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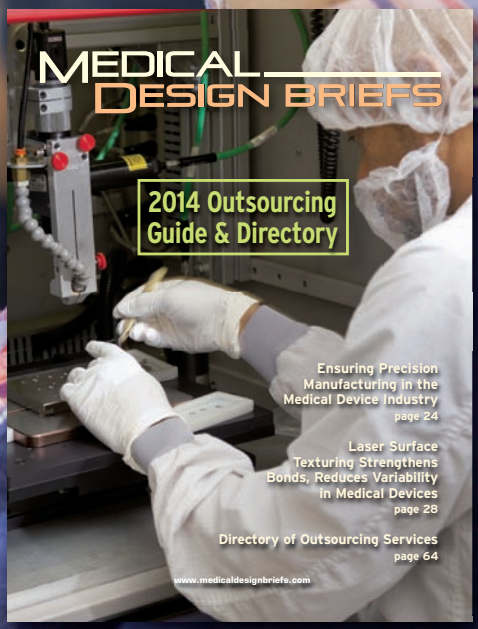

From the Publishers of TECH BRIEFS

Ensuring Precision Manufacturing in the Medical Device Industry

The English (North America) dictionary definition of the word "precision" is *accuracy* (noun) or *relating to accuracy* (adjective). You will find the word "precision" takes on all the synonyms of the word "accuracy" in the manufacturing world. This rings especially true in the medical device industry. Let's examine some synonyms of the word "precision" to see how they relate to device industry regulations and good manufacturing practices.

Care: Think about and attention to detail (planning)

Meticulousness: Thoroughness and diligence (standards and regulatory compliance)

Correctness: Rightness and truth (process validation/objective evidence)

Exactitude: State of being exact, precise or accurate (maintaining the validation state)

Care (Planning)

For any medical device program, planning is the most important aspect. The program's success depends not only on a good and thorough plan, but also the plan's well done execution. Therefore, it is essential that thoughtful care and attention be taken in defining the requirements upfront in the device development life cycle. The planning team for any device program should consist of representatives from all functional areas of the organization. However, at a minimum, the team should have representation from engineering, manufacturing, quality assurance, and regulatory functions. A master validation plan needs to be developed for every program. Although the master validation plan is not required to comply with medical device industry regulations, it is one of the most sought after documents by auditors and investigators. The contents of a typical master validation plan include, but are not limited to:

- Purpose and Scope
- Responsibilities
- Reference Documents
- Product/Process Specifications
- Process Overview
- Validation Approach
- Risk Analysis
- Project Timeline

This master validation plan will act as a roadmap for the validation team and also as a reference document for the management team to make sure enough resources are available to develop a device. A typical process validation flowchart is shown in Figure 1.

Meticulousness (Quality and Regulatory Compliance)

Organizations that develop medical devices for distribution in the United States have to comply with federal regulations. Following are some of the standards and guidance documents that are useful in setting up the quality systems for a manufacturer to comply with the medical device industry's regulatory requirements.

21 CFR Part 820 – Medical Devices; Current Good Manufacturing Practice (CGMP) Final Rule; Quality System Regulation

21 CFR Part 11 – Electronic Records; Electronic Signatures

ISO 13485:2003 – Medical Devices-Quality Management Systems – Requirements for Regulatory Purposes

ISO 14971:2007 – Medical Devices-Application of Risk Management to Medical Devices

QSIT – Guide to Inspections of Quality Systems

GHTF/SG3/N99-10:2004 – Final Document, Process Validation Guidance

General Principles of Software Validation; Final Guidance for Industry and FDA Staff

Correctness (Process Validation/ Objective Evidence)

Process validation is defined as "establishing by objective evidence that the process consistently produces a result or a product meeting its predetermined requirements." Any manufacturing process in which the output cannot be verified should be validated according to

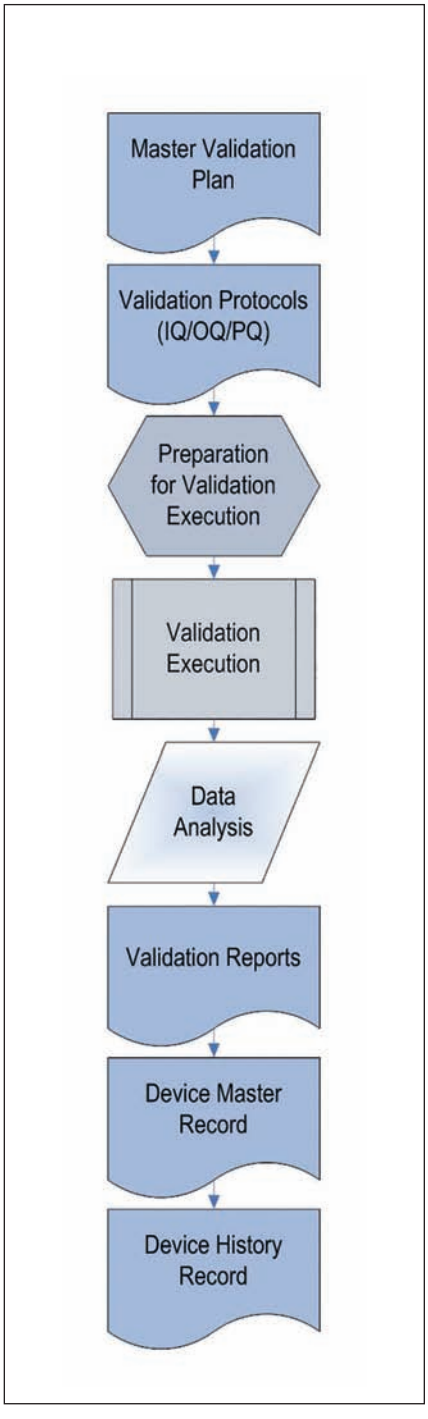

Fig. 1 – Process Validation Flowchart (Credit: Donatelle Plastics Incorporated)

the regulations. Typical examples of processes that should be validated are injection molding, welding, sterile packaging, sterilization, and manufacturing environment (clean room conditions, utilities, and facilities).

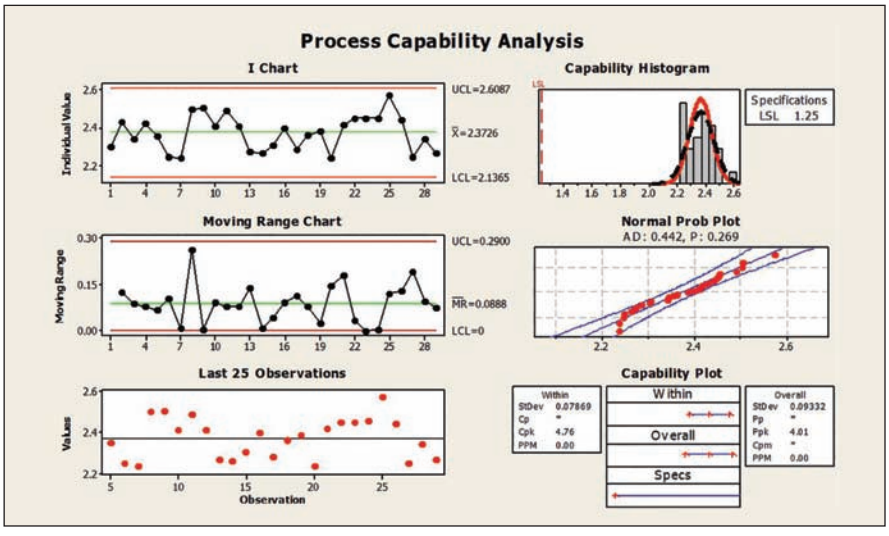

Fig. 2 – Process Capability Analysis (Credit: Donatelle Plastics Incorporated)

Process validation will be successful only when it is used as a confirmation tool, not as a fact finding tool. Process validation should be considered as an exercise of documenting the performance of an already developed manufacturing process that is under control to show evidence that under a production environment and challenged or anticipated conditions, it will produce an acceptable product.

Process validation activities include:

- Assigning a multi-functional team
- Defining requirements
- Developing process flow diagrams
- Performing risk analysis
- Deciding on validation or verification
- Creating a master validation plan
- Developing validation protocols
- Executing validation protocols
- Developing validation reports
- Determining process controls

Manufacturing processes are much more sophisticated now. The evolution in technology demands new requirements, such as equipment operational qualifications and software validations along with the process validations. Process validations become much easier if an emphasis is placed on understanding process input and output variables, along with product characteristics. As the definition of process validation suggests, its success depends on the use of statistical tools during the validation.

As described by the International Medical Device Regulators Forum, Global Harmonization Task Force, ***www.imdrf.org/documents/doc-ghtf-sg3.asp***, typical statistical tools that can be used during manufacturing process development and validation are:

- Failure Modes and Effects Analysis (FMEA)
- Tolerance Analysis
- Measurement System Analysis (MSA)
- Design of Experiments
- Analysis of Variance
- Control Charts
- Histograms
- Capability Studies

Every statistical tool mentioned above includes evaluation of data. The data comes from a wide variety of sources. These sources are in the form of end user requirements, material data, similar product data, and measurement data. Now, we will examine the source of data for each tool and what you can glean out of that data to help you make the decisions needed during the medical device manufacturing process.

Failure Modes and Effects Analysis (FMEA): FMEA includes identifying the device critical characteristics and developing the data pools for failure modes, causes, and their effects. Performing both design FMEA and process FMEA is critical to improve product and process reliability and quality. Analysis of this data will not only help in preventing failures in the future, but also in developing a better product.

Tolerance Analysis: The tolerance analysis tools will help in studying the dimensional relationships within the assembly and to determine individual part tolerances.

Measurement System Analysis (MSA): MSA is one of the most important tools to use during product and/or process development because the measurement system variations alone can influence the decisions made for making things better or worse during the early stages of development. The measurement system needs to be characterized by its accuracy, linearity, stability, repeatability, and reproducibility.

Design of Experiments and Analysis of Variance: Design of Experiments, which is also called Experimental Design, can be used to understand the effect of process variables on the product features. This analysis will help in determining whether the process variable has any effect on the product feature or not, and also help to establish control limits on the same to minimize variation.

Capability Studies: Process capability studies are performed to analyze the extent that the processes are capable to meet the predetermined requirements when the processes are under control. The process capability studies compare the process output to the specification limits.

Histograms and Control Charts: Histograms are used to understand the data distribution and frequencies in a continuous data. Control charts are helpful in monitoring the behavior of the process over a time period. The control charts can also be used to differentiate between common cause variations and special cause variations. Over the years, the manufacturing industry relied up on the monitoring of process outputs to ensure that the processes are under control. With the advent of technology, it has become much easier to monitor the process itself to make sure no defective product is produced. To accommodate this, the relationship between the process variables and the product fea-

tures needs to be established.

Some of the statistical software products available in the market are capable of performing all the above mentioned analyses. Figure 2 shows a graphical representation of process capability analysis.

Device manufacturers need to prepare and maintain a device master record that contains product specifications, process specifications, acceptance activities, packaging, and labeling specifications.

Exactitude (Maintaining the Validation State)

Maintaining the validation state for any manufacturing process used in the production of medical devices is an important device life cycle activity. This can be achieved by instituting process controls and continuous monitoring of process parameters, as well as product features. Monitoring process parameters that affect product features will help in minimizing the product nonconformance and costs associated with it. Validated manufacturing processes need to be performed by qualified individuals trained in device defects.

Conclusion

Precision manufacturing is not a chance event, but a process developed using scientific methodology. Decisions will be made based upon the data, backed by sound statistical principles. Understanding the requirements, communication, and cooperation between the functional areas, and training are the foundations of an organization that is striving for manufacturing excellence.

Recent trends show medical device manufacturing is being outsourced to contract manufacturers. These trends necessitate due diligence on the device developer or manufacturer's part to make sure the contract manufacturers not only comply with quality system regulations, but also have appropriate personnel with the necessary skills, experience, and knowledge in medical device manufacturing.

This article was written by Raghu Vadlamudi, Chief Research & Technical Director, at Donatelle Plastics Inc., New Brighton, MN. For more information, visit ***http://info.hotims.com/49746-162.***

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