Process Validation For Electronic Medical Devices: Fundamental Things To Know

By Alec Alpert

If you are an engineer involved with the manufacturing of medical devices you may be assigned to perform process validation, which is mandated by FDA regulations and the applicable international standards.

Let's define process validation. Here is the FDA's definition of process validation (21 CFR 820.3 Definitions):

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

This is, of course, a broad definition that applies to all process validations in the industry. However, depending on the product and process, each process validation can be different. Injection molding validation, sterilization validation and validation of the manual assembly of electronic systems will be very different validations. Hence, each manufacturer must establish their process validation procedures and policies corresponding to the type of products and processes at hand.

This article addresses the process validation of the manual assembly of electronic medical devices.

Although procedures, instructions and policies will be unique to each company, they all, however, must comply with the following criteria:

21 CFR 820.75 Process Validation

> *(a) 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.*
>
> *(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.*
>
> *(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.*

ISO 13485:2016 Medical Devices - Quality Management Systems Requirements

> *7.5.6 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 or is not 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 consistently.*
>
> *The organization shall document procedures for validation of processes, including:*
>
> *a) defined criteria for review and approval of the processes;*
>
> *b) equipment qualification and qualification of personnel;*
>
> *c) use of specific methods, procedures and acceptance criteria;*

d) as appropriate, statistical techniques with rationale for sample sizes;

e) requirements for records;

f) revalidation, including criteria for revalidation

g) approval of changes to the processes.

The organization shall document procedures for the validation of the application of computer software used in production and service provision. Such software applications shall be validated prior to initial use and, as appropriate, after changes to such software or its application. The specific approach and activities associated with software validation and revalidation shall be proportionate to the risk associated with the use of the software, including the effect on the ability of the product to conform to specifications.

Records of the results and conclusion of validation and necessary actions from the validation shall be maintained (see .4...2.A and 1:.2..5.).

EU MDR 2017/745 Regulation of the European Parliament and of the Council

DESIGN AND MANUFACTURING INFORMATION

(a) information to allow the design stages applied to the device to be understood;

(b) complete information and specifications, including the manufacturing processes and their validation, their adjuvants, the continuous monitoring and the final product testing. Data shall be fully included in the technical documentation;

(c) identification of all sites, including suppliers and sub-contractors, where design and manufacturing activities are performed.

Let's translate these formal definitions into process validation nuts and bolts.

Basically, process validation analyzes a product and processes data to verify the typical range of variation for the process output and demonstrates if the processes are in a state of control.

In addition to satisfying regulatory requirements, the validated process improves product quality, reduces operational costs, eliminates scrap, and ensures customer satisfaction.

Although companies have their own process validation procedures, the following steps most likely would be included in process validations associated with the manual assembly of medical devices:

1. Prepare a Master Validation Plan (MVP), which is the top-level document that outlines the required validation activities.
2. Prepare validation protocols that outline how process specific requirements will be validated.

3. Execute protocols and analyze raw data.
4. Prepare validation reports associated with individual protocols.
5. Prepare a Master Validation Report (MVR) that provides evidence of process validation completion.

Having identified the key validation steps above, keep in mind that there are three process qualifications that are the foundation of the overall process validation and that are usually performed in the following order:

1. **Installation Qualification (IQ).** The purpose of IQ is to ensure that the equipment has been correctly installed to meet the manufacturer's specifications and that it will operate within the expected range. IQ establishes the foundation for all other qualification activities.

2. **Operational Qualification (OQ).** The purpose of OQ is to establish that, under the extremes of process parameters (worst-case conditions) anticipated under manufacturing conditions, a product will still meet all defined requirements. If no worst-case conditions exist for the affected outputs, then an OQ is not required.

3. **Performance Qualification (PQ).** The purpose of the process performance qualification is to demonstrate that individual processes will consistently produce an acceptable product under normal operating conditions.

IQs, OQs and PQs are process validations in and of themselves that require stand-alone validation protocols, protocol execution and reports.

Master Validation Plan

Process validation activities begin with the Master Validation Plan (MVP) that defines the scope of the validation effort and serves as a communication and planning tool for the validation team.

Although companies have their own guidelines for MVPs, resulting in MVP structures unique to a specific company, from my hands-on experience with process validations, the typical sections to be included in the MVP document are:

Purpose

This section states that the purpose of the protocol is to document the validation activities required to demonstrate that the manufacturing process for the product XYZ performed at the [Name] manufacturing facility located in [Town], [State] meets all requirements.

Scope

The validation scope should describe the products and processes that are being validated, including specific model numbers and associated information, manufacturing process names, and the facility the validation pertains to.

Applicable Documents

For protocols, list all documents that define the requirements and provide guidance for the content and approach described in the protocols.

For reports, list all documents that were involved in the execution of the protocols.

Background

This section describes the history of the product and the main reason for the validation. This may explain the validation activities associated with new product development, changes in the existing design or process, or facility relocation.

Validation Prerequisites

The prerequisites are items that must be completed and verified prior to the execution of the MVP, such as:

- Operators trained in the most recent process documentation before participating in the process validation.
- All suppliers are approved per applicable procedures and listed on the approved supplier list.
- Drawings for tooling and fixtures, manufacturing procedures, inspection procedures, logs, test methods, and traceability documentation released and controlled for the processes being validated.
- Process FMEA (PFMEA), Design FMEA (DFMEA) and Use FMEA (UFMEA) are released and controlled documents. Redlined or draft approved PFMEAs may be used for operational and performance qualifications (OQ and PQ).

Process Flow Overview

The purpose of the process flow overview is to explain the essential elements of the processes being validated in a way that can be understood by someone who is not an expert in the process.

This section of the MVP might include two sub-sections:

1. A sub-section describing the process(es) being validated.
2. A sub-section providing a process map of the manufacturing process, which is usually a step-by-step process flow chart.

The first sub-section should contain a description of each of the processes within the scope of the MVP. The descriptions should explain what is happening at each step of validation, what materials are used, how the process is executed, and any key requirements and controls.

Validation Team and Responsibilities

Define in this section the responsibilities of those functional areas that will be involved in the validation activities.

Validation Strategy

This section describes the general approach to validation and determines what qualifications will be required (i.e., IQ, OQ, PQ), the protocol execution progression, the purpose of qualification activities, and any special requirements or deviations from typical practices.

Process Qualifications (IQ, OQ, PQ)

Describe in this section the specific equipment and individual process qualifications, including an assessment of each qualification area defined in the Validation Strategy section above.

The assessment should include the following:

- A general description of equipment and material qualification requirements.
- Identification of the equipment involved, a description of the equipment, and a rationalized decision(s) on whether test method validation (TMV), IQ, software validation, preventative maintenance, and/or calibration are required.
- The names of the processes involved.
- The applicable inspections.
- A description of the key process outputs.
- A determination on whether the process outputs are fully verifiable.
- A determination on whether an OQ and PQ are required (with rationale if not required).
- A determination on whether process verifications need to be performed to qualify the inspections.

Validation Sampling

This section addresses sampling plans based on the needs of the validation and the product, process, or equipment, etc., being tested.

When determining a minimum sample size for OQ and PQ, distribution (variable, attribute), confidence level, process FMEA risk classification and reliability should be used, and guidance for how to arrive at the appropriate sample size should be provided in the sampling plan procedure.

Alternate sample sizes can be used based on guidelines from ISO, ASTM, ASQ or other standards, provided they support an alternate sample size with a rationale relevant to how the sample effectively meets the default confidence and reliabilities.

Acceptance Criteria for Process Release

In this section, establish the acceptance criteria for all deliverables that must be completed and confirmed before the product release. Usually, a completed and released Master Validation Report (MVR) serves as a gating item for the product release.

Attachments

Describe in this section how and what attachments should be included in the protocols for completion.

Master Validation Report (MVR)

State in this section that the MVR is the final report created at the end of all planned validation activities and that it reflects the complete execution of all activities outlined in the Master Validation Plan (MVP).

Explain that the MVR references and summarizes all executed protocols and their results. Individual validation reports may be completed for individual protocol activities, but the content for both the MVR and individual reports should include the following, at the minimum:

- Deviations to the plan, protocols, and test data.
- A list of all associated IQs, OQs and PQs, and outcomes of process verifications with reference to acceptance criteria.
- Conclusions regarding the validation status of the overall process.
- Explain how unacceptable validation results are to be handled. Typically, corrections, deviations and/or full or partial re-validation may be required. Perhaps new or revised validation protocols may be needed. Some validation results and the closure of the MVR must be approved by senior management.

MVP Execution

After the MVP and all associated documentation have been approved and released and all pre-requisites have been implemented, the MVP execution stage commences as described below:

- All validation activities shall be performed in the anticipated manufacturing environment.
- The manufacturing records of validation activities shall document the associated validation protocols.

- Qualified personnel shall build sample product for validation. Personnel qualifications shall be documented.

- The personnel performing required validations and the dates they were performed shall be documented.

- All IQ qualifications shall be completed, and the IQ report approved and released before the execution of associated OQ and/or PQ.

- All test and inspection methods shall be qualified, and the report approved and released before the execution of associated OQ and/or PQ.

- Execution of the OQ protocol shall not start until nominal design verification testing results have been obtained.

- All supplied components to be used for OQ and PQ must have demonstrated conformance to specifications.

Master Validation Report (MVR)

As mentioned in the Master Validation Plan (MVP) section of this article, the Master Validation Report (MVR) is the final report created at the end of all planned validation activities and reflects the complete execution of all activities detailed in the MVP. The MVR references and summarizes all executed protocols and the results.

Keep in mind that the MVP and MVR are usually required for full-scale process validations associated with new manufacturing or manufacturing transfers but may not be needed for smaller revalidation activities; criteria regarding the scope of validations should be addressed in respective procedures and work instructions.

About the Author

Alec Alpert is a Quality Engineer and Consultant with an extensive background in quality and compliance for medical devices from new product development, to operations, to post-market activities. He has helped to improve product quality and compliance at the leading medical device companies in applications ranging from linear accelerators, anesthesia systems, and implantable orthopedic devices to electronic imaging systems, infectious disease diagnostic systems, and electrosurgical generators. Alec is the owner of Alpert Engineering, LLC, an engineering consulting company that provides services to medical device companies. Alec is also the owner of www.alecalpert.com, where he publishes articles and white papers with practical advice on medical device technology, quality assurance, and compliance.