TO VALIDATE OR NOT TO VALIDATE? THAT IS THE QUESTION FOR PLASTICS PROCESSORS IN THE MEDICAL DEVICE INDUSTRY.
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SPE European Conference on Medical Polymers, Belfast, Northern Ireland, September 9, 2010

Abstract
The Global Harmonization Task Force’s new guidance document on “the Controls of Products and Services Obtained from Suppliers” was published in December 2008. It details the requirements and the expectations that manufacturers must meet to exert more control over their suppliers. There is thus an increased emphasis and requirement that suppliers (especially of critical parts and components) monitor and control their processes to provide consistent, reliable, high quality products to the manufacturers of finished devices. This article will explain how the principles of process validation can be used to meet that consistency and quality, and, their applicability to plastics processors.

Background
The use of plastics in medical devices continues to grow especially with the growth in disposable products. Plastics have superior design flexibility compared to metals, ceramics and glass. They can be processed into innumerable shapes, sizes, thicknesses and colors, and their properties can be tailored to meet a wide spectrum of physical, mechanical, chemical, and biocompatibility requirements. Additives and fillers can be used to render plastics flexible or rigid, insulating or conductive, hydrophilic or hydrophobic, transparent or opaque and chemically and sterilization resistant.

Plastics can be processed by many different methods ranging from injection molding and extrusion to machining to form-molded parts, films and fibers. They are light weight compared to metals, ceramics and glass and can have an excellent balance of strength, stiffness, toughness, ductility and impact resistance. Many applications are using plastic to replace either metal or glass to reduce costs, leverage design flexibility and still maintain performance.

Trends in outsourcing and globalization have allowed medical device manufacturers to obtain parts, components, sub-assemblies and even finished devices from various suppliers from around the world. It is however important that those outsourced products meet stringent requirements and specifications to ensure that the final, finished device which the medical device manufacturer distributes and sells is consistent, reliable, safe and effective.

Recent events like diethylene glycol-contaminated toothpaste; lead in toys; contaminated heparin and heparin-containing pre-filled syringes; melamine in milk, and salmonella tainted peanut butter has led to several illnesses, injuries and deaths.
Each instance was caused, in large part, by poor or insufficient supplier controls. To this end, a Global Harmonization Task Force (GHTF) guidance document was issued in December 2008. The US Food and Drug Administration (US FDA) has adopted this guidance document, and will put more emphasis on medical device manufacturers to exert more stringent controls over their suppliers.

There is a lot of confusion within the plastics processors and suppliers industry as to how these controls apply and what these controls mean to them. The extent and level of controls will depend upon:

1. where they are in the value or supply chain, and
2. the criticality, complexity and quality requirements of the material or part.

Figure 1 illustrates that a plastics processor or resin supplier may be a Tier 1, Tier 2 or even a Tier 3 supplier in the value chain or supply chain. The material, parts or components that they supply might be low, medium or high risk depending upon the functionality or the type of medical device in which they are used. Thus, a Tier 1 supplier providing a high risk or critical part will be subject to a higher level of controls, whereas a Tier 3 supplier with a low risk material or part may be expected to comply with basic good manufacturing processes or be certified to applicable regulations and standards. These controls will come from the medical device manufacturers and not from the regulatory bodies. It is the responsibility of the medical device manufacturers to have appropriate supplier controls in place.

**Production Controls and Process Validation**

One aspect of supplier controls is ensuring that the components and parts are manufactured in a controlled manner to provide consistency and high quality product. The US FDA Medical Device Regulation and ISO standards call out the requirements for production controls which include specific requirements for process validation.

The intent of process validation is to produce components, parts or products that consistently meet quality, performance and other predetermined product requirements or specifications by proactively controlling the process parameters in real time. The product specifications and requirements come from the design of the part or product. It is thus important that those specifications, and (especially) their risk, importance or criticality be determined and communicated to the suppliers or manufacturers of those parts. Critical design parameters and their specifications as well as the critical process parameters and their tolerances must be determined during the design and development stage (Figure 2, next page).

Process validation is the formal documentation and confirmation of the data and information obtained in design and development. Process validation is conducted on manufacturing equipment, i.e. the equipment that has been identified to manufacture the part or product.

The question thus arises: Should a supplier validate or not? These requirements will originate from the supplier’s respective customers or the medical device manufacturers since it is the responsibility of the medical device manufacturers to communicate to their suppliers the type, extent and level of controls, including the need for process validation.

Processes can be either verified or validated.

**Verification** is defined as confirmation by examination and provision of objective evidence that specified requirements have been fulfilled (i.e. ensuring that the parts or products are tested and meet all quality requirements and specifications).

**Validation** is defined as confirmation by examination and provision of objective evidence that the particular requirements for a specific intended use can be consistently fulfilled.

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Process Validation is defined as establishing documented evidence which provides a high degree of assurance that a specific process will consistently produce a product meeting its pre-determined specifications and quality attributes (i.e. ensuring that the process parameters and inputs are controlled to produce parts or products that consistently meet all quality requirements and specifications).

The expectation however is that most processes must be validated. Processes like visual checks, manual cutting processes and pH measurements may be verified. Figure 3 details a validation decision tree. The first question that should be asked is — Can a process be fully verified? — i.e. — Can all the parameters of the product be measured and tested with full confidence that they will meet all quality and performance specifications at reasonable cost and time? If the answer is Yes then verification procedures are sufficient.

However, when several hundreds or thousands of parts are made every day, it is almost impossible to conduct an effective 100% verification of each part or component at a reasonable cost or in a sufficient amount of time. In addition where destructive tests are involved, verification is out of the question. For all such processes, validation is the only option. Examples of processes that should be validated are:

- Injection molding
- Extrusion
- Mixing
- Sterilization
- Welding
- Plastic bonding
- Wave/hand soldering
- Heat treatment
- Plating
- Dipping
- Sealing
- Formulations
- Software controlled processes
- Cleaning
- Filling
- Packaging; sterile packaging

Process validation consists of three qualification steps (Figure 4, next page):  

1. Installation Qualification (IQ)
2. Operational Qualification (OQ)
3. Performance Qualification (PQ)

The process is considered validated upon completion of the three qualification steps with appropriate documentation, reports, results and conclusions. All three qualification steps must be conducted according
to reviewed and approved protocols. Individual IQ, OQ, and PQ reports must be written to document results and confirm that the protocols were executed.

**Step 1 — Installation Qualification (IQ)**
The purpose of this step is to ensure that the equipment identified for the production of the part or component has been installed and is operating according to predetermined requirements and specifications. Some of the activities that should be included in an IQ activity are:

- Installation checks (connections, utilities, hardware, software, wiring etc.)
- Verification of installation drawings or instructions
- Equipment documentation (drawings, schematics, spare parts list, manuals, etc.)
- Purchased software documentation
- Critical equipment features (i.e. materials of construction, process limits, fixtures, etc.)
- Environmental conditions (such as clean room requirements, temperature, humidity)
- Preventative maintenance schedule
- Calibration requirements

- Safety features and requirements
- System start-up, operation and shutdown

**Step 2 — Operational Qualification (OQ)**
After completion and approval of the IQ, the second step is Operational Qualification (OQ). In this step, the process window for the production of the specified part is documented. These process parameters and windows are obtained from the process development studies that identified the critical raw material and process parameter values and tolerances. The purpose of this step is to determine the robustness of the process and set the raw material and process tolerances.

- Process limits (examples — time, temp, pressure, line speed, setup)
- Determine impact of process parameters and process limits on product outputs / specifications
- Determine impact of critical raw material specifications on process and product
- Product capability versus specifications with appropriate sampling plans
- Process capability studies, evaluations for failure modes and worst case conditions
- Software parameters

**Step 3 — Performance Qualification (PQ)**
After completion and approval of the OQ, the third step is Performance Qualification (PQ). In this step, the process is run at the nominal conditions across shifts, time, operators etc. to demonstrate that the process consistently produces product that meets quality and performance specifications under normal operating conditions.

- Running at nominal conditions using typical manufacturing environments
- Running a statistically valid number of lots / batches (across shifts, operators, time etc.)
- Process control and stability: control charts, run charts; determining process capability
- Product performance evaluation (impact of the raw material and process on product functionality); determining product capability
- Deviations from or changes to protocol and resolution
- Conclusion / documentation: Is the process considered validated?

The output from the process validation are the raw material and process parameter settings, tolerances and controls; test methods; quality and acceptance criteria and work instructions for the commercial production of the component or part.

**Process Validation Life Cycle**
The validated process must be monitored, tracked and trended to ensure the process is in control, continues to produce consistent product and any material shifts, drifts and changes are identified, evaluated and resolved. When raw material or process parameters fall outside the tolerances and specifications documented during process validation, the raw material or process is considered to be non-conforming. The root cause of the nonconformance and corrective actions to resolve or eliminate
additional occurrences must be conducted. This is part of the process validation life cycle.

**Case Study**

**The Product Specifications**

A plastic part used in the assembly of a class II device was identified as a very critical / important component of the finished device.

The following specifications were provided by the device manufacturer to the plastic injection molder. The critical design parameters were the dimensions because the component had to fit into a vital assembly of the finished device.

**Dimension A** 3.5 ± 0.05 cm  
**Dimension B** 1.5 ± 0.08 cm  
**Weight** 2.0 ± 0.1 grams  
**Color, delta E** 2

**Process development**

During process development, a polyester resin was chosen and the following process parameters and tolerances were identified:

- **Melt temperature** 225 ± 5 °C  
- **Mold temperature** 100 ± 1.5 °C  
- **Injection pressure** 95 ± 5 MPa  
- **Screw** 70 ± 20 rpm  
- **Resin viscosity** 200 ± 25 Pa·s  
- **Crystallization temperature** 150 ± 0.5 °C

The IQ of the production injection molding machine was conducted.

The OQ was conducted with an approved protocol and statistically valid sampling plans. The OQ confirmed that within the ranges of all the above parameters, and especially the critical parameters (mold temperature and resin crystallization temperature), the resulting part always met the design specifications.

The PQ was conducted at the nominal settings (center points) of the process parameters. Five lots were made in a span of 5 weeks. Testing the parts with appropriate sampling plans, the product met all performance requirements and quality metrics.

Statistical process control was used to monitor and control the process to ensure continued production of consistent high quality product.

**Conclusion**

There is an increased emphasis by the regulatory bodies to ensure medical device manufacturers exert better controls over their suppliers. The extent and level of controls will depend upon where the plastics processor is in the supply chain, and the criticality, complexity and quality requirements of the material or part. It is the responsibility of the medical device manufacturer to communicate with their suppliers and provide them the controls expected and needed.

Controlling the critical process and raw material parameters by validating manufacturing processes ensures that products consistently meet quality metrics and performance specifications. Process validation consists of three qualification steps, installation qualification (IQ), operational qualification (OQ) and performance qualification (PQ).

The benefits of validating the process are:

- Knowing the fundamentals of the product and process
- Producing consistent high quality product
- Proactive process control and minimal testing
- Low scrap
- Less rework
- Increased productivity
- Increased revenues and profitability
- Ability to conduct a quick and efficient root cause analysis

**References**


2. 21 CFR Part 820 Quality System Regulation for Medical Devices

