Current Trends in Process Validation: the New Paradigm

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Agenda

- Historical Basis for Validation
- Review of key points in FDA new Process Validation Guidance
- Use of Statistical Tools for Validation throughout the Product Life Cycle
Where we started

- The basis of Process validation in FDA GMP terminology started in the 1970’s with sterility assurance.
  - The need for validation is based on the inability to test enough samples to provide adequate assurance of quality when destructive testing is required (i.e. Sterility Testing).
  - The requirement for sterility is less than one failure per 1,000,000 units ($SAL = 10^6$).
Where we went from there

- FDA and industry applied the same validation principles to processes other than sterilization, such as blending and granulation.
- The reasoning is the same; quality cannot be tested into the product or assured by end product testing alone.
Historical Validation Principles

- The original concept was based on an assumption that extensive product and process testing on a limited number of batches would be sufficient to assure quality of future batches.
- Thus the development of validation as an exercise on three batches.
Where we all went astray

- Process validation in the pharmaceutical industry has evolved into an exercise in documentation, with little thought given to the scientific rationale for the exercise.

- Process validation as conducted in many firms does not add substantially to the assurance of quality that we all seek.
Current Trends

- FDA and some firms have addressed the situation with a new approach to Process Validation.
- New FDA Guidance was issued in November, 2008 with a totally different approach to Process Validation.
- The new Guidance is based on scientific principles and adopts some best practices from the industry today.
Process Validation

New FDA Definition:

- The collection and evaluation of data, from the process design stage throughout production, which establishes scientific evidence that the process is capable of consistently delivering quality products.
What’s New

- Life Cycle Approach to Process Validation instead of a single “3 batch” exercise
  - The definition is expanded to include the full life cycle of a product from development to production
- The words “documented evidence” are replaced by “scientific evidence” in the definition
What stays the same

- The requirement to demonstrate consistency
- The requirement to assure conformance to specifications or quality attributes
Product Life Cycle Stages

- Stage 1: Process design: Development and scale-up activities leading to a commercial process
- Stage 2: Process qualification: Verification that the design is capable of reproducible commercial scale manufacturing
- Stage 3: Continued Process Verification: Ongoing assurance during routine production through monitoring and evaluation of data
Process Validation

- What does this really mean?
  - Quality, safety and efficacy are designed or built into the product
  - Each step of the manufacturing process is controlled to assure that the finished product meets all design characteristics and quality attributes including specifications
  - Continuous verification of process performance throughout the Life Cycle of the process
Process Validation

- Process validation should predict future success:
  - “Before any batch from the process is commercially distributed for use by consumers, a manufacturer should have gained a high degree of assurance in the performance of the manufacturing process such that it will consistently produce APIs and drug products meeting those attributes relating to identity, strength, quality, purity and potency.”
Process Validation

- How do we define a high degree of assurance in measurable terms?
  - Process must be well-defined
  - Process must be stable and reproducible every time
    - Variation is understood and controlled to acceptable limits
  - Product must meet the specification limits and quality attributes consistently
Process Qualification

- This term roughly replaces the both the previous terms:
  - Equipment and facility qualification
  - Process validation

- The term “process validation” as we know it has been replaced by “performance qualification”

- The requirement to complete this stage prior to commercial distribution of a product remains in place
Continued Process Verification

- This requirement is essentially new in the 2008 Guidance, however, it refers back to 211.180 (e)
  - “Written records required by this part shall be maintained so that the data therein can be used for evaluating, at least annually, the quality standards of each drug product to determine the need for changes in drug product specifications or manufacturing control procedures.”
Continued Process Verification

- “at least annually” has been replaced by “continually”
- The guidance also strongly recommends statistical methods of evaluation
- The requirement also links to change control
Continued Process Verification

- Does it make sense to evaluate a high volume product that you produce every day only once per year?
  - That’s what many companies do today
- Annual product reviews are frequently only another documentation exercise and not used for their intended purpose
- Companies typically only react to failure and conduct an investigation only when the product fails
  - Isn’t that too late?
Applying Statistical Tools to Validation

- We will look at the scientific and practical aspects of process validation
- We will apply common statistical tools
- We will focus on critical to product quality aspects of validation
- We will look at maintaining a validated process once it is established
Applying Statistical Tools to Validation

- Apply specific statistical and practical tools for achieving a scientifically sound process validation approach
  - One that consistently and reproducibly delivers acceptable quality product to our customers
  - Also meets regulatory requirements
Tools

- Process Mapping or Flow-Charting
- Risk Analysis
- Statistical Process Control Charting
  - Common cause and Special Cause Variation
- Process Capability Analysis
Process Design and Scale-up

- The prerequisites to validation begin with developing a body of knowledge about the process and product
  - What is the process?
  - What are the acceptable operating ranges?
  - What variables are critical to success?
  - How do we measure and control these during the process?
Process Design and Scale-up

- There is no value in beginning Process Qualification (Stage 2) if we do not understand and believe that we are in control of the process.

- How many examples can you think of where we learned something critical about the process while making the process validation batches?

- Where we learned something critical about the process after validation?
How do we gain this knowledge?

- Development and scale-up studies
- Engineering batches
- Literature about the technology
- Experience with this product or similar products
- Risk analysis or other tools to link the critical process parameters to the output
- Design of experiments to gain the most valuable information from the development studies
What is a Process?

- A process is a step-wise series of activities that converts inputs into outputs

- Example:
  - Converts raw materials into finished product delivered to the customer
Flow Charting the Process

- Flow charting is a good way to visualize the process for understanding of all the steps, and to later identify those critical to quality
Simple Process Flow Chart

- Weighing
- Mixing
- Granulation
- Tablet Compression
- Packaging
Expanded Flow Chart: Weighing Raw Materials

- Who are the suppliers?
- Are the suppliers qualified?
- How long can I store the raw materials under these conditions without impacting quality?
- How are the raw materials stored?
- Weighing raw materials
- What are the critical attributes of the raw materials?
- What are the specifications and test methods for the raw materials?
- Are the test methods validated for this laboratory?
- How are the raw materials sampled? Is this a representative sample?
Raw Materials

- How often have you seen problems with raw materials cause failures in the finished drug product?

- Do we adequately consider these potential problems during process development and process qualification?
Complete flow charts

- A good flow chart includes all the steps in the process from beginning to end including sampling and testing, in-process controls, decision points, storage and shipping.
- Helps identify missing information in your development and scale-up data.
Risk Analysis

- Evaluate the potential impact of variations in the process steps to the outcome
  - What is the degree of impact?
    - High, Medium, Low
  - What is the probability that it will occur?
  - What is the probability that it will be detected before it is too late?
Questions to ask during Risk Analysis

- What will happen if this variable is not controlled? (Impact)
- How do we control this variable? (Process controls)
- How do we measure and detect variation in it? (tests, in-process controls, process measurements)
- How do we detect and measure the output affected by this variable?
Example

- We will consider two similar products using the three criteria that I showed earlier:
  - Impact
  - Probability of occurrence
  - Probability of detection
Product A

- Product A is an aseptically filled vial with a sterile-filtered aqueous product
  - Impact of failure of aseptic processing: HIGH
  - Probability of occurrence: HIGH (approximately $10^{-3}$)
  - Probability of detection: LOW
  - Risk: Extremely High
- Product A will require extensive Performance Qualification and on-going verification of numerous process parameters to maintain acceptable assurance of sterility
Product B

Product B is the same product as A, but it is terminally sterilized

- Impact of failure of sterilization: HIGH
- Probability of occurrence: LOW (typically < 10\(^{-6}\))
- Probability of detection:
  - Detecting a sterility failure: LOW
  - Detecting a process failure: HIGH

On-going Performance Qualification and Verification: Focus on Process Controls and Monitoring to maintain the probability of failure to extremely low level (less than 10\(^{-6}\)) and maintain probability of detection of a process failure at a high level.
Product C

- Product C is a direct compression tablet of 100mg size with 75 mg of active ingredient used for minor pain relief (i.e. acetaminophen)
  - Impact of blend non-homogeneity (mixing failure): LOW
  - Probability of Failure: LOW
  - Probability of detection of non-homogeneity: MEDIUM
  - While blend uniformity has to be confirmed during process qualification and checked with content uniformity test on every batch, we would not apply extraordinary measures to this quality attribute
Product D

- Product D is a direct compression tablet of 100mg with 1 mg of active ingredient per tablet and is used to control blood clotting
  - Impact of blend failure: HIGH
  - Probability of occurrence: HIGH
  - Probability of detection: MEDIUM
  - Control Measures: Blending process should be tightly controlled and monitored to assure that no uniformity failures occur. This is a candidate for PAT.
Risk Analysis Outcome

- Are all risks adequately controlled by the process controls in place?
  - Do we need more information from Development studies?
  - Do we need to make changes to improve the controls?
  - For those that are critical to product quality and which are difficult to measure or control during the process, we include more testing during process development and performance qualification.
Risk Analysis

- At the end of flow charting and risk analysis we will:
  - Identify the critical process steps, parameters and ranges
  - Identify the means to measure and control them
  - Identify the critical control points for qualification and on-going verification
Risk Analysis

- The input into understanding and assessing the status of development is a multi-disciplinary exercise using the expertise of experts in many fields.
Successful Validation Program

- Depends upon information and knowledge from product and process development.
- Focusing on qualification efforts without understanding the manufacturing process may not lead to adequate assurance of quality.
Process control

- Understanding of process variability is critical to successful process control
- Understanding the causes and corrective actions for variability are critical to improving the process
In Control of the Process

- What does this mean?
  - Understand sources of variation
  - Detect the presence and degree of variation
  - Understand the impact of variation on the process and ultimately the product attributes
  - Control the variation in a manner commensurate with the risk it represents to the process and product

- Control of variation = control of the process
Sources of variability

- **From a GMP perspective:**
  - Is the equipment qualified?
  - Is the equipment properly maintained?
  - Are the measuring devices calibrated?
  - Are the test methods validated?
  - Do we have detailed procedures describing the work?
  - Are the personnel trained in those procedures?
  - Are the raw material suppliers qualified?
Intra batch and inter batch variability

- **Intra batch variability**
  - For example: blend homogeneity, content uniformity of tablets

- **Inter batch variability**
  - Variability in either the mean of data or the standard deviation of data between batches
  - For example, variation due to raw material changes
Measuring and Evaluating Variability

- Use data and statistics to define the process and product attributes
  - Quantitative Measurements
  - Trending
  - Continuous Data Collection and Evaluation
  - Use of statistical tools for analysis
    - Statistical Process Control
    - Cpk
Normal Distribution

- Most processes follow the statistical model of a normal distribution
- Defined by the mean and standard deviation
- The “bell-shaped curve”
Any process with controlled inputs and which produces many outputs over time will produce a distribution of the outputs.

Those outputs will tend to distribute in a specific pattern based on the inputs.

Examples:
- Tablets off a compression machine
- Bottles off a filling line
- Samples of the same product analyzed multiple times by the same analytical system (system suitability)
Only processes which exhibit a typical normal distribution can be analyzed using the statistics discussed in the next section.

You need some information and data upfront to determine which tools are appropriate to use.

Normal distributions are defined by a mean and standard deviation.
Normal Distributions

- The measurement system must be accurate and reproducible, and the variability associated with the measurement is part of the overall variability.
- Know what this is.
- Start with accurate measurements:
  - Sampling is part of the measurement process.
  - Testing is also part of the measurement process.
Normal Distributions

- A minimum of 25 data points are desirable, 50 to 100 ideal
- It is also useful to know where the sources of variability are likely and control these as much as possible before taking measurements
- Calculate mean and standard deviation for your data
Histograms

- Histograms are a way to plot data to visualize the normal distribution pattern
- Major deviations from normal will be obvious
- It is necessary to start with a normal distribution before proceeding to other statistical tools
Non-normal distributions

- The following data often do not yield a normal distribution so be careful when evaluating these:
  - Microbiological contamination
  - Impurities data (boundary=0)
  - Particle size distributions (often tail on one side)
Statistical Process Control Charts

- SPC charts are trend charts with statistical limits applied as control limits to evaluate processes over time
- One chart trends means and a second chart trends variability
- Control limits are derived from the standard deviation of the data
SPC Charts

- SPC charts are used to evaluate the performance of a process over multiple data points and to identify non-normal patterns in the data that indicate a change in the process.

- In process control, we will use SPC charts to demonstrate stability of the process by trending variability.

- Control limits are not related to the specification limits.
Common Cause: The inherent variability of a process

Special Cause: A specific event changes the either the mean and/or the variability in the process resulting in non-normal patterns in the data
Special cause patterns

- **Examples:**
  - Any point outside the control limits
  - 7 consecutive points on one side of the mean
  - 5 or 6 points going in the same direction

- **Non-normal patterns indicate that something in the process has changed**
  - Find out what and fix it!
How to Calculate an Mean Chart

- Use Process Data with a minimum of 25 points
- Calculate the mean and standard deviation of the data
- The Lower Control Limit (LCL) = Mean – 3 STD
- The Upper Control Limit (UCL) = Mean + 3 STD
- Graph process data sequentially along with the mean, UCL and LCL lines

1 If each datapoint is an average, then calculate the average and STD of the averages
Example Mean Chart
How to calculate range chart

- Range charts can be used when you have multiple measurements for the same data point, for example, content uniformity and dissolution data, tablet compression data.

- The range chart works the same as the mean chart but you will calculate the max-min value for each point and the mean and standard deviation of the ranges between the min and max.
Example Content Uniformity

Range Chart CU

Sample #
Difference % LC
Difference
mean
UCL
LCL

Sample #
Range and Mean Charts

- If you are using a parameter with means and ranges, calculate the range chart first.
- The ranges must be in statistical control before you start the mean chart.
- Use the mean of the points from each sample for the value, and calculate the mean of the averages.
- The combination of the range and mean charts corresponds to intra and inter-batch variability.
Guidelines for Charting

- Data used to establish the baseline control chart and to calculate the LCL and UCL should follow a normal distribution with no obvious non-normal trends or data points.

- Use a minimum of 25 data points for good statistics.
Where does fit with validation?

- Use charting if possible on data collected prior to PQ to determine if the process is stable.
- Use charting during PQ batches to verify that the process is stable.
- A stable process is one that does not have any special cause variation.
Where does fit with validation?

- **On-going process verification**
  - Continue to monitor the process during production to detect unexpected changes
  - Use SPC as a tool during investigations
SPC and Validation

- SPC charts help you understand whether a process is stable and reproducible, and can help predict future success (or failure)
- SPC charts help to interpret the causes of variation and where they occur to aid in the investigation and corrective actions
SPC and Performance Qualification

How do you make SPC Charts on a limited number of batches?

- Take samples at more frequent intervals
- Compare qualification data with previous charts if available
- Continue charting after process qualification to collect more data and see if the process remains the same
Special causes

- If special causes are present before process qualification, correct these before starting.
- What will it mean if special causes are present during the PQ batches?
- Another word for special cause is DEVIATION.
Process Capability

- Process capability is a comparison of the normal distribution curve to the specification limits.
- $C_p =$ Two sided calculations, assumes the mean is centered.
- $C_{pk} =$ One sided calculation, mean is not centered.
Process Capability

- The range of ±3 standard deviations of the data may be larger or smaller than the range of the specification limits
- The mean may be centered or skewed
How to Calculate

\[
C_p = \frac{\text{High Spec limit} - \text{Low Spec Limit}}{6 \text{ STD}}
\]

\[
C_{pk} = \frac{\text{Mean of the data} - \text{Lower Spec Limit}}{3 \text{ STD}}
\]

Or

\[
C_{pk} = \frac{\text{Upper Spec Limit} - \text{Mean of the data}}{3 \text{ STD}}
\]
What does this mean?

- Cpk > 1 means that there is only a small probability that a data point will be outside the specification limits if the process does not change.

- Cpk < 1 means that the probability exists that a data point will be outside the specification limits even if there is no change in the process.
## Probability of Failure

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<tr>
<td>2.0</td>
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</table>
Process Capability

Equals:

- Scientific evidence that provides a high degree of assurance that a process will consistently deliver quality product meeting its specifications
- Looks at both the mean and variability of the process to achieve this goal
Process Capability

- A process that is capable will be:
  - Centered on the desired mean
  - Capable of operating consistently within the specification limits
  - Follows the normal distribution pattern and be free of uncontrolled sources of variation

- Process Capability = Scientific evidence = Validation
Process Capability vs SPC

- Process capability calculations compare the process data to the specification limits.
- SPC charts are independent of the specifications and measure the actual performance of the process over time and multiple measurements.
Sampling Issues

- More samples will give you a more reliable prediction of future results
- However errors can occur
  - More samples within one batch or more batches?
    - What is needed?
  - Depends on the sources of variability: intra-batch vs inter-batch variability
Sampling Issues

- Sample Bias
  - Are the samples representative of the batch?
  - The ideal situation is true random samples, but we rarely do this
  - Are beginning, middle and end samples random?
  - Are top, middle, and bottom samples random?
  - Does the sampling technique cause error?
Testing Issues

- Analytical variation
  - This will be component of the total variation that you see
Sampling and Testing Issues

- The conclusions that you base on your data are only as reliable as your measurements.
- Inaccurate measurements can lead to very inaccurate conclusions.
Summary of Key Points

- Use of Statistical tools can be really valuable in scientifically evaluating data
- Use of simple statistics can put real numbers behind “high degree assurance of quality”
- Statistical tools are valuable in conducting failure investigations and determining the root cause
  - Or can be even more valuable in preventing the failure from happening