Process Validations

an Integrated Quality Systems Approach

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PROCESS VALIDATIONS

An Integrated Quality Systems Approach

- My Validations
- Definitions
- Regulations and Standards
- ACME Medical
  - Quality System
  - Catheter Manufacturing
  - Process Validation Plan
- Process Validation Deep Dive
- Summary
- Questions?

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Process Validations

an Integrated Quality Systems Approach

My Validations

- Insert Molding Equipment
- Test Equipment
- Ultrasonic Welding Equipment
- Grinding / Mixing (ball-mill) Equipment
- Joining Equipment
- Inspection System
- Custom Chemical Process
- Laser Cutting Equipment
- Process Performance Qualifications (both prospective and retroactive)
- Gauge R&R
- Attribute Test Method Validations
- Etc.

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Definitions

What is a Process?

A Process is an activity that transforms an Input (raw material, component and / or components) into an Output (component, sub-assembly or finished product) which has (a) specification(s) which is / are used to confirm the suitability of the Process.

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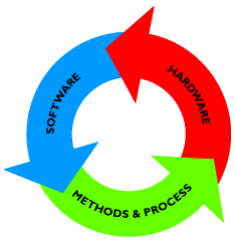
Definitions

What is a Process Validation?

The collection and evaluation of data, from the process design stage through commercial production which establishes scientific evidence that a process is capable of consistently delivering quality product.



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Widely used regulations, standards, and guidance documents containing process validation.

Regulations & Standards

- 21 CFR 820 [Medical Device Current Good Manufacturing and Quality System Regulation
- 21 CFR 211 [Drug Current Good Manufacturing Practices Regulation]
- Food and Drug Administration; Guidance for Industry. Process Validation: General Principles and Practices.
- ISO 13485 Medical devices – Quality management systems – Requirements for regulatory purposes
- Technical Report 14969 Medical devices – Quality management systems – Guidance on the application of ISO 13485:2003:
- EN ISO 9001:2008/AC Quality Management Systems – Requirements
- GHTF/SG3/N99-10:2004 Quality Management Systems – Process Validation Guidance
- BS EN ISO [Standard] 11607-2:2006 Packaging for terminally sterilized medical devices – Part 2: Validation requirements for forming, sealing and assembly

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Regulations & Standards

Food and Drug Administration; Guidance for Industry. Process Validation: General Principles and Practices. Dated January 2011

- "For purposes of this guidance, *process validation* is defined as the collection and evaluation of data, from the process design stage through commercial production, which establishes scientific evidence that a process is capable of consistently delivering quality product.
- Process validation involves a series of activities taking place over the lifecycle of the product and process. This guidance describes process validation activities in three stages.

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Regulations & Standards

Food and Drug Administration; Guidance for Industry. Process Validation: General Principles and Practices. Dated January 2011

- Stage 1 – Process Design: The commercial manufacturing process is defined during this stage based on knowledge gained through development and scale-up activities.
- Stage 2 – Process Qualification: During this stage, the process design is evaluated to determine if the process is capable of reproducible commercial manufacturing.
- Stage 3 – Continued Process Verification: Ongoing assurance is gained during routine production that the process remains in a state of control."

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Regulations & Standards

21 CFR 211 [Drug Current Good Manufacturing Practices Regulation], Section 211.110 Sampling and testing of in-process materials and drug products

- (a) To assure batch uniformity and integrity of drug products, written procedures shall be established and followed that describe the in-process controls, and tests, or examinations to be conducted on appropriate samples of in-process materials of each batch.
- Such control procedures shall be established to monitor the output and to **validate the performance of those manufacturing processes** that may be responsible for causing variability in the characteristics of in-process material and the drug product.

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Regulations & Standards

21 CFR 820 [Medical Device Current Good Manufacturing and Quality System Regulation, Section 820.3 Definitions

- (z-1) **Process validation** means establishing by objective evidence that a process consistently produces a result or product meeting its pre-determined specifications.

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Regulations & Standards

21 CFR 820, Section 820.70(i) Automated Processes

- When computers or automated data processing systems are used as part of production or the quality system, the manufacturer shall validate computer software for its intended use according to an established protocol.
- All software changes shall be validated before approval and issuance.
- These validation activities and results shall be documented.

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Regulations & Standards

21 CFR 820, Section. 820.75 Process Validation

- (a) Where the results of a process cannot be [*or will not 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.
- (b) 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.

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Regulations & Standards

21 CFR 820, Section. 820.75 Process Validation

- (1) Each manufacturer shall ensure that validated processes are performed by qualified individual(s).
- (2) For validated processes, the monitoring and control methods and data, the date performed, and, where appropriate, the individual(s) performing the process or the major equipment used shall be documented.
- (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.

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Regulations & Standards

ISO 13485 Medical devices – Quality management systems – Requirements for regulatory purposes

- **7.5.2 Validation of processes for production and service provision**
  - ***7.5.2.1 General Requirements***
  - 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.
  - Validation shall demonstrate the ability of these processes to achieve planned results…

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Regulations & Standards

ISO 13485 Medical devices – Quality management systems – Requirements for regulatory purposes

- *The organization shall establish documented procedures for the validation of the application of* ***computer software*** *(and changes to such software and/or its application)* ***for production and service provision*** *that affect the ability of the product to conform to specified requirements. Such software applications shall be validated prior to initial use.*
- *Records of validation shall be maintained (see 4.2.4)*

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Regulations & Standards

Technical Report 14969 Medical devices – Quality management systems – Guidance on the application of ISO 13485:2003:

- **7.5.2.1.1 General**
- **7.5.2.1.1.1** Process validation is the mechanism or activity used by the organization to ensure that a process whose output is not fully verifiable is capable of consistently providing product that meets specifications.
- Process validation includes the development of a plan, the staged conduct of a number of evaluations of a particular process, and the collection and interpretation of recorded data. …four phases:

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Regulations & Standards

Technical Report 14969 Medical devices – Quality management systems – Guidance on the application of ISO 13485:2003:

- a) review and approval of equipment specifications;
- b) initial qualification of the equipment used and provision of necessary services — also known as **Installation Qualification (IQ)**;
- c) demonstration that the process will produce acceptable results and establishment of limits (worst case) of the process parameters — also known as **Operational Qualification (OQ)**;
- d) establishment of long-term process stability — also known as **Performance Qualification (PQ)**.

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Regulations & Standards

Technical Report 14969 Medical devices – Quality management systems – Guidance on the application of ISO 13485:2003:

- **7.5.2.1.1.3** Processes that should be validated include
  - sterilization,
  - maintenance of specified conditions in environmentally controlled areas,
  - aseptic processing,
  - sealing of sterile packaging,
  - lyophilization [freeze-drying], and
  - heat-treatment.

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Regulations & Standards

Technical Report 14969 Medical devices – Quality management systems – Guidance on the application of ISO 13485:2003:

- **7.5.2.1.2 Statistical methods and tools for process validation**
- There are many statistical methods and tools which may be used in process validation. Control charts, capability studies, designed experiments, tolerance analysis, robust design methods, failure modes and effects analysis (FMEA), sampling plans and mistake-proofing are some examples.

- **7.5.2.1.3 Computer software used in process control**
- The requirements of ISO 13485 regarding the validation of the application of computer software used in process control **apply**, whether or not such software is purchased, developed, maintained, or modified for automated production or process control purposes.

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Regulations & Standards

EN ISO [Standard] 9001:2008/AC Quality Management Systems – Requirements

- **7.5.2 Validation of processes for production and service provision**
- The organization shall validate any processes for production and service provision where the resulting output cannot be verified by subsequent monitoring or measurement and, as a consequence, deficiencies become apparent only after the product is in use or the service has been delivered.

- Validation shall demonstrate the ability of these processes to achieve planned results. The organization shall establish arrangements for these processes including, as applicable,

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Regulations & Standards

EN ISO 9001:2008/AC Quality Management Systems – Requirements

- a) defined criteria for review and approval of the processes,
- b) approval of equipment and qualification of personnel,
- c) use of specific methods and procedures,
- d) requirements for records (see 4.2.4), and
- e) revalidation.

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Regulations & Standards

BS EN ISO [Standard] 11607-2:2006 Packaging for terminally sterilized medical devices – Part 2: Validation requirements for forming, sealing and assembly

- **5 Validation of packaging processes**
- **5.1 General**
- **5.1.1** Preformed sterile barrier systems and sterile barrier system manufacturing processes shall be validated.

- **5.2 Installation qualification (IQ)**
- **5.2.1** Installation qualification shall be performed. Some installation qualification considerations are:
- equipment design features;
- installation conditions such as wiring, utilities, functionality, etc.;
- safety features;
- equipment operating within the stated design parameters;
- supplier documentation, prints, drawings and manuals;
- spare-parts lists;

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Regulations & Standards

BS EN ISO 11607-2:2006 Packaging for terminally sterilized medical devices – Part 2: Validation requirements for forming, sealing and assembly

- **software validation;**
- environmental conditions such as cleanliness, temperature, humidity;
- documented operator training;
- operating manual or procedure.
- **5.2.4** Alarms, warning systems, or machine stops shall be challenged in the event that critical process parameters exceed predetermined limits.
- **5.2.5** Critical process instruments, sensors, displays, controllers, etc. shall be certified as calibrated and have written calibration schedules. Calibration should be performed before and after performance qualification.
- **5.2.6** There shall be written preventive maintenance and cleaning schedules.

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Regulations & Standards

BS EN ISO 11607-2:2006 Packaging for terminally sterilized medical devices – Part 2: Validation requirements for forming, sealing and assembly

- **5.2.7** The application of **software systems**, such as programmable logic controller, data collection, and inspection systems, shall be validated to ensure that they function as intended.

  Functional tests shall be performed to verify the correct functioning of the **software** and hardware, and especially the interfaces.

  The system shall be checked (e.g. by entering correct and incorrect data, by simulating a loss of electrical power) to detect the availability, reliability, identity, accuracy and traceability of data or records.

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Regulations & Standards

BS EN ISO 11607-2:2006 Packaging for terminally sterilized medical devices – Part 2: Validation requirements for forming, sealing and assembly

- **5.3 Operational qualification (OQ)**
  - **5.3.1** Process parameters shall be challenged to assure that they will produce preformed sterile barrier systems, and sterile barrier systems, that meet all defined requirements under all anticipated conditions of manufacturing.
  - **5.3.2** Preformed sterile barrier systems, and sterile barrier systems, shall be produced at both the upper and lower parameter limits, and shall exhibit the properties that meet predefined requirements.

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Regulations & Standards

BS EN ISO 11607-2:2006 Packaging for terminally sterilized medical devices – Part 2: Validation requirements for forming, sealing and assembly

- **5.4 Performance qualification (PQ)**
  - **5.4.1** The performance qualification shall demonstrate that the process will consistently produce acceptable preformed sterile barrier systems, and sterile barrier systems, under specified operating conditions.
  - **5.4.2** Performance qualification shall include:
    - the actual or simulated product;
    - process parameters established in the operational qualification;
    - verification of product/package requirements;
    - assurance of process control and capability;
    - process repeatability and reproducibility.

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Regulations & Standards

BS EN ISO 11607-2:2006 Packaging for terminally sterilized medical devices – Part 2: Validation requirements for forming, sealing and assembly

- **5.4.3** Challenges to the process shall include conditions expected to be encountered during manufacture.

  NOTE These challenges can include, but are not limited to, machine set-up and change-over procedures; process start-up and restart procedures; power failure and variations, and multiple shifts, if applicable.

- **5.4.4** Challenges to the process shall include at least three production runs with adequate sampling to demonstrate variability within a run and reproducibility between different runs. The duration of a production run should account for process variables.

- **5.5 Formal approval of the process validation**
- **5.6 Process control and monitoring**

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Regulations & Standards

Food and Drug Administration; Guidance for Industry. Process Validation: General Principles and Practices. Dated January 2011

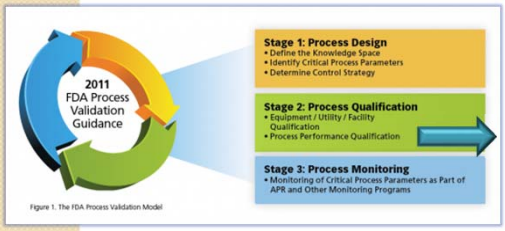

Figure 1. The FDA Process Validation Model

***Process Performance Qualification* [PPQ]**

- The PPQ combines the actual facility, utilities, equipment (each now qualified), and the trained personnel with the commercial manufacturing process, control procedures, and components to produce commercial batches [of drugs, but can certainly be adapted to Medical Devices].
- A successful PPQ will confirm the process design and demonstrate that the commercial manufacturing process performs as expected

Success at this stage signals an important milestone in the product lifecycle.

A manufacturer must successfully complete PPQ before commencing commercial distribution of the drug [or other] product.

Process Validations

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Regulations & Standards

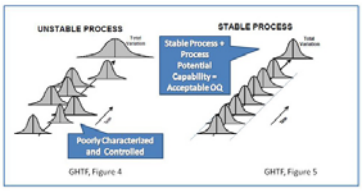
GHTF/SG3/N99-10:2004 Quality Management Systems – Process Validation Guidance

Purpose:

- Understanding quality management system requirements concerning process validation with general applicability to manufacturing processes

Contents:

- Validation decision tree
- Statistical methods & tools for process validation
- Protocol Development
- IQ/OQ/PQ
- Maintaining a state of validation (monitor & control)



Let's take a quick break!

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Introducing ACME Medical:

- Acme Medical is a completely, absolutely fictitious Medical Device Manufacturer, with global operations, who sell their products to the US, EU, Australia, Canada, Japan and what Acme calls the Rest of the World (ROW, which includes China and India).
- They have a mature Quality System, and they are routinely inspected by the FDA, and audited by their European Union Notified Body. In addition, they are also routinely audited by Australians, Canadians, Japanese, and the Chinese.
- **Acme's Validation Documentation has been included in numerous Regulatory Filings, and found to be adequate!**

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ACME: Quality System

Acme Medical's Quality System is detailed in their Quality Manual:

- Acme Medical Device, Inc: Quality Manual, QM 001.
- For Process Validation, we need to go to Section 7 in Acme's Quality Manual: Product Realization. That section points to Acme's Global Quality Policy (GQP) 7.5 *Production and Service Policy*
- Let's look at what GQP 7.5 *Production and Service Policy* say:
- "Acme Medical Device, Inc. has established procedures requiring validation of processes for production and service provision. All processes that affect quality and the output of which cannot be or will not be 100% verified by inspection and / or testing shall be validated."
- Furthermore, the GQP points to Acme's Global Quality Operating Procedure (GQOP) 7.5.001 *Process Validation*

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Process Validations

an Integrated Quality Systems Approach

ACME: Quality System

Let's look at Acme's Global Quality Operating Procedure (GQOP) 7.5.001 *Process Validation.* It contains the following sections:

- Section 1: Overview
- Section 2: Validation vs. Verification
- Section 3: Retrospective Validations
- Section 4: Validation Planning
- Section 5: Validation Documentation Structure (this is a pictorial of how this process works):

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Process Validations

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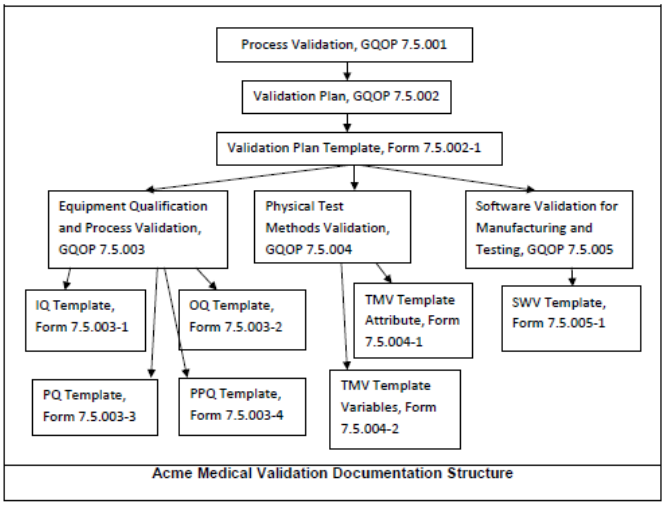
ACME: Quality System



Acme Medical Validation Documentation Structure

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Process Validations

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ACME: Quality System

Now, let's look at Acme's Global Quality Operating Procedure GQOP 7.5.002 *Process Validation Plan*. This document has the following section:

"Validation Plan:

- The validation plan must identify the validation activities required for each process listed in the plan. The required validation activities are identified in GQOP 7.5.001 *Process Validation*, GQOP 7.5.003 *Equipment Qualification and Process Validation*, GQOP 7.5.004 *Physical Test Methods Validation* and GQOP 7.5.005 *Software Validation for Manufacturing and Testing* as noted.
- The validation activities include but are not limited to:

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Process Validations

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ACME: Quality System

- Installation Qualification (IQ),
- Operational Qualification (OQ),
- Process Qualification (PQ) and
- Process Performance Qualification (PPQ), per GQOP 7.5.003
- Software Validation per GQOP 7.5.005
- Test Method Validation (TMV), per GQOP 7.5.004

- **Note:** Validation plan activities will be documented in the Validation Plan Matrix contained in the Validation Plan Template, Form 7.5.002-1."

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Process Validations

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ACME: Quality System

- Form 7.4.002-1 Validation Plan Template identifies the required signatures (RA, QE, ME, R&D, etc). The Validation Plan is revision controlled, so that progress can be tracked. It also contains a matrix in order to summarize the activities:
- Form 7.5.002-1 Validation Plan Matrix Template looks something like this:

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ACME: Quality System

Process Name and Standard Operating Procedure (SOP) number	Equipment Name and Identification	IQ Needed? Protocol and Report Number	OQ Needed? Protocol and Report Number	PQ Needed? Protocol and Report Number	SWV Needed? Protocol and Report Number	TMV Needed? Protocol and Report Number	PPQ Needed? Protocol and Report Number	Target Completion Date
Process no. 1	Equipment no. 1	Yes / No / TBD	Yes / No / TBD	Yes / No / TBD	Yes / No / TBD	Yes / No / TBD	Yes / No / TBD	MM/DD/YY YY
Process no. 2	Equipment no. 2	Yes / No / TBD	Yes / No / TBD	Yes / No / TBD	Yes / No / TBD	Yes / No / TBD		MM/DD/YY YY
Process No. 3	Equipment no. 3	Yes / No / TBD	Yes / No / TBD	Yes / No / TBD	Yes / No / TBD	Yes / No / TBD		MM/DD/YY YY

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Process Validations

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ACME: Quality System

Let's look at Acme's Global Quality Operating Procedure 7.5.003 *Equipment Qualification and Process Validation:*

Process Validation Elements: The elements of process validation are a / an;

- **Installation Qualification (IQ)**. The IQ should answer the question "Is the equipment installed correctly?"
- **Operational Qualification (OQ)**. The PQ should answer the question "Is the equipment suitable for use at the full process operating ranges, including foreseeable fluctuations?"
- **Performance Qualification (PQ)**. The PQ should answer the question "Is the equipment sufficiently stable and reliable for use repeatedly at the nominal process settings?"
- **Process Performance Qualification (PPQ)**. The PPQ should answer the question "Are all of the sub-processes sufficiently integrated so that when all of the processes are used in the process, do they collectively produce a salable product that will fulfill all of the product requirements and specifications?"

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Process Validations

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ACME: Quality System

Installation Qualification (IQ) Template, Form 7.5.003-1

- This template has the following items to be verified (much of the text can be found in ISO 11607-2):
- wiring, utilities, functionality, etc.
- safety features;
- supplier documentation, prints, drawings and manuals;
- spare-parts lists;
- documented operator training;
- operating manual or procedure.
- Alarms, warning systems, or machine stops
- Critical process instruments, sensors, displays, controllers, etc. shall be certified as calibrated and have written calibration schedules.
- written preventive maintenance and cleaning schedules.

- Also, the template identifies the required signatures (RA, QE, ME, R&D, etc).

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ACME: Quality System

Operational Qualification (OQ) Template, Form 7.5.003-2 (much of the text taken straight from ISO 11607-2)

- This template is used so that [p]rocess parameters shall be challenged to assure that they will produce a Widget that meet all defined requirements under all anticipated conditions of manufacturing.
- The Widget shall be produced at both the upper and lower parameter limits, and shall exhibit the properties that meet predefined requirements.

  For instance:
  - Temp: Low / High
  - Pressure: Low / High
  - Time: Short / Long

- Oftentimes, the products are bracketed so that most sizes are encompassed. If you have a product that has sizes such as 20mm, 24mm, 28mm, 32mm and 34mm, maybe you can qualify 2mm, 28mm and 34mm, and not all of the sizes.
- Also, the template identifies the required signatures (ME, QE, RA, R&D, etc)

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Process Validations

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ACME: Quality System

Performance Qualification (PQ) Template, Form 7.5.003-3 (much of the text taken straight from ISO 11607-2)

- This template is used so that [t]he performance qualification shall demonstrate that the process will consistently produce acceptable Widgets under specified operating conditions
- For instance, the PQ Template includes;
  - the identification of
  - the actual or simulated product
  - verification of product requirements
  - assurance of process control and capability;
  - process repeatability and reproducibility.

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ACME: Quality System

Performance Qualification (PQ) Template, Form 7.5.003-3
continued...

- Challenges to the process shall include conditions expected to be encountered during manufacture.
- These challenges can include, but are not limited to, machine set-up and change-over procedures; process start-up and restart procedures; and multiple shifts, if applicable. Challenges to the process shall include at least three production runs with adequate sampling to demonstrate variability within a run and reproducibility between different runs. The duration of a production run should account for process variables.
- The template also identifies the required signatures (ME, QE, RA, R&D, etc)

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Process Validations
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ACME: Quality System

Process Performance Qualification (PPQ) Template, Form 7.5.003-4

- Process Description / Name
- Sequence of sub-processes and equipment
- PPQ runs (should be at least 3)
- PPQ sampling plan / acceptance criteria
- Pre-Requisites Verification
- The template also identifies the required signatures (ME, QE, RA, R&D, etc)

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ACME: Quality System

Acme Medical Device, Inc. Global Quality Operating Procedure 7.5.004 *Physical Test Methods Validation*

- This procedure discusses how a Test Method Validation is to be carried out:
- Determine if the Test Method is to be used for Attribute Data (Pass/Fail, Black/White, Yes/No, etc) or Variables Data (Length, Weight, Temperature, Diameter, etc)
- Develop the Methodology / Qualification Approach
- Establish the Acceptance Criteria
- Develop the Protocol, using the appropriate Template
- Prepare Test Samples
- Prepare and Train the Test Operators
- Execute the Protocol
- Analyze the Test Results / Qualification Report

Note that Test Method Validations encompass Gauge Repeatability and Reproducibility (R&R) studies, studies of Go / No-Go Gauges, compendia test method studies, etc.

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ACME: Quality System

Attribute Test Method Validation (TMV) Form Template 7.5.004-1

- Test Method Procedure Number
- Type (Destructive – Non-Destructive)
- FMEA source document
- Part numbers affected
- Rationale for sample size
- Calibration Records for the gauge(s) and / or test equipment
- References
- Required Signatures

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Process Validations
an Integrated Quality Systems Approach

ACME: Quality System

Variables Test Method Validation (TMV) Form Template 7.5.004-2

- Test Method Procedure Number
- Type (Destructive – Non-Destructive)
- FMEA source document
- Part numbers affected
- Rationale for sample size
- Calibration Records for the gauge(s) and / or test equipment
- References
- Required Signatures

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ACME: Quality System

Let's look at Acme's Global Quality Operating Procedure 7.5.005
Software Validation for Manufacturing and Testing

Purpose:

- This procedure identifies the requirements, process and documentation for validating software used within the Acme Medical's Quality System for device designing, manufacturing or testing."

Method:

- Functional tests shall be performed to verify the correct functioning of the **software** and hardware, and especially the interfaces. The system shall be checked (e.g. by entering correct and incorrect data, by simulating a loss of electrical power) to detect the availability, reliability, identity, accuracy and traceability of data or records.

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ACME: Quality System

Software Validation (SWV) Form Template 7.5.005-1:

- Software Purpose
- System Overview
- Software Overview
- Validation Plan

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ACME: Quality System

May want to address the FDA 11 Elements of FDA's Software V&V Model:

- Risk Analysis (ISO 14971 / ICH Q9 = recommended
- model; ultimately to the user / patient / clinician)
- LOC (Level of Concern: Min, Mod, Maj)
- SW Description
- SRS (SW Requirements Specification)
- Design Specification
- Architecture
- Development
- V&V [T] - can't be achieved w/o being **risk based**
- Traceability (common para. numbering or matrix)
- Unresolved Anomalies ('Bugs') – **risk based**
- Rev. Nos / Release Number

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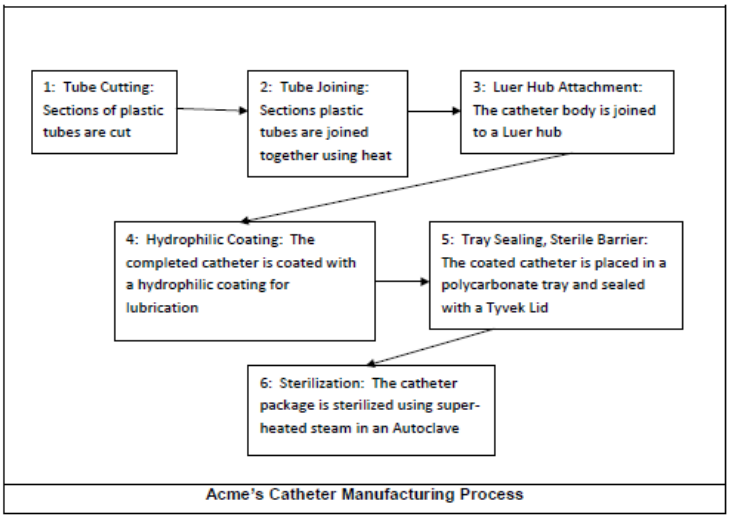
ACME: Manufacturing



Acme's Catheter Manufacturing Process

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Process Validations

an Integrated Quality Systems Approach

ACME: Manufacturing

Process no. 1: Tube Cutting

- This Acme custom machine cuts catheter tubing in pre-set lengths, 30cm, +/- 1mm sections. The machine is software controlled for correct length and feed speed. Machine cuts 6 sections per minute, 2 shifts, 7 hours each. Total daily output 5,040 tube sections.
- The sections are measured using a calibrated ruler that has 0.5mm as the maximum resolution. Each section takes 30 seconds to measure. One inspector can inspect 120 tube sections per hour, for a total of 840 tube sections per day.
- Manufacturing Standard Operating Procedure (MSOP) 1001 *Tube Cutting Process* and Inspection Standard Operating Procedure (ISOP) 1001 *Tube Section Inspection* drive the activity
- Process Validation: Yes/No?
- Software Validation: Yes/No?
- Test Method Validation: Yes/No?

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ACME: Manufacturing

Process no. 2: Tube Joining

- This custom machine joins five (5) 30cm sections using heat shrinking. The machine is software controlled for heating element temperature and heating element speed. The output is measured using tensile testing. Minimum requirement is 5 lbs absolute tensile strength.
- **The testing is destructive**; i.e. the joined sections are cut from a completed catheter, and then tested for tensile strength. This test system uses a Chatillon Tensile Tester with a motor driven Test Stand and a Load Cell.
- MSOP1002 *Tube Joining Process* and ISOP 1002 *Tube Joint Strength Testing* drive the activity
- Process Validation: Yes/No?
- Software Validation: Yes/No?
- Test Method Validation: Yes/No?

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Process Validations
an Integrated Quality Systems Approach
ACME: Manufacturing

Process no. 3: Luer Hub Joining

- This process joins the 5-section catheter body to a Luer hub using Cyanoacrylate (Super Glue) adhesive and UV light curing. This process uses two pieces of equipment: An EFD adhesive dispenser (no software) and a Dymax UV curing light system (no software). Minimum requirement is 5 lbs absolute tensile strength.
- **The testing is destructive**; i.e. a joined Luer hub and a catheter coupon (short section of sacrificial catheter tubing) are tested for tensile strength. This test system uses a Chatillon Tensile Tester with a motor driven Test Stand and a Load Cell.
- MSOP 1003 *Luer Hub Joining* and ISOP 1003 *Luer Hub Joint Strength Testing* drive the activity

- Process Validation: Yes/No?
- Software Validation: Yes/No?
- Test Method Validation: Yes/No?

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an Integrated Quality Systems Approach
ACME: Manufacturing

Process no. 4: Hydrophilic Coating

- This process uses two pieces of equipment:
- An Acme custom coating machine dips the catheter in the coating tank and removes it within a preset time. This machine is software controlled.
- A commercially available Blue M curing oven is used for the curing of the hydrophilic coating. This oven is software controlled for ramp-up temperature, curing temperature and curing time.
- Minimum requirement is a coating no thinner than 10 µm and no thicker than 20 µm. **The inspection is destructive**. The coating is inspected by cutting perpendicular slices of the coated catheter and using a RAM optical inspection system to measure the thickness of the coating.
- MSOP 1004 *Catheter Hydrophilic Coating Process*, MSOP 1005 *Catheter Hydrophilic Coating Curing Process* and ISOP 1004 *Hydrophilic Coating Thickness Inspection* drive the activities

- Process Validation: Yes/No?
- Software Validation: Yes/No?
- Test Method Validation: Yes/No?

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Process Validations

an Integrated Quality Systems Approach

ACME: Manufacturing

Process no. 5: Tray Sealing

- This process uses a commercially available Alloyd tray sealer with custom sealing platens to seal the catheter in a polycarbonate tray and a Tyvek lid, to **form the sterile barrier**. This tray sealer has three parameters: Pressure, Temperature and Time.
- The sealer's temperature and time are computer controlled. Minimum requirement is 5 N peel strength. Also, no buckling of the tray and no burned Tyvek. The Tray Sealing process is validated using peel testing with a Chatillon Tensile Tester, bubble testing (packaging lab test), dye penetration (packaging lab test) and a Medical Engineering Technologies Burst Tester for burst strength testing.
- MSOP 1006 *Tray Sealing using the Alloyd Sealer*, ISOP 1005 *Burst Testing* and ISOP 1006 *Peel Testing* drive the activity

- Process Validation: Yes/No?
- Software Validation: Yes/No?
- Test Method Validation: Yes/No?

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ACME: Manufacturing

Process no. 6: Sterilization using a commercially available Gettinge Autoclave (super-heated steam).

- Requirement: A Sterility Assurance Level (SAL) of 10^{-6} which means that there is only one chance in a million that a product would be non-sterile after the sterilization.
- This sterilization is validated in accordance with AAMI ANSI ISO 17665-1:2006 *Sterilization of Health Care Products – Moist Heat – Part 1: Requirements for the development, validation and routine control of a sterilization process for medical devices*, which is an FDA Recognized Consensus Standard (no. 14-261).

  http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfStandards/search.cfm

- The catheter sterilization uses conventional product release, i.e. Biological Indicators (BIs) are placed with each sterilization load, and the BIs are subsequently tested to ensure that they are not viable.
- MSOP 1007 *Catheter Autoclave Sterilization Process* and ISOP 1007 *Conventional Release of Products Sterilized by Autoclaving* drive the activity

- Autoclave Validation: Yes/No?
- Software Validation: Yes/No?
- Process (Sterility) Validation: Yes/No?
- Test Method Validation: Yes/No?

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ACME: Manufacturing

Lastly, the whole process is validated using a PPQ

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ACME: Process Validation Plan

The Process Validation Plan may look like this:

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Process Validations
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ACME: Process Validation Plan

Process Name and Standard Operating Procedure (SOP) number	Equipment Name and Identification	IQ Needed? Protocol and Report Number	OQ Needed? Protocol and Report Number	PQ Needed? Protocol and Report Number	SWV Needed? Protocol and Report Number	TMV Needed? Protocol and Report Number	PPQ Needed? Protocol and Report Number	Target Completion Date
Tube Cutting: MSOP 1001 *Tube Cutting Process*	Acme Tube Cutter, ID 7000	Yes / XXXX	Yes / XXXX	Yes / XXXX	Yes / XXXX	No	Yes / XXXX	MM/DD/YY YY
Tube Section Inspection: ISOP 1001 *Tube Section Inspection*	N/A	No	No	No	No	Yes / XXXX		MM/DD/YY YY
Tube Joining: MSOP1002 *Tube Joining Process*	Acme Tube Joiner, ID 7001	Yes / XXXX	Yes / XXXX	Yes / XXXX	Yes / XXXX	No		MM/DD/YY YY
Tube Joint Strength Testing: ISOP 1002 *Tube Joint Strength Testing*	Chatillon Tensile Tester / Load Cell, ID 7003	Yes / XXXX	No	No	Yes / XXXX	Yes / XXXX		MM/DD/YY YY
Luer Hub Joining: MSOP 1003 *Luer Hub Joining*	EFD Adhesive Dispenser, ID 7004	Yes / XXXX	Yes / XXXX	Yes / XXXX	No	No		MM/DD/YY YY
	Dymax UV Light Curing Station, ID 7005	Yes / XXXX	Yes / XXXX	Yes / XXXX	No	No		MM/DD/YY YY
Luer Hub Joint Strength Testing: ISOP 1003 *Luer Hub Joint Strength Testing*	Chatillon Tensile Tester / Load Cell, ID 7003	Yes / XXXX	No	No	Yes / XXXX	Yes / XXXX		MM/DD/YY YY
Hydrophilic Coating: MSOP 1004 *Catheter Hydrophilic Coating Process*	Acme Hydrophilic Coating Machine, ID 7006	Yes / XXXX	Yes / XXXX	Yes / XXXX	Yes / XXXX	No		MM/DD/YY YY

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Process Validations

an Integrated Quality Systems Approach

ACME: Process Validation Plan

Process Name and Standard Operating Procedure (SOP) number	Equipment Name and Identification	IQ Needed? Protocol and Report Number	OQ Needed? Protocol and Report Number	PQ Needed? Protocol and Report Number	SWV Needed? Protocol and Report Number	TMV Needed? Protocol and Report Number	PPQ Needed? Protocol and Report Number	Target Completion Date
Hydrophilic Coating Curing Process: MSOP 1005 *Catheter Hydrophilic Coating Curing Process*	Blue M Curing Oven, ID 7007	Yes / XXXX	Yes / XXXX	Yes / XXXX	Yes / XXXX	No		MM/DD/YY YY
Hydrophilic Coating Thickness Inspection: ISOP 1004 *Hydrophilic Coating Thickness Inspection*	RAM Optical Inspection System, ID 7008	Yes / XXXX	No	No	Yes / XXXX	Yes / XXXX		MM/DD/YY YY
Tray Sealing: MSOP 1006 *Tray Sealing using the Alloyd Sealer*	Alloyd Tray Sealer, ID 7009	Yes / XXXX	Yes / XXXX	Yes / XXXX	Yes / XXXX	No		MM/DD/YY YY
Tray Burst Testing: ISOP 1005 *Burst Testing*	Medical Engineering Technologies Burst Tester, ID 7010	Yes / XXXX	No	No	Yes / XXXX	Yes / XXXX		MM/DD/YY YY
Tray Peel Testing: ISOP 1006 *Peel Testing*	Chatillon Tensile Tester / Load Cell, ID 7003	Yes / XXXX	No	No	Yes / XXXX	Yes / XXXX		MM/DD/YY YY
Sterilization: MSOP 1007 *Catheter Autoclave Sterilization Process*	Gettinge Autoclave, ID 7011	Yes / XXXX	Yes / XXXX	Yes / XXXX	Yes / XXXX	No		MM/DD/YY YY

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Process Validation Deep Dive

- Let's do a deep dive into one of the Validations, the Sterile Barrier Packaging.
  - Let your Quality System Drive the Activities!
  - If your product is CE marked, then you need to comply with BS EN ISO 11607.
- Do a feasibility study or Design of Experiments Study to find the sweet spot.
  - Remember that you have two competing objectives; a good seal and a pretty package.
- IQ for the equipment.
  - Don't forget to get all of the gauges into the calibration system, and get a first article on the sealing platens! Get draft procedures in place, and operator training records.

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Process Validation Deep Dive

OQ: Remember three parameters; time, temperature and pressure! Do Low-Low-Low for seal strength, and High-High-High for cosmetics. If you are using trays and Tyvek lids from different manufacturers, then throw them in as well:

- Low-Low-Low, Supplier A Trays, Lids from Mangar
- Low-Low-Low, Supplier B Trays, Lids from Mangar
- Low-Low-Low, Supplier A Trays, Lids from Oliver-Tolas
- Low-Low-Low, Supplier B Trays, Lids from Oliver-Tolas
- High-High-High, Supplier A Trays, Lids from Mangar, etc.
- PQ: Three runs at nominal, maybe on three different days, or three different shifts
- SWV: Follow the template, this would probably be for the temperature controller
- Do your seal strength testing, burst testing, dye penetration, peel-back testing, etc.

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Process Validations

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Summary

Let Your Quality System Drive Your Validation Activities!

- It is important that process validation follow a planned and documented Process Validation Plan (if applicable), and that the individual processes are validated using a documented protocol.
- The team that will perform the process validations should write the protocols, and the team should include representatives from the functional groups that will be affected by or will participate in the process validation (usually Manufacturing Engineering, Quality Engineering, R&D Engineering and Regulatory Affairs). It is imperative that someone with process validation expertise work directly with the team to develop the protocol.
- It is also a good idea for members of the process validation team to be given primer training in process validation if they have not been involved in such a validation previously.

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Process Validations
an Integrated Quality Systems Approach

Summary

- Process Validations are very resource-intensive activities, including personnel, equipment time and raw materials. Most medical device companies underestimate the time and resources that are needed for a process validation.
- The costs of a process validation must be weighted against the costs associated with verification of process outputs, when it is possible to do both.
- Most medical device companies that I have been with has several pieces of un-used equipment, which go unused because of a lack of resources to validate the equipment and the process!

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Process Validations
an Integrated Quality Systems Approach

Summary

- For organizations that must validate many processes, it can be useful to set priorities for the performance of these validations based on the risks associated with the processes.
- Processes that can have a direct effect on the safety and effectiveness of the medical device, or processes that cannot be inspected should be validated first:
  - Joining
  - Welding
  - Sterile Packaging
  - Sterilization

Note that the Summary section has borrowed from "The FDA and Worldwide Quality System Requirements Guidebook for Medical Devices, Second Edition by Amiram Daniel and Ed Kimmelman, page 149

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Any questions?

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Thank You!

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References

References:

- Food and Drug Administration; Guidance for Industry. Process Validation: General Principles and Practices. Dated January 2011
- 21 CFR 211, Section 211.110 Sampling and testing of in-process materials and drug products
- ISO 13485 Medical devices – Quality management systems – Requirements for regulatory purposes
- Technical Report 14969 Medical devices – Quality management systems – Guidance on the application of ISO 13485:2003:
- EN ISO 9001:2008/AC Quality Management Systems – Requirements
- BS EN ISO 11607-2:2006 Packaging for terminally sterilized medical devices – Part 2: Validation requirements for forming, sealing and assembly

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