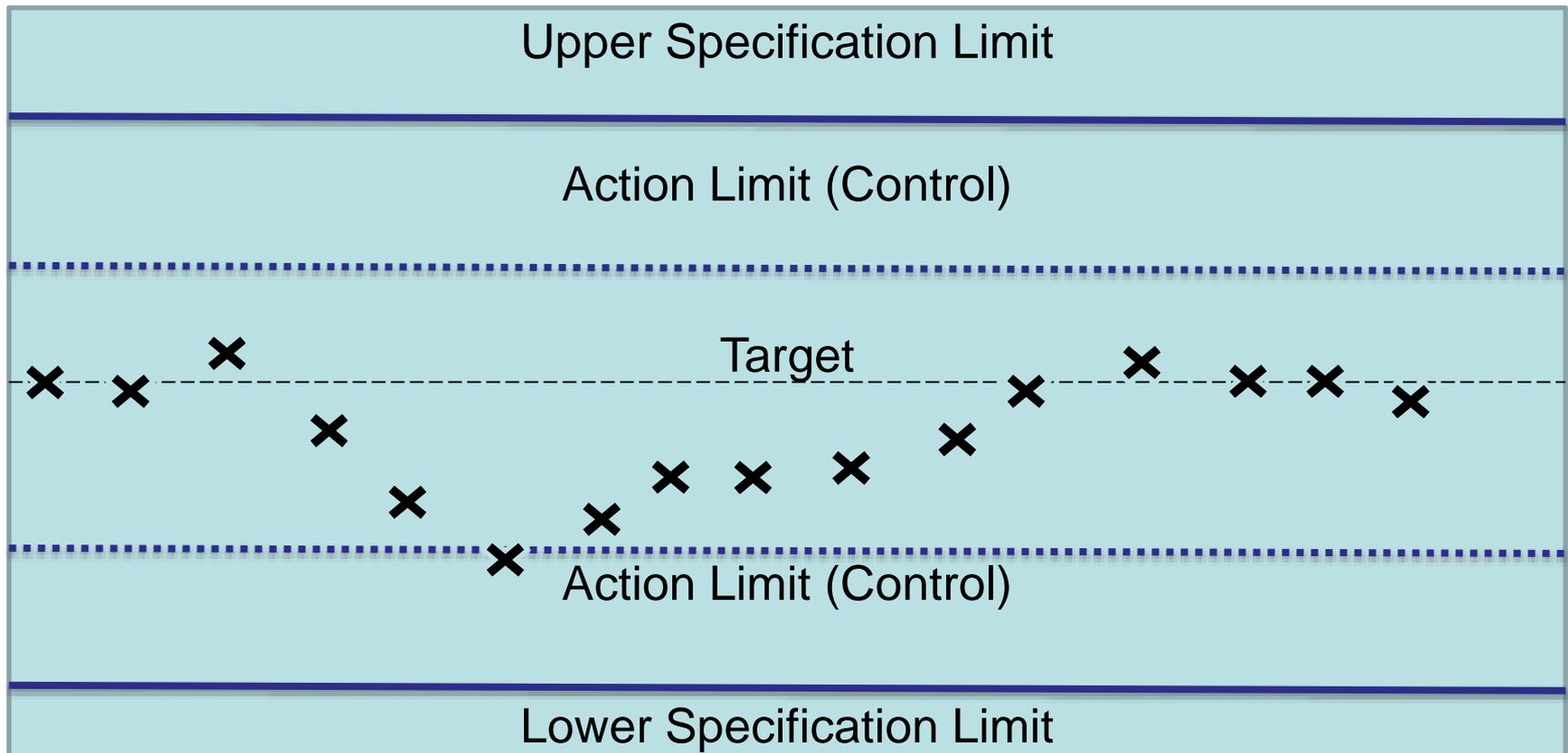
21 CFR 820.75(b)

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

Process Monitoring Control Chart



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)

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. While terms such as “retrospective validation” are used they generally do not provide adequate information by themselves. Also any validation type can use historical data.

CY2014 FDA Form 483 (483) Observations Data

- Source of data - FDA's Turbo Establishment Inspection Reporting (EIR) Database
- Timeframe January 1 – December 31, 2014
- **2213** Inspections performed, 1619 domestic
- **3,740** FDA Form 483 observations cited for 21 CFR 820 (Quality System regulation) deficiencies

CY2014 483 Observations Data

QS Subsystem	# of Observations	Percentage
P&PC	1,197	32%
CAPA	1,148	31%
DES	515	14%
MGMT	497	13%
DOC	383	10%
	3,740	

CY2014 Top 5 P&PC 483 Observations

Observation (QS Regulation)	# of Observations	Percentage
21 CFR 820.75(a)	175	15%
21 CFR 820.50	143	12%
21 CFR 820.70(a)	95	8%
21 CFR 820.72(a)	74	6%
21 CFR 820.80(b)	56	5%

FDA Warning Letter (WL) Citations

- Source of data - FDA's warning letters and FDA's Compliance Management System (CMS)
- Timeframe January 1 – December 31, 2014
- **121** warning letters with 21 CFR 820 (Quality System regulation*) deficiencies



CY2014 Top 5 P&PC Subsystem Warning Letter Cites

WL Citations	# of WL Cites
21 CFR 820.70	56
21 CFR 820.50	54
21 CFR 820.75	48
21 CFR 820.80	48
21 CFR 820.72	17

Summary

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

Providing Industry Education

Three Resources

1. CDRH Learn – Multi-Media Industry Education

- over 80 modules
- videos, audio recordings, power point presentations, software-based “how to” modules
- mobile-friendly: access CDRH Learn on your portable devices

<http://www.fda.gov/Training/CDRHLearn>

2. Device Advice – Text-Based Education

- comprehensive regulatory information on premarket and postmarket topics

<http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance>

3. Division of Industry and Consumer Education (DICE)

- Contact DICE if you have a question
- Email: DICE@fda.hhs.gov
- Phone: 1(800) 638-2014 or (301) 796-7100 (Hours: 9 am-12:30 pm; 1 pm-4:30pm EST)
- Web: <http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/ContactUs--DivisionofIndustryandConsumerEducation/default.htm>

Questions?

Please complete the session survey:

surveymonkey.com/r/DEV-D2S5