US FDA Process Validation Guidance

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The risk based approach to validation must be used to determine:

- What to validate
- When to validate
- How to validate
- How much effort needs to be afforded
The key messages within this document include:

- The lifecycle approach to validation
- Reduce variability
- Continuous improvement
- Alignment with the ICH Tripartite documents
US FDA – data in a validation context

“The collection and evaluation of data, from the process design stage throughout production, which establishes scientific evidence that a process is capable of consistently delivering quality products.”
US FDA Process Validation stages

Stage 1
- Process Design

Stage 2
- Process Qualification

Stage 3
- Continued Process Verification
Stage 1 Process Design

What is it? Define the commercial process

Considerations
• Design of Experiments
• Risk assessments
• Limit of failure testing

Outcomes
The design of a process suitable for routine manufacture that will consistently deliver product that meets its critical quality attributes
Process Design

Building process knowledge and understanding

Mechanisms for capturing knowledge must be formalised

Documentation and Pharmaceutical Quality Systems controls should be in place whether GMP is required or not
Process Design

Establishing a process control strategy

- Identify critical variables from process knowledge and understanding
- Consider process variability and the controls to reduce and/or adjust for this variability
Process Design

Build and capture process knowledge and understanding

- Document the significant variables and the justification

Establish a strategy for process control

- Control mechanisms may include operational limits and in-process monitoring

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<th>Unit operation</th>
<th>Variable</th>
<th>Rationale</th>
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<th>Variable</th>
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Stage 2 Process qualification

**What is it?**
- Verification of the process design phase
- Verification and validation of components within the system

**Considerations**
- Commissioning and Qualification
- Validation as we understand it
- Equipment

**Outcomes**
- Confirmation of the process design as capable of reproducible commercial manufacture
Process Qualification

Design of a facility and qualification of utilities and equipment.

› The design of a facility is critical and is likely to impact every part of the process
Process Qualification

Process Performance Qualification (PPQ)

This combines the facility, utilities, equipment and the trained personnel with the likely commercial manufacturing process, control strategies and components to manufacture commercial batches.

This process is likely to be heavily scrutinised and is a valuable opportunity to gain knowledge.
Process Qualification

- Process performance qualification
  - What monitoring and testing should be sufficient to confirm product quality throughout the batch

PPQ protocol
- Specify the manufacturing parameters and limits
- Consider sampling
- Statistical analysis

PPQ protocol, execution and report
- Consider ‘normal’ manufacturing conditions
- Routine processes and interventions

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<th>Variable</th>
<th>Monitoring</th>
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Stage 3 Continued Process Verification

What is it?
- Ongoing assurance that the process remains in a state of control during routine production

Considerations
- Data collection and evaluation from every batch
- Product quality reviews
- Data trends and statistical analysis

Outcomes
- Continuous improvement
- Knowledge
Continued Process Verification

Continual assurance that the process remains in the validated state (or in control) during routine manufacture

- An ongoing program to collect and analyse product and process data must be established
- Statistical analysis and trending of data
Continued Process Verification

Words of wisdom

“Focussing exclusively on qualification efforts without also understanding the manufacturing process and associated variations may not lead to adequate assurance of quality.”
Continued Process Verification

Sampling and monitoring of data

• Collect and analyse production data to determine process capability and the impact of variables

Assessing and interpreting data

• Identify variability in the process
• Identify process improvements

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<th>Variable</th>
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<tr>
<td>Limits</td>
<td>Alert</td>
<td>Review</td>
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<td>Frequency</td>
<td>Action</td>
<td>Approval</td>
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Sampling

\[ \sqrt{n+1} \]

\[ \sqrt{35+1} = 6 \]
Sampling

First 6
Sampling

Random 6
Sampling

Stratified
Sampling

Systematic
Sampling

Targeted

First

Last
Sampling

Knowledge / Risk
Key trending principles

- Ensure data is collected and analysed according to a pre-determined plan.
- Provide evidence of process control and product characteristics.
- Ensure suppliers raw material manufacturing processes are in control.
Production data and trending

Trending production data provides assurance that the process is in control and allows the identification of Out of Trends (OOT).
Definitions

- **Acceptance criteria**: Conditions a product needs to meet
- **Alarm limit**: Established criteria requiring immediate action
- **Alert limit**: Statistically established criteria that provide an early warning of potential drift
Responsibilities

The area manager or delegate would typically be responsible for:

- Gathering data
- Trending data
- Assessing data

The information gained would drive continuous improvement.
**Trending**

Analysing process trends can:

- Discover the underlying root cause of an issue.
- Determine areas of improvement.
- Prevent a problem from occurring.
Trending

Trending may be performed on the following type of results:

- QC batch release test results
- Incoming raw material properties
- In-process test results
- Supplier batch release data
Statistics – Normal distribution

-3σ  -2σ  -1σ  μ  1σ  2σ  3σ

68%
95%
99.7%
PPQ – Process in control?

Need to evaluate overall process variation over time
More realistic

Variance Components Model

Intra=Within batch: $\sigma_w$  Inter=Between batch: $\sigma_b$
Special Cause Variation

Process not in Statistical Control - Special Cause Variation
Process Capacity/Performance Statistic Ppk

Measures process capability of meeting the specifications

\[ P_{pk} = \text{Min} \left[ \frac{USL - \bar{x} - LSL}{3\sigma_{LT}}, \frac{\bar{x} - LSL}{3\sigma_{LT}} \right] \]

\( \sigma_{LT} \) is long-term sd, usual formula, includes variation over time; Cpk uses short-term estimate of sd
Control charts

- Control charts are used in the application of statistical process control (SPC).
- Can be created using Excel, Minitab or other software systems.
- The control chart provides an ‘alert’ if there are undesired changes in a process.
Common vs special causes of variation

• Understanding the difference between common and special cause variation is critical to interpreting a control chart.
• Knowing the difference will help understand when corrective or preventive actions are required.
• Process control can only be achieved by controlling the key inputs to a process.
Common vs special causes of variation

- We use control charts to determine the difference between common cause and special cause variation.

Common cause variation
- Inherent to the process
- Present all the time

Special cause variation
- Change that occurs because something different or unusual occurred in the process
Control charts

An "in control" process will exceed $3\sigma$ limits (Shewhart Limits) only $3$ times in $1000$ and $2\sigma$ limits $46$ times in $1000$!
Control chart rule 1

- One or more points beyond the upper or lower control limit(s).
Control chart rule 2

- 9 consecutive points in Zone C or beyond (on one side of the mean).
Control chart rule 3

- 6 consecutive points steadily increasing or decreasing.
Control chart rule 4

- 14 consecutive points alternating up and down.
Control chart rule 5

- Two out of three points in Zone A or beyond.
Control chart rule 6

• Four out of five successive points on the same side of centre line and in Zone B or beyond.
Control chart rule 7

- 15 consecutive points in Zone C on either side of centre line.
Control chart rule 8

- 8 points in a row on either side of the centre line with none in Zone C.
Examples of assignable causes of variation

- Human error
- Editing or tampering with data
- Incorrect test or inspection
- Faulty raw materials
- Equipment breakdown or malfunction

- Wrong test method or equipment used
- Change in method, procedure or operator
- Power failure
- Solutions made incorrectly
- Using expired materials
What to look for......

- Alerts and actions not included in the trending of results
- Laboratories not following internal trending SOPs (6.7, 6.9)
- Process trends not periodically reviewed (1.4)
- Out of specification or atypical trends not investigated thoroughly (6.32)
It is common to see in industry that data is collected and not used effectively.

Remember these 3 rules:

- **Rule 1**
  - No measurement without recording

- **Rule 2**
  - No recording without analysis

- **Rule 3**
  - No analysis without action

If we are not prepared to take action then why do we take the measurements?
Stage 1 – **Process Design**: The commercial manufacturing process is defined during this stage based on knowledge gained through development and scale-up activities.

Stage 2 – **Process Qualification**: During this stage, the process design is evaluated to determine if the process is capable of reproducible commercial manufacturing.

Stage 3 – **Continued Process Verification**: Ongoing assurance is gained during routine production that the process remains in a state of control.

**Identify source of Variability**

**Control of Variability**

**Statistics**

The terms IQ, OQ and PQ are not directly referenced in the US FDA Guidance document but if appropriate remain relevant

- Manufacturers can determine the terminology however the deliverables of the validation effort are clear
US FDA

Concurrent and Retrospective validation

• Least preferred mechanisms

Advantages may include experience with a process and Quality Management Systems data

Disadvantages may include inadequate risk analysis and ‘blinkered vision’
Summary

- Identify the sources of variability
- Use a risk based methodology to establish a control strategy
- Implement mechanisms to monitor the ongoing performance of the product and the process
Assessment

- Open book assessment
- 10 minutes
- Hand in Assessment and Feedback form.

Thank-you!
Thank you for your time.
Questions?

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