Process Validation for Medical Devices

by: Dan O'Leary, President, Ombu Enterprises, LLC

Process validation is an essential part of medical device manufacturing but doesn't always receive the attention it deserves (and requires). The regulations provide the requirements (FDA QSR 820.75 and ISO 13485 7.5.2), but often manufacturers don't completely understand them and don't fully implement them. The consequences can be audit findings from a Notified Body or Inspectional Observations on an FDA 483.

While the wording of the requirements differs between QSR and ISO 13485, the intent is the same. You should validate processes when you do not verify everything the process produces. Process validation means knowing the range of process inputs that assure the process produces only conforming product.

The Definitions

The starting point, as in most regulatory issues, is the definitions. For QSR, the definitions are in 820.3, while for ISO 13485 they are in ISO 9000. In general, ISO 9000 defines more terms and is the more comprehensive source. For process validation, however, QSR includes specific definitions not included in ISO 9000. For example, 820.3(z)(1) defines process validation as "establishing by objective evidence that a process consistently produces a result or product meeting its predetermined specifications".

For our purposes, we take "fully verify" to mean 100-percent inspections or 100-percent tests

Looking at some of the phrases in the QSR definition provides insight for process validation.

- "Predetermined specifications" means that the manufacturer knows the required process output. The (production) process output comes from design output, 820.30(d) and "arrives" on the production floor through design transfer, 820.30(h).
- "Consistently produces a result or product" means that the process output satisfies the "predetermined specification."
- "Establishing by objective evidence" means you conducted the appropriate tests and inspections and have the data to support the results and conclusions.

The Regulations

Validation is in 820.75, and has three components: 820.75(a) relates to the initial validation of a process; 820.75(b) applies to process performance after validation; and 820.75(c) covers process changes or problems.

FDA published a draft QSR for comment, made revisions, and published the final regulation. The reasoning behind some choices FDA made is in the QSR preamble. The preamble, divided into numbered sections, is a good source of information to help clarify the requirements.

When Do You Need to Validate A Process?

QSR says that when the output of a process "cannot be fully verified by subsequent inspection and test[ing], the process shall be validated." The preamble (#143) gives some examples, including sterilization, aseptic processing, injection molding, and welding. The most common application for process validation involves destructive testing. For example, in sterilization you cannot open up all the packages to ensure each one is sterile (i.e., you cannot fully verify the sterilization process output).

QSR doesn't define "fully verify" and the preamble doesn't provide an explanation. For our purposes, we take "fully verify" to mean 100-percent inspections or 100-percent tests. This raises the question when sampling plans are included. What happens when we can fully verify the process but we choose not to - verification with sampling instead of 100-percent inspections?

The FDA addressed this issue in a January 2009 Warning Letter to the Hammill Manufacturing Company in Ohio. The FDA says that Hammill failed to implement 820.75(a) because they didn't validate a static ultrasonic cleaning and passivation process or a tumbling, cleaning, and passivation process. Hammill responded and in the Warning Letter the FDA said, "We have reviewed your response, which lists several other manufacturing processes (for example, your CNC processes and polishing) that you state you do not need validation because you perform in-process and final inspections/tests. We have concluded that your response is inadequate because you are not testing every device to assure it meets specifications and the results are not fully verified." The FDA continues, "**All of these processes must be validated** to ensure the specifications are consistently met or **you must test all devices**" (bold emphasis added).

The FDA is telling Hammill to either perform 100-percent inspections (every device) or validate the process.

What Does Validation Achieve?

When validation is required, QSR says, "The process shall be validated with a high degree of assurance." The validation should assure that when the process operates correctly, the process output—the product—is correct. In other words, when the process input parameters are in the acceptable range, the process produces only conforming product. The process model in Figure 1 shows the relationship between the input parameters and the output.

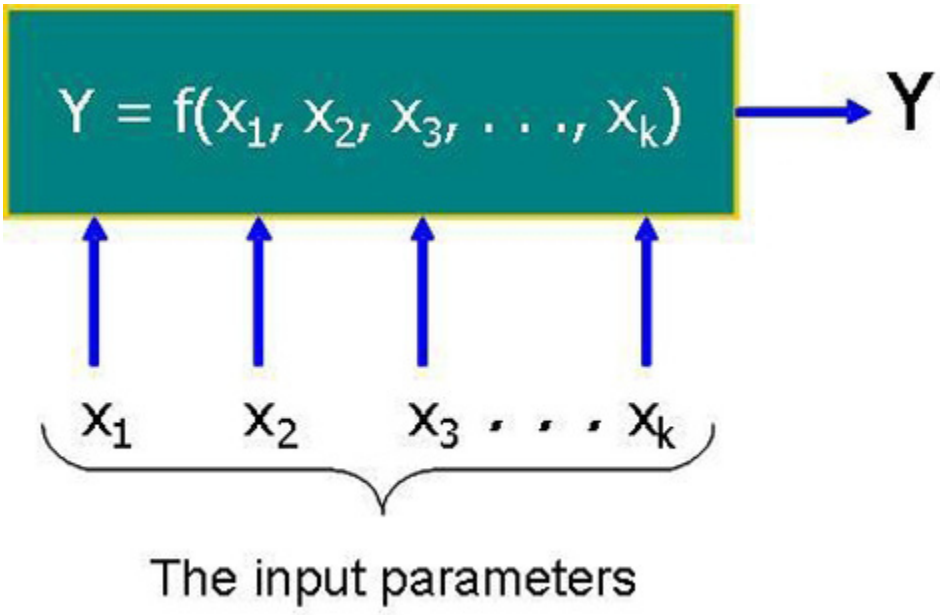

Figure 1

Cast into statistical terms, this means the process is capable of meeting the product's specification. The standard approach is to use a process capability index. The most appropriate is Cpk, defined below.

$$C_{pk} = \min\left(\frac{USL - \hat{\mu}}{3\hat{\sigma}}, \frac{\hat{\mu} - LSL}{3\hat{\sigma}}\right)$$

The index measures the distance from the estimated process mean to the nearest specification limit using the estimated standard deviation. The index value is 1.00, if the nearest specification is 3 standard deviations away. A process with a "high degree of assurance" of producing conforming product will have a Cpk ≥ 1.33. This means that the nearest specification limit is at least 4 standard deviations away from the process mean; the proportion of nonconforming material is, consequently, very small.

To validate a process, you should understand the acceptable range of the input variables. Understanding the input parameter space means understanding the process output that corresponds to every point in the input space. Consider a simple case of a bag sealing machine. The output variable is the bag's seal strength. Two sides of a heated clamp form the seal. For our simple example, consider two input variables as clamp temperature and clamp pressure. We need to determine the combinations of pressure and temperature that consistently (with a high degree of assurance) produce the specified seal strength. We want to explore the input parameter space in Figure 2.

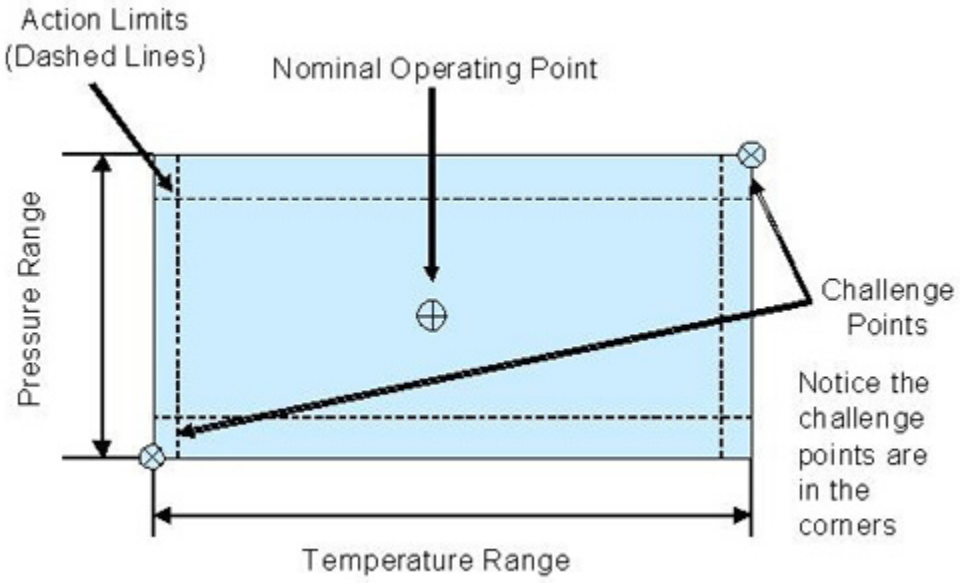

Figure 2

The rectangle defines the input parameter space. We look at three points in the space, under the assumption that two of them are the worst-case conditions; we call these the challenge points. At the upper right point, the input parameters are set to their high values. At the lower left point, the parameters are set to their low values.

If we don't know the worst case conditions, we can explore the parameter space using designed experiments. This is an ideal application for full or fractional factorial two-level experiments. The output variable should include both the mean and standard deviation. You want to establish a Cpk ≥ 1.33.

After successful process validation, the statistical model follows Figure 3. You know the allowable range of each input variable, you have challenged the process at the corners (worst case conditions) and the process output has a Cpk ≥ 1.33.

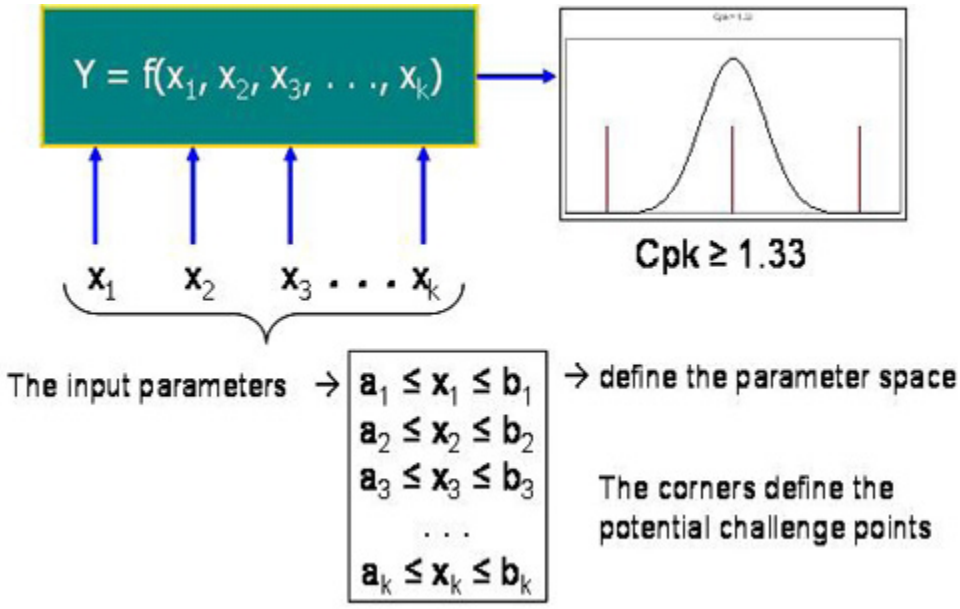

Figure 3

Operating the Process

QSR, 820.75(b) requires that you have procedures for monitoring and the control of process parameters to ensure you meet specified requirements. The preamble (#145) says that you monitor at a determined interval and frequency depending on the type of validated process. (The initial draft required continuous monitoring.) You should periodically evaluate the monitoring interval and frequency as well—especially if you change the process or uncover a process deviation.

The process parameters are the inputs defined above. After validation, you will establish the specification limits for the process parameters. You should also set up action limits. If the input parameters go beyond the action limits, you need to adjust them. The requirement is to:

- Monitor the parameters - check them often enough that you know their values;
- Control the parameters - adjust them if they get too far away from nominal (i.e., if they cross the action limits).

In addition, you need to qualify the process operator using appropriate means. Ensure the operator is aware of device defects that could result from improper performance of the process, 820.25(b)(1). One common method of operator qualification uses the driver's license model. Use a test on the basics of the process (the written test) coupled with a skill demonstration (the road test).

Process Records

When you operate the process, you need to keep records. While 820.75(b)(2) has a mix of required and optional records, it is better to keep all of them.

The records include:

- The monitoring and control methods - You established them in the procedure, so you should record that you followed the procedure or had to deviate. For example, you might use an alternate piece of measuring

equipment because the primary piece was out for scheduled calibration.

- The monitoring and control data - Record the values of the process input parameters and note if you made any adjustments. If you use sampling inspection to verify the process output, be sure to record the sample size, acceptance number, and the result.

- The date performed - Always record when you performed the process. If the run takes multiple days, record the start and end dates.

- The individual(s) performing the process - Record the names of the people who ran the process. QSR asks for this, "where appropriate" and Part 820.1(a)(3) says, "When a requirement is qualified by 'where appropriate,' it is deemed to be 'appropriate' unless the manufacturer can document justification otherwise."

- The major equipment used - Record the equipment used by noting the name and serial number, asset ID number, equipment log number, etc. The "where appropriate" conditions described above apply.

Process Changes

The validated process may continue unchanged for a long time, but eventually some change could be necessary. This could be a new product model, a revised specification, an upgrade to the process equipment, etc. You need to review and evaluate the process. The result should be a decision to revalidate the process or a documented reason why revalidation would not be required.

Process Deviations

Process deviations occur when the process produces nonconforming material. This means the process output is outside the specification range. Because this is a validated process (i.e, validated with a high degree of assurance) this should not happen. In the best case, the sampling plan detects the problem. In the worst case, the product escaped to the customer and you learned of the problem through a complaint. Investigate the problem immediately and determine what went wrong. The records you kept should help you uncover the cause and allow for effective corrective action.

Sampling Plans

The process output may use a sampling plan for verification. If you change the process or encounter a deviation, you should also review the sampling plan; see 820.250(b). Document your review.

Conclusion

Process validation is a very powerful tool that can help you achieve highly effective processes (i.e., processes that always produce conforming product). Setting up a process validation is a good use of statistical methods. There will be work involved but the work will pay solid benefits.

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Dan is a regular speaker at international conferences and teaches courses in reliability methods, medical device regulations and practices, statistical methods, management systems (ISO 9001, FDA QSR and ISO 13485), and project management. Dan is a member of the American Mathematical Society, American Statistical Association, Society of Industrial and Applied Mathematicians, Institute for Supply Management, Project Management Institute, APICS, and is a Senior Member of the American Society for Quality and has held leadership positions in ASQ sections. He is an ASQ Certified Biomedical Auditor, Quality Auditor, Quality Engineer, Reliability Engineer, and Six Sigma Black Belt; he holds an APICS certification in Resource Management. He can be reached at 603-209-0600 or Dan@OmbuEnterprises.com.

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