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The Elements of Process Validation: A Preview of Medical Device Validation Handbook

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In March 2018, IVT Network is slated to publish their Medical Device Validation Handbook, coordinated and co-authored by none other than Roberta Goode of Altrec, LLC (formerly Goode Compliance International). Below is a sample from her chapter, "Principles of Process Validation." Stay tuned for the official launch of this tremendous publication, led by some of the top experts in the medical device validation space.

The Elements of Process Validation

The elements of process validation ideally follow a chronological order, as presented in this chapter. Exceptions to this order of operations include, but are not limited to, remediation of legacy processes, and partially leveraged existing process validations.

Determine Risk

Process validation begins with determining risk, not only in the manufacturing process but also in the design and use of the device. Risk assessment and management is the logical foundation of engineering, especially in the medical device industry, and it is required by regulatory bodies. Risk determination can take many forms, including hazard analysis (HA), fault tree analysis (FTA), failure modes and effects analysis (FMEA), and others. The medical device industry follows ISO 14971 for the implementation and maintenance of risk management, and the reader is referred to the international standard for details. However, for purposes of illustration, the failure modes and effects analysis will be described as an input to process validation. Most other risk analysis or risk assessment tools can be seamlessly substituted for the FMEAs in the following examples.

Example: Assess risk for a class III medical device, an implantable cardiac defibrillator.

Step 1: Determine the combined risk for each potential hazard and failure mode the cardiac surgeon and patient may encounter during surgical implant of the device. Include these as functions of both the severity of the harm, if the harm were to occur, and the frequency with which the harm is expected to occur. Note that the severity of the harm is objective (and should be routinely updated as post-market performance information becomes available), whereas the frequency of the defect's occurrence is subjective. For this reason, it is imperative to periodically monitor the frequency of events in the customer complaints logs and to update the FMEAs as a result of those evolving reports. In this example, there's a possible failure mode by which the surgeon fails to (do something) with the leads, possibly resulting in cardiac arrest and serious

injury. Assume the misattachment of leads happens, what is the worst case reasonable outcome? If it is cardiac arrest, assign a numeric value to that outcome, such as 5 on a scale of 1-5. Next determine the frequency with which this is reasonably expected to happen. We'll assume a worst case of 1 in 100 or .01, and assign a numeric frequency to this value, say a 2 on a scale of 1 through 3. The combination of 5 and 2 will then yield an overall risk index of 3:

Table 1: Risk category as a function of severity and frequency

	severity				
frequency	1	2	3	4	5
1	1	1	1	2	2
2	1	1	2	2	3
3	2	2	2	3	3

Step 2: A higher risk index should be associated with a higher reliability, and this relationship should be explicitly documented in a procedure. In this example, risk indices range from 1 to 3, with 3 the greatest risk. The precise reliability required for this risk category or even for this product is not prescribed in any regulatory guidance; there's no minimum value that FDA or any other regulatory agency will find acceptable. The requirement is for the manufacturer to determine a value that makes sense for the intended use of the device, its classification, the patient population in which it will be used (with special consideration for vulnerable patient populations such as the elderly or children), and with an understanding of the clinical performance of the device. For a risk category of 3, the procedure calls for a reliability of 99.7% and a confidence level of 95%.

If we were to take a representative sample of the population one hundred times, the confidence level tells us the likelihood that those 100 samples would contain the true value of the population. A 95% confidence level means that 95 times out of 100, the true value of the population will be represented in the sample.

Reliability = 100% - % Defective

99.7% Reliability = 100% - % Defective

99.7% Reliability = 0.3% Defective

Table 2: Reliability and confidence level as a function of risk

Risk Category	Reliability	Confidence Level
1	95%	95%
2	97%	95%
3	99.7%	95%

Step 3: Select a sampling plan that, if met, will provide for the required reliability and confidence level. A sampling plan consists of a sample size, or number of discrete parts to be measured, and acceptance criteria which, when met, establish the required reliability and confidence level. In this example, a variables-type sampling plan that provides for 99.7% reliability and 95% confidence level is n=100, Ppk=1.06, Pp=1.12 This sampling plan requires a representative sample of 100 units to be selected from each of the multiple validation production runs, and each group of 100 units evaluated for process capability measures Ppk and Pp. If the selected values meet or exceed the values denoted in the sampling plan, the batch is considered accepted and the 99.7% reliability and 95% confidence level are confirmed. In order to pass the validation,

all tested batches must meet the sampling plan’s requirements.

The reliability, confidence level, and sampling plan must be selected at this point in the validation process to enable these parameters to be documented in the validation protocol, and to inform the next phase of the validation, the Master Validation Plan.

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