

Process Validation

FDA's 2011 Guidance

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PDA

Capital Area Chapter

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Process Validation

A User Perspective

- What is PV?
- Why do it?
- What is the consequence of failing to have a “validated process”?
 - ❖ What is a “validated process”?

Background

- 1987 Guidance, based primarily on 211.110
 - ❖ 211.110 was finalized on 29 Sept. 1978, and amended 8 Sept. 2008)
 - “...Such control procedures shall be established to monitor the output and to validate the performance of those manufacturing processes that may be responsible for causing variability in the characteristics of in-process material and the drug product....”

- 2002 Drug Product Quality Initiative started
 - ❖ 2003 “Process Validation” became an internal topic of consultation and review

 - ❖ Draft PAT guidance issued 2003, and finalized 2004
 - PAT guidance was the first guidance breaking the mold in terms of type, language and purpose

Process Validation

- Do I have confidence in my manufacturing process?
 - ❖ Confidence based on science & statistically sound
- How will I know if my process work as intended, and vice-versa?
 - ❖ Before distribution
 - ❖ After distribution
- How do I demonstrate - at any given time-that my process works as intended?

PV & CFR

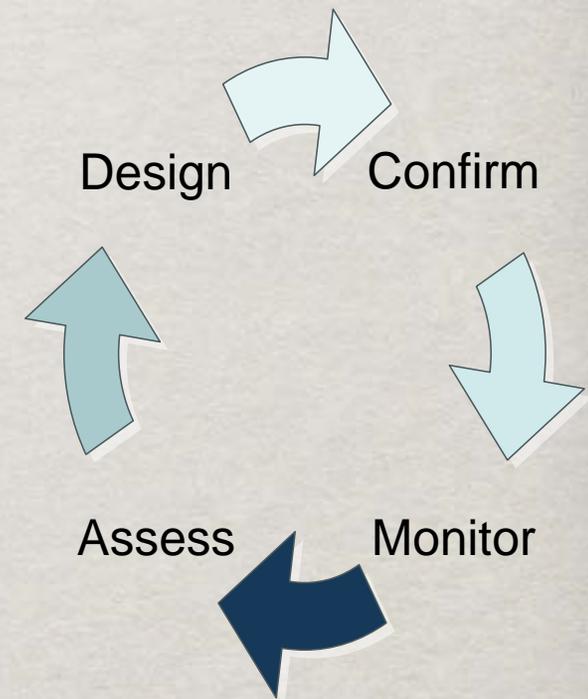
- 211.110(a) [Sampling & testing of in-process materials & drug products]
- 211.110(b)
- 211.165(d) [testing & release for distribution]

- 501(a)(2)(b), and ICH Q7A

- 211.42, 211.63, 211.68, 211.84, 211.113, 211.160(b), 211.165©

Process Validation: A lifecycle

- Stage 1: Process design: Based on development activities, commercial process is designed
- Stage 2: Process Qualification: Process design is evaluated to see if it is capable of reproducible operation.
- Stage 3: Continued Process Verification: Ongoing assurance during production that process is in control.



Lifecycle Approach to Process Validation

- **Process Design:**
 - The commercial process is defined during this phase based on knowledge gained through development and scale-up activities
 - Lab, pilot, small-scale, and commercial scale studies to establish process
- **Process Qualification:**
 - The process design is confirmed as being capable of reproducible commercial manufacturing
 - Facility, utilities, and equipment
 - Confirm commercial process design

Lifecycle Approach to Process Validation

- Continued Process Verification (Commercialization):
 - Ongoing assurance is gained during routine production that the process remains in a state of control
 - Monitor, collect information, assess
 - Maintenance
 - Continuous verification
 - Process improvement

Statistical procedures

211.110(b)

- Valid in-process specifications for such characteristics shall be consistent with drug product final specifications and **shall be derived from previous acceptable process average and process variability estimates where possible and determined by the application of suitable statistical procedures where appropriate.** Examination and testing of samples shall assure that the drug product and in-process material conform to specification.

Statistical Sampling

211.160(b)(3)

- Samples must represent the batch under analysis

211.165(d)

- meet specifications & statistical quality control criteria as condition of approval & release

Recommendation for sampling/monitoring after Stage 2

- *“We recommend continued monitoring and sampling of process parameters and quality attributes at the level established during the process qualification stage until **sufficient data are available to generate significant variability estimates.** These estimates can provide the basis for establishing levels and frequency of routine sampling and monitoring for the particular product and process. Monitoring can then be adjusted to a statistically appropriate and representative level. **Process variability should be periodically assessed and monitoring adjusted accordingly.**”*

Stage 3 - Continued Process Verification

CGMP requirements, specifically, the collection and evaluation of information and data about the performance of the process, **will allow detection of undesired process variability.** Evaluating the performance of the process identifies problems and determines whether action must be taken to correct, anticipate, and prevent problems so that the process remains in control (§ 211.180(e)).

Be aware of the limitations of USP compendial tests!

- Conclusions from sampling and testing are probabilistic.
- Interplay between sample size, process variability, confidence desired and probability.
- The outcome from conducting a single USP test cannot be assumed for all the untested units in the batch.

Validation Activities

- Design the process
 - ❖ Must be fit for the product
 - ❖ If done right, PV can give corporate advantage
 - ❖ Process controls need to be designed here
- Test the design (using sound science, and good engineering practices)
 - ❖ The PPQ protocol is key here
 - Think out of the box
 - Be willing (and able) to defend when inspected
 - Multiple batches may NOT be necessary
 - An assessment of your control strategy

Validation Activities

- Perform the PPQ
 - ❖ Review the results
 - ❖ Should have defined “expectations” in the PPQ document
 - Are expectations met?
- Manufacturing begins
 - ❖ “monitoring’ continues
 - ❖ Controls must be maintained and assessed
 - ❖ “sampling” must be statistically significant
- Without appropriate controls, PV 3rd cycle can be burdensome

PV & PAT

“More advanced strategies, which may involve the use of process analytical technology (PAT), can include timely analysis and control loops to adjust the processing conditions so that the output remains constant.

Manufacturing systems of this type can provide a higher degree of

process control than non-PAT systems. In the case of a strategy using PAT, the approach to process qualification will differ from that used in other process designs. Further information on PAT processes can be found in FDA’s guidance for industry on *PAT — A Framework for Innovative Pharmaceutical Development, Manufacturing, and Quality Assurance.*”

2011 Process Validation Guidance

PV & PAT

- “Systems that promote greater product and process understanding can provide a high assurance of quality on every batch and provide alternative, effective mechanisms to demonstrate validation (per 21 CFR 211.100(a), i.e., production and process controls are designed to ensure quality). In a PAT framework, validation can be demonstrated through continuous quality assurance where a process is continually monitored, evaluated, and adjusted using validated in-process measurements, tests, controls, and process end points.”

FDA’s PAT Guidance, 2004

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