Directive Agenda
Process Validation

Scope:

This document discusses the validation of processes used in the manufacture and testing of medical devices, pharmaceuticals, and other biotechnology products.

Objective:

To present the concepts of process validation by transforming general concepts into concrete directions and steps that a company can take to continuously improve its effectiveness and performance in this area.

Disclaimer:

This is presented by Atzari Consulting, L.L.C. to its existing and prospective customers as a way to review and assess their current state and use this as a tool to guide their efforts in this area. It is not intended to replace existing guidance for regulatory compliance in this area.

Philosophy and Discussion:

A Master Validation Plan (MVP) is a key document that charters a plant's path towards full process validation. Such a document identifies which processes are to be validated, when these are to be validated, how they are related, and how often they are to be re-validated [Ref. http://www.ghtf.org/sg3/inventorysg3/sg3_fd_n99-10_edition2.pdf, Sec. 5.1]. Validation applies to special processes, which are defined as ones that cannot be verified by subsequent inspection. Validation, however, is the end result of a series of steps that a company has taken to establish a high level of assurance that its processes will consistently provide products that meet predetermined specifications.

Establishing the case for a complete validation begins with demonstrating that the facilities and the equipment are capable of providing what the process demands of them. The next step, in turn, establishes that the process can provide what the product specifications demand of it.

Philosophy and Discussion (continued):

The foundation and all the structural elements must be established before the process is ready to be validated.

By its nature, a manufacturing process is the interaction of various process parameters (for example: time, temperature, pressure and rotation) with equipment, operators, utilities, chemicals and various materials to produce a product or component to certain specifications. The effect that any one factor has on a process often depends on the relative settings of the other parameters and factors. For example, time may not be very important when the temperature is at 200 degrees, but becomes critical at 400 degrees depending on the material that is being processed.

A common approach used by some scientists and engineers is the "trial and error" method of simply trying various combinations of parameters until satisfactory product is made. The limitation of this approach is that the interaction of the various parameters may not be properly understood or mapped and the engineer has not quantitatively established how far the process is from its edge of failure. Establishing a high degree of assurance should be done utilizing a more reliable method.

Another common approach is that of holding all parameters fixed and changing one at a time. The problem here is that the engineer has not mapped how a given parameter changes as other parameters change. For example, one engineer may hold time at 30 seconds duration and try temperatures of 200, 250 and 300 degrees F, drawing certain conclusions about the role of temperature. Another engineer may hold the temperature at 400 degrees F and try cycle times of 30, 60 and 90 seconds duration, arriving at completely different conclusions about a process and/or technology.

Properly mapping a process as part of its development calls for a designed experiment where various levels are planned in a matrix. The results will yield the most reliable process as well as its edge of failure. Validation then becomes the confirmation of these results. The difference is that, with this approach, the engineer will have already established a high level of statistical confidence and knowledge about a process.

Philosophy and Discussion (continued):

There are also economic reasons for using design of experiments (DOE). A DOE will provide a process that produces product near the mean of the specification as well as a relatively low standard deviation. The likelihood of rejects from this process is very low and this has a beneficial effect on material inventories and on the resources necessary to manufacture the product. The most economical time to conduct DOEs is the in the development stage of a process. The most expensive time is after a process is already released to manufacturing. Since a startup company's processes may initially be handled by outside vendors, there is a good window of opportunity to conduct DOEs on critical processes and ensure high manufacturing yields at the onset of in-house operations.

While DOEs will help make processes robust, it must be clearly understood that a process is never better than the equipment, materials and people that comprises it. The qualification of all of these factors is a foundation for a successful validation.

While the Quality System Regulation, 21 CFR Part 820 Section 820.75, provides requirements for validating processes with a high degree of assurance it is up to each manufacturer to establish the specific validation activities and procedures that will provide this level of confidence. Subpart O, Sec. 820.250 on Statistical Techniques also establishes that valid statistical techniques must be used. Utilizing DOEs, as an integral prerequisite for the validation program, is an excellent and proven approach to a successful validation.

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Stages of Development—Hierarchy of Needs:

Startup—Vital Level:

(1)Has your company/plant identified all processes, and classified them as to whether or not they are special processes?
(2)Does your company/plant have a Master Validation Plan (MVP)?
(3)Does your MVP indicate how processes are related to each other?
(4)Does your MVP indicate the schedule for validating each special process?
(5)Does your company's new product introduction process include provisions for process validation?

Operation—Functional Level:

(1)Have you performed IQs on all your process equipment?
(2)Have you performed OQs on your special processes to identify a process window?
(3)Have you performed PQs on your special processes?

Systems Integration—Interactive Level:

(1)Do you use Computer Integrated Manufacturing (CIM?)
(2)Do you collect process data via software and hardware?
(3)If so, has your software been validated?
(4)Will new products be added to your existing special processes?
(5)Do your process validation results provide feedback to your CAPA system?

Future Growth—Developmental Level:

(1)Does your MVP include provisions for new product introduction and new process development?
(2)Does your MVP include provisions for plant expansions?
(3)Does your MVP include provisions for expanded utilities?

Strengths, Weaknesses, Opportunities, and Threats (SWOT):

Strengths / Weaknesses (Internal):

(1)Plant equipment and processes are fairly new and robust
(2)Plant has a history of compliance with existing process validation standards
(3)Plant has a strong preventive maintenance program
(4)Plant itself is fairly new, hence utilities have recently been installed
(5)Utilities have been properly validated, including HVAC, cleanrooms, etc.

Opportunities / Threats (External Opportunities or Challenges):

(1)Your company is being acquired by another company, or is acquiring another company
(2)A major client is coming to audit you
(3)Your new product has just been approved (PMA or 510(k) and your plant will soon be audited
(4)Local codes have required you to upgrade or replace key utilities and/or process equipment
(5)Have your suppliers changed their processes? If so, have they informed you of this? Have they validated changes to their special processes?
(6)Has your marketing forecast increased, causing significant new challenges for your process output?

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Proposed Direction for Improving Process Validation at Your Company:

(Examples)

(1)Establish or update plant-wide Master Validation Plan to existing GHTF standards.
(2)Create a checklist for IQ, OQ, and PQ protocols to ensure compliance.
(3)_____
(4)_____
(5)_____
(6)_____
(7)_____
(8)_____
(9)_____