The Transition from Validation to Continuous Verification

Concept Heidelberg
October 2011

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Overview

- Definition of Terms
- The Process of Change
- The Legal requirements

Process Validation (US FDA, 1987)

- Part of the GMP's
- 2 part guidance document
  - "FDA's current thinking"
  - "Not binding on FDA or Industry"
- 1st Part in the same spirit as the 2011 guidance
- 2nd part: Offered and example!

The 1987 Guidance

- "3 consecutive batches"
  - To identify and address variability
    - Make 3 batches with as few as possible variables
  - "Sign off & forget about it"
    - "Blinkers"
- Observed variability
  - Changing the process not an option
    - Regulatory process took too long
  - Send the "observer" for retraining

Undefined Terms

- Sample size
- Statistically significant
- Zero Tolerance
- The role of USP

Undefined or Ignored?

The Process of Change

- 2001-2002: Advisory committee meetings
  - "Current paradigm untenable"
  - Need to change
- 2002: cGMPs for the 21st Century initiative
- 2003: PAT Guidance
  - Guidance drafted in 3 months
  - Process Validation practices challenged
    - Team from OC begins to look at process validation and review of 1987 Guidance
    - Input from the PAT core team

The Process of Change

- Change people to change the practice
- 2008: Common agreement on a new concept for validating a process
  - CDER, OC
  - CDER, OPS
  - ORA
  - CBER, OC & Senior advisor to Center Director
  - CVM

2008: ASTM E2537

Standard Guide for Application of Continuous Quality Verification to Pharmaceutical and Biopharmaceutical Manufacturing

- This guide describes Continuous Quality Verification (CQV) as an approach to process validation where manufacturing process (or supporting utility system) performance is continuously monitored, evaluated and adjusted (as necessary).

The Process of Change

- No change of regulations (CFR or the Act) needed
- Stay true the CFR
  - Validation
  - Statistically significant sampling
  - Continuous improvement

This guidance represents the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the appropriate FDA staff. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

The Law

- US FD&C Act 501(a)(2)(b)
- CFR
  - 211.110(a) [Sampling & testing of in-process materials & drug products]
  - 211.110(b) [Valid in-process specifications … derived from previous acceptable process average and process variability estimates]
  - 211.165(d) [testing & release for distribution]

- ICH Q7A

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

The Foundation of Process Validation

- "…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…."

Which Means…

- What?
- E2537
  - What is it doing?
  - How is it being used?
  - How does it fit in with the FDA Guidance?

Process Validation- 2011

- Finalized February 2011
  - More like the PAT Guidance
  - Process validation is not voluntary
    - But every FDA Guidance is
- Mentions PAT, and ties up with the PAT Guidance
  - Reference in PAT Guidance to PV still valid
- More aligned with CFR, and more parts of the CFR

2011 Process Validation
The fundamental questions

- 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?

Process Validation- 2011

- "Criticality" specifically not addressed
  - A continuum and not binary
- Asks for the "science" to stand up to scientific scrutiny
- Continual Process Improvement during the life time of the process
- Asks for statistical sampling
- Foundation: Process Understanding & Control
- Open to alternative methods/ practices

Process Validation Stages

3 Stages

Stage 1- 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

Stage 2- Process Qualification:

- The process design is confirmed as being capable of reproducible commercial manufacturing
  - Facility, utilities, and equipment
  - Confirm commercial process design

Phase 2 and the PPQ

- PPQ is drafted and approved by QMS
  - Accurate prediction corresponds with sound science and good process understanding
  - PPQ success is the requirement for progressing to next phase: supply for the market
  - How many consecutive batches should one produce?

More Appropriate PPQ Questions

- Is process/ product knowledge reflected in the sampling plans?
- Are the controls based on
  - process understanding
  - Process measurement
  - Appropriate control strategy
- Does it *confirm* confidence in process?

Process Validation- 2011

Stage 3- 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

Which Means…

- What?
- How?
- When?

PV 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

PV 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

And from the Guidance

- *"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."***

Which Means…

- How many samples need to be tested per batch?
- Is there another alternative?
- How is process variability measured?

CFR & 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

Sampling and Statistics
21 CFR 211.165(d)

Acceptance criteria for the sampling and testing conducted by the quality control unit shall be adequate to assure that batches of drug products meet each appropriate specification and appropriate statistical quality control criteria as a condition for their approval and release. **The statistical quality control criteria shall include appropriate acceptance levels and/or appropriate rejection levels.**

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.

Process Validation Guidance

- *"We recommend that a statistician or person with adequate training in statistical process control techniques develop the data collection plan and statistical methods and procedures used in measuring and evaluating* ***process stability and process capability****."*
- *"We recommend that the manufacturer use quantitative, statistical methods whenever appropriate and feasible. Scrutiny of intra-batch as well as inter-batch variation is part of a comprehensive continued process verification program under § 211.180(e)."*

Understand the Process
Study the Process

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)).*

Acknowledgments

- Brian Hasselbalch, OMPQ, CDER, FDA
- Grace McNally, OMPQ, CDER, FDA
- The FDA's Process Validation Review team
- Alex Viehman, OPS-IO, CDER, FDA