

Process Validation for Medical Devices

Jon L. Nickerson

The current GMP regulation for Medical Devices (21CFR Part 820, subpart G, Section 820.75) requires that where the results of a process cannot be fully verified by subsequent inspection and test, the process shall be validated. In this context, validation is defined as confirmation by the provision of objective evidence that a process consistently produces a result that meets its predetermined specifications.

A good example of a process that needs to be validated is sterilization. Testing each unit that has been sterilized is not practical—the testing itself would likely introduce bacterial contamination—so a sterilization process protocol must be developed, validated and followed to assure proper results. Importantly, the FDA's QSIT program includes specific instructions for auditing sterilization process controls, the only manufacturing process to receive this attention. FDA inspections are likely to include a careful review of the validation study for any sterilization process.

An article on preventive action in a previous newsletter¹ discussed the establishment of a process capability as a preventive action tool. This same tool is the “kernel” of process validation. Repetitive testing, under all conditions including worst case, yield results which are quantified. If all such results fall safely within the predetermined specification, the documents process together with the documented testing (validation study) constitute a validated process. The number of tests performed should be proportionate to the risk to safety that would occur if the output of the process were out of specification.

The scope of a process validation can vary considerably. The validation of a manufacturing facility, including plant, equipment and manufacturing processes, requires a complex validation plan. The validation of a single manufacturing step may require only a single validation protocol. A manufacturer may exclude from the validation requirement those processes that do not affect product performance or safety. Written justification for the exclusion should be part of the validation plan.

A complete validation plan specifies the overall scope of the project and the individual elements included. It defines the responsibilities for planning, performing, reviewing, documenting and approving each validation study. It should include a schedule and budget. For complex processes, sub-processes need to be identified with defined inputs and outputs, along with flow diagrams illustrating the sub-process relationships to the complete process being validated.



Process Validation is a fact of life for manufacturers of medical devices. This photo of an Integrity AFx™ pacemaker is supplied courtesy of St. Jude Medical's Cardiac Rhythm Management Division.

Product planning

Ideally, validation begins with product planning, where the product specifications are tied to the user needs and the intended use. All aspects of the product that affect safety and effectiveness are considered, including performance, reliability and stability. Product characteristics must be expressed in readily measurable terms and allowable vari-

ations expressed in acceptable ranges. The validity of the acceptance specifications are verified through testing and challenge of the product on a sound scientific basis. These measurable acceptance specifications are documented prior to carrying out process validation studies.

Process validation elements

The elements of a process validation are:

1) Installation qualification

Establishing confidence that the process equipment used is capable of consistently operating within established limits and tolerances. This phase of the validation includes examination of equipment designs; design; determination of calibration, maintenance and adjustments requirements; and identification of critical equipment featured that could affect the process. The information obtained from these studies is used to establish written procedures covering equipment maintenance, calibration, cleaning, monitoring and control.

2) Operational qualification

Verifying that the equipment is functioning properly by dynamic testing. These functional tests verify the operating ranges and simulate actual production conditions. These tests are repeated a sufficient number of times to assure reliable results. All acceptance criteria must be consistently met. If not, an evaluation must be performed to identify the cause of the failure. After corrections are made, the tests must be repeated.

The observed variability of the equipment, between and within runs, can be used as a basis for determining the total number of trials to be used for the subsequent performance qualification studies.

Once the equipment configuration and performance characteristics are estab-

Message from GMP Labeling

We hope this newsletter includes information that you can use. Our goal is to periodically publish articles, written by quality professionals, that are timely and informative to the companies in our marketplace. Of course, along the way, we also hope to reinforce our image as a valuable resource to our customers.

Businesses regulated by the FDA and/or are ISO 9000 registered will find GMP Labeling products helpful in maintaining compliance. More than 5000 facilities in the U.S., Canada and Europe use GMP Labeling products on a daily basis.

lished, they are documented. Equipment monitoring and control procedures need to be written.

3) Process performance qualification

Testing to demonstrate the effectiveness and reproducibility of the process. In this phase of validation, the process specifications have been established and essentially proven acceptable through laboratory or other trial methods. The equipment has been judged acceptable on the basis of suitable installation studies. Each process is defined and described with sufficient specificity, such that employees understand what is required.

Parts of the process which may vary, so as to affect product quality, are challenged. The challenge conditions simulate those that will be encountered during actual production, including “worst case” conditions. The challenges are repeated enough times to assure that the results are meaningful and consistent.

Where applicable, tests of reproducibility and statistical analysis of the plan and results are included. Each specific manufacturing process is appropriately qualified and validated. All process performance qualification activities are documented in the formal process validation files.

4) Product performance qualification

Product performance qualification activities apply only to medical devices. These activities demonstrate that the specified process has not adversely affected the finished product. Where possible, product performance qualification testing includes performance testing under conditions that simulate actual use. Such testing verifies that the manufacturing process produces a product that meets the predetermined specifications and quality attributes.

After actual production units have successfully passed product performance qualification, a formal technical review is conducted. This review includes a comparison of the approved product specifications with the actual qualified product; determination of the validity of test methods used to determine compliance with the approved specifications; and determination of the adequacy of the specification change control procedure. All product performance qualification activities are documented in the formal process validation files.

Revalidation

Revalidation is required whenever there are changes in packaging, formulation, components, equipment or the manufacturing processes which could impact on

product effectiveness, product characteristics, product performance, or product safety. A specific revalidation procedure defines the requirements for revalidation including the individuals who are responsible for deciding when revalidation is required. The extent of revalidation depends upon the nature of the changes and how they impact upon the different aspects of production that have been previously validated.

Document your work

Lastly, the first rule of working with GMP regulations applies—document your work! Each validation test must be recorded on a test report, which includes the test data, analysis of the data, conclusions, ongoing monitoring procedures, signatures and dates of the person performing the test and those approving the report. All validation documentation should be maintained in permanent validation files and referenced in the Device Medical Records.

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✓✓✓✓✓✓✓✓✓✓ A 7-Point Checklist ✓✓✓✓✓✓✓✓✓✓ for Avoiding Pitfalls in Validation

Avoid unpleasant surprises: plan ahead!

Pamela Hardt-English

There are many critical steps in the successful planning of a validation project. The greater care taken with each one, the less stressful—and more efficient—the project will be.

✓ 1. Project scope

One of the most critical tasks in validation is to first determine an accurate and proper project scope. A poorly described or thought-out project scope can lead to a vague objective and unclear acceptance criteria, which can result in poor validation test procedures.

✓ 2. Acceptance criteria

When determining an acceptance criterion, it is important to understand what parameter is critical to the system or equipment being tested, as well as the tolerance requirement for intended use. One can test a system or piece of equipment within a tight tolerance range if the intended use (process requirement) dictates the tolerance. Sometimes one assumes that a higher degree of accuracy is better and therefore sets the acceptance criterion within an unnecessarily tight tolerance that may lead to unnecessary system control issues or failure of the validation study.

A company may consider running some pre-validation tests to ensure the acceptability of the imposed criteria prior to routing the protocol for signatures.

✓ 3. Protocol approval

Make sure all relevant parties sign off on protocols and SOPs prior to beginning work. By obtaining protocol approval from all relevant parties, you will ensure that the individuals involved with the project agree to the test methodology and acceptance criteria specified in the protocols, and you will also be getting buy-in from their departments, indicating that they will be supporting the project—for example, that Engineering will support providing the installation documentation, as applicable, and that QC will support sample taking and sample analysis, etc.

✓ 4. Properly calibrated instruments

Validation is only as good as the selection and calibration of the instruments and sensors. If the calibration reference has not been calibrated within its specified time interval, there is no point using it as a reference for anything. Appropriate and accurate data logging instruments are essential: a data logger and sensors that are accurate to $\pm 1.0^{\circ}\text{C}$, when the instrument being calibrated needs to record at $\pm 0.5^{\circ}\text{C}$, would not be appropriate.

In some temperature monitoring equipment, the thermocouples or thermistors may be used in difficult circumstances; in a rotating autoclave with a slip ring, for example, a percentage of thermocouples may fail.

Acceptance criteria must take into account what is needed to properly conduct the validation. Map the autoclave and be practical related to the predicted number of surviving thermocouples, or use a different system of data collection such as wireless data loggers.

Check the calibration dates of all critical sensors on equipment prior to using those instruments in a validation test. If the recording thermometer on an incubator should be calibrated every six months and is outside that range, then it needs to be calibrated before starting the tests.

✓ 5. Installed equipment

Compare the actual installation of equipment and its components and utilities with the engineering drawings and user's manual. There should always be a standard against which to check. Prior to purchasing any equipment, one should set a specification for what the requirements are, then verify that the purchased equipment is installed per specification. Make sure all of the vendor's specifications are met and promises are kept.

When verifying an existing piece of equipment, if the specification for that equipment is not available, one can document information for the equipment (as installed) and review the documentation to ensure that the equipment is acceptable for the process.

✓ 6. Appropriate scheduling

Make sure that the schedule you plan works with the necessary parties involved. If validating a piece of production equipment, the validation may have to take place during a scheduled shutdown or between certain hours. Calibration of sensors may have to fit into the Metrology Department's schedule for calibrations. We don't always get to do things when we want to do them, and validation may take longer than expected.

The number of days required for validation can sometimes be reduced when performing an Installation Qualification (IQ) or an Operation Qualification (OQ) by working longer hours or adding personnel. With most Performance Qualification (PQ) testing, however, you cannot shorten the validation interval needed, especially when PQ sampling is required. You cannot, for example, shorten four weeks of sampling once a day by taking samples twice a day for two weeks.

Review the data as they are collected. During or after the test, review the data to determine if there is any problem with the sensors or the data collected. If the sensors are registering values that are out of the acceptable range, the equipment controls may need to be adjusted and the validation begun again. There's no point conducting numerous tests that all fail on a piece of equipment.

(Continued on back cover.)

✓ 7. Qualifications of the validation team/company

Many companies, because of their size and/or the infrequency of their validation needs, don't have validation engineers onstaff. Rather than hiring specialists for each phase of the validation process, such companies will hire a single organization to handle all phases of the validation, including the process and the equipment. Few, if any, of even the largest validation organizations have the in-house expertise in all phases of a total facility validation.

Company A, for example, hired a major validation organization to complete a process, equipment, and facility validation. Validation of the sterilization process for manufacturing components was one of their many requirements. The engineer assigned to complete this phase was a recent graduate with no experience in sterilization. He had no knowledge of the standards that had to be met. More

serious was the fact that his supervisor had little experience himself. Rather than sub-contract this critical requirement to a company specializing in validation, they decided to attempt to learn validation on the job. As a result, the validation was not completed correctly and the project was delayed about three months.

When selecting an outside service to validate multiple systems, make sure that their proposal states, in writing, that they have expertise in each phase. The contract should be specific in the penalties that would apply if they failed to fulfill their commitments properly or in a timely fashion.

Efficient and effective validation requires good project definition, planning, coordination, and qualified validation professionals. Every aspect of the work needs complete and clear documentation.

If that's done, then validation may take only twice as long as you expect.

Pamela Hardt-English is affiliated with PhF Specialists Inc., a consulting company specializing in global safety of food and pharmaceutical products, based in San Jose, CA. PhF Specialists is recognized by the FDA and USDA as an authority in HACCP (Hazard Analysis and Critical Control Points).

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