

# Pharmaceutical Quality System (ICH Q10) Conference

*A Practical Approach to Effective Lifecycle Implementation  
of Systems and Processes for Pharmaceutical Manufacturing*

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*Welcome*

# State of Control Over the Lifecycle and Process Validation (New and Legacy Products)

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# Agenda

- ICH Q10, FDA & EU
  - State of Control and Process Performance and Product Quality Monitoring (PP&PQM) and Process Validation
- Focus on Variation
- CGMP Regulations and PV Guidance recommendations link to ICH Q10
- Milestones and Transitions in the PV Lifecycle
- Verifying Continuing State Of Control
- Data Analysis and Statistical Tools for PP&PQM

# PQS: Three Main Objectives

- A modern PQS assures quality over the drug lifecycle
  1. Achieve *product realization*, e.g., by effective knowledge transfer from development to commercial production
  2. Establish and maintain a *State of Control*
  3. Facilitate *Continual Improvement*

## ICH Q10, State of Control:

A condition in which the set of controls consistently provides assurance of continued process performance and product quality.

FDA Guidance For Industry; Process Validation: General Principles and Practices

**Process Validation:**  
collection and evaluation of data, from the process design phase throughout production, which establishes scientific evidence that a process is capable of consistently delivering quality products.

EU Guide to GMP, Annex 15:

**Process Validation:**  
Documented evidence that the process, operated within established parameters, can perform effectively and reproducibly to produce a medicinal product meeting its predetermined specifications and quality attributes.

# ICH Q10

## *Establish and Maintain a **State of Control** (1.5.2)*

To develop and use effective monitoring and control systems for process performance and product quality, thereby providing assurance of continued suitability and capability of processes.

## *Facilitate Continual Improvement (1.5.3)*

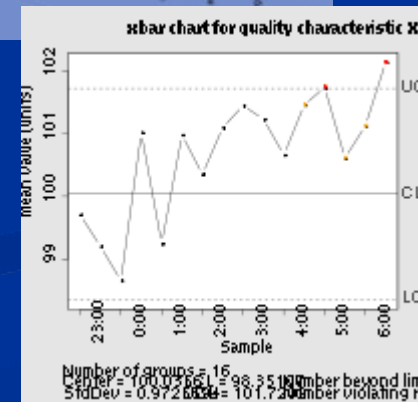
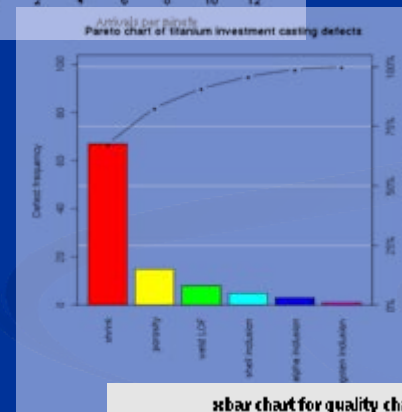
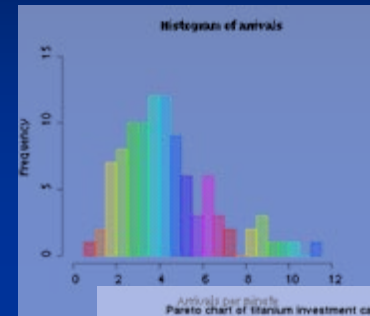
To identify and implement appropriate product quality improvements, process improvements, variability reduction, innovations, and pharmaceutical quality system enhancements, thereby increasing the ability to fulfill a pharmaceutical manufacturer's own quality needs consistently. Quality risk management can be useful for identifying and prioritizing areas for continual improvement.

# ICH Q10, Section 3.2.1, PP&PQM

- (b) Provide the tools for measurement and analysis of parameters and attributes identified in the control strategy (e.g., data management and statistical tools).
  - *Tool don't work themselves! Need personnel credentialed and qualified to apply statistics to manufacturing data. Qualified to choose the tools appropriate for the analysis, i.e., the question being asked.*
  
- (c) Analyze parameters and attributes identified in the control strategy to verify continued operation within a state of control.
  - *Trending activities.*

# Some examples of statistical tools

- From ICH Q9:
    - Design of experiments (DOE)
    - Histograms
    - Pareto charts
    - Control charts
  - Process capability analysis
- There are many other tools available.





# What about Standards?

Footnote in the FDA PV Guidance:

Some references that may be useful include the following:

ASTM E2281-03 “Standard Practice for Process and Measurement Capability Indices”

ASTM E2500-07 “Standard Guide for Specification, Design, and Verification of Pharmaceutical and Biopharmaceutical Manufacturing Systems and Equipment,” and

ASTM E2709-09 “Standard Practice for Demonstrating Capability to Comply with a Lot Acceptance Procedure.”

This is not a complete list of all useful references on this topic. Many industry standards, books, and guides on these topics are available.

# ICH Q10, Section 3.2.1, PP&PQM

- (d) Identify sources of variation affecting process performance and product quality for potential continual improvement activities to reduce or control variation.
  - *Does this refer to common cause variability or special cause variability? Both! Need to know your common cause variability. May want to reduce it. Also need to be able to detect special cause and then correct it."*
  
- (e) Include feedback on product quality from both internal and external sources (e.g., complaints, product rejections, nonconformances, recalls, deviations, audits and regulatory inspections, and findings).
  - *Very valuable and a required practice but not proactive. It's too late to increase the product's quality at this point!*

# Annex 15 (2001) under Prospective Validation

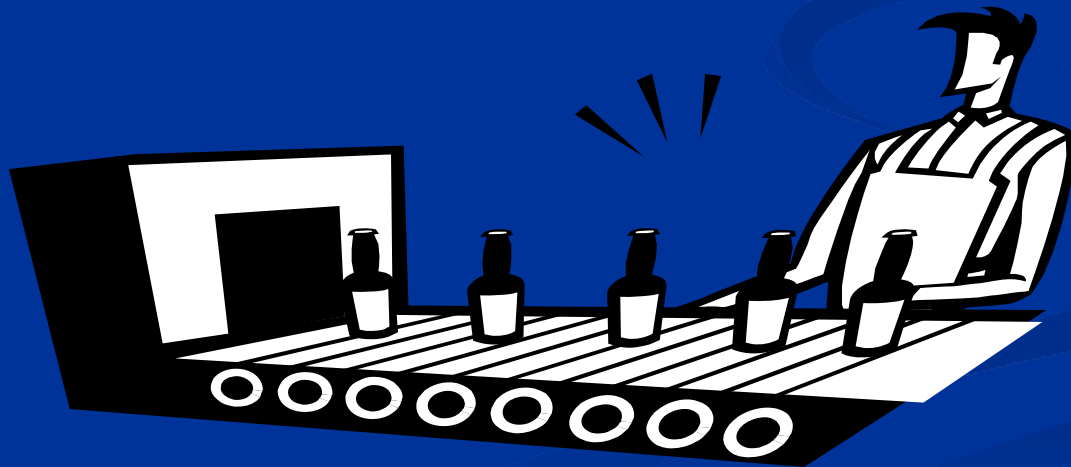
“Using this defined process (including specified components) a series of batches of the final product may be produced under routine conditions. In theory the number of process runs carried out and observations made should be sufficient to allow the normal extent of variation and trends to be established and to provide sufficient data for evaluation.

# Sources of Input Variability

How can these factors impact the output variability?

- Materials (APIs, Excipients, Process aids)
- Equipment
- Measurement Systems
- Procedures/Master Records
- Environment
- Operators

Analyze process performance and control batch-to-batch variability!



# Opportunities for Variability Reduction and Innovation

“Implement appropriate product quality improvements, process improvements, variability reduction, innovations and pharmaceutical quality system enhancements”

[ICH Q10 ]

*Intellectual growth should commence at birth and cease only at death. Albert Einstein*

# FDA PV Guidance

“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 21 CFR§ 211.180(e).”

# FDA CGMPS on process control, variability and performance

## Section 211.110(a)

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”

## Section 211.110(b)

requires that in-process specifications “. . . 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.”



# FDA CGMPS on periodic evaluation and change

Firm must evaluate, at least annually, the quality standards of each drug product to determine the need for changes in drug product specifications or manufacturing or control procedures.  
(211.180(e))

*Why change specifications?*

*Why change a manufacturing procedure?*

*Why change a control procedure?*

*Some times to increase process efficiency.*

*Some times to correct a design flaw/problem that was not revealed during design and process qualification.*

*Overall, to maintain a state of control based on new knowledge and increasing process understanding!*

# Milestones and Transitions

- Application or MA is approved - A Major Milestone!!
  - May or may not include the initial demonstration of the process at commercial scale. Depends on the type of drug, type of process (e.g. is it considered a special or non-standard process?), and review policies/guidance from the particular regulator.
  - Recognize that while a significant milestone has been reached, the job is not done. Weave this philosophy through PQS fabric
- A basis to begin commercial distribution of product
  - Before commercial distribution, Initial commercial process evaluation
  - Recognition that initial commercial production provide first picture of process control to which more understanding and knowledge will be added.

# Milestones and Transitions

- Transition from Stage 2 to Stage 3 (FDA PV Guidance)

analogous to

Tech Transfer to Commercial Production (ICH Q10)

- Seek to understand and measure commercial process inherent variability; its natural behavior when in control and not acted upon by any special causes.
- **Necessary to establish process control limits.**
- Be circumspect, realistic and open-minded
- Move from uncertainty and estimates to certainty and knowledge over time.

?

Assumptions

Estimates

Uncertainty

?

# FDA PV Guidance

## Heightened 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.**”*

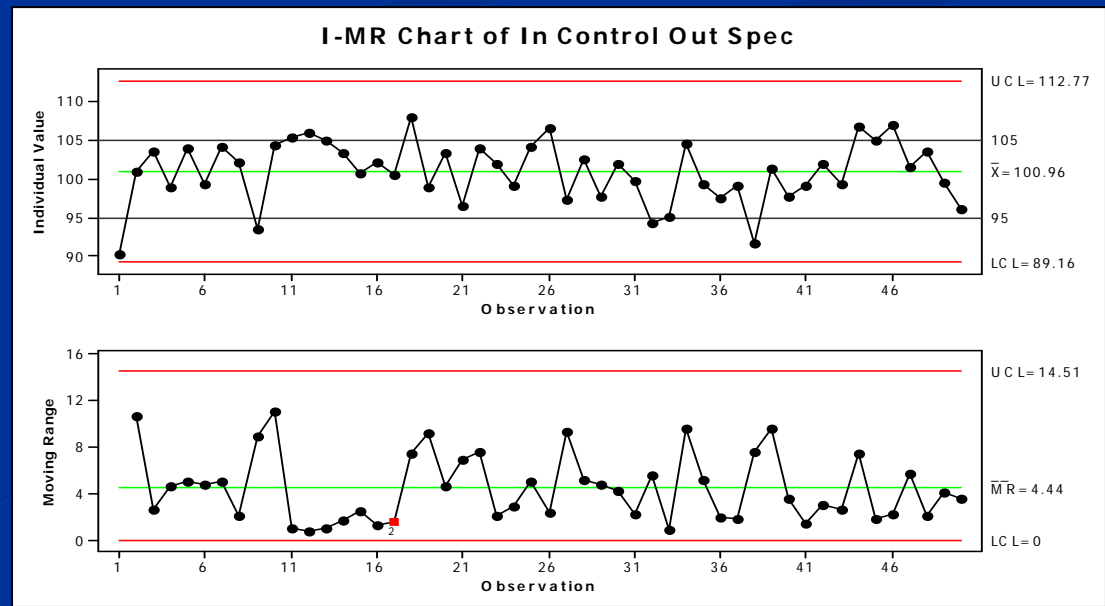
# FDA PV Guidance

## Heightened sampling/ monitoring after Stage 2

- Purpose of the recommendation?
  - To establish the appropriate levels and frequency of routine sampling and monitoring for that particular product and process.
  - Stepped down approach to monitoring, particularly for new processes, or significantly changed processes, for which there is little previous comparable experience.

# Statistical Control Charts

- *Statistical control charts are used to monitor a process for statistical control and are time plots with control limits added.*
- *Control limits are an estimate of the natural variability of the process. Control limits are not specifications limits.*



# CPV? CQV?

## Continued? Continuous?

### What does it all mean?

- Continuous Process Verification: An alternative approach to process validation in which manufacturing process performance is continuously monitored and evaluated ([ICH Q8 –Glossary](#)).
- Continued Process Verification – Third stage process validation lifecycle after design and qualification. The goal is to continually assure that the process remains in a state of control (the validated state) during commercial manufacture. ([FDA Guidance on Process Validation](#))
- 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) ([ASTM E2537](#)).



# Process Performance & Product Quality Monitoring

- Where do you start?
  - What defines product quality?
  - How are specifications set for raw materials, In- process, and finished product
- More Questions
  - What defines process performance?
  - How are sources of variation identified, monitored, and controlled?
  - What are the measurement tools?
  - What analysis is being done?
  - Can inferences be made about untested units? With what confidence level?
  - Is there a feedback mechanism?
- Use answers to determine best data collection methods and data analysis tools.

## “It met specifications”

- 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.

# USP 33–NF 28 Reissue General Notices

- At times, compendial standards take on the character of statistical procedures, with multiple units involved and perhaps a sequential procedural design to allow the user to determine that the tested article meets or does not meet the standard. **The similarity to statistical procedures may seem to suggest an intent to make inference to some larger group of units, but in all cases, statements about whether the compendial standard is met apply only to the units tested.**
- Repeats, replicates, statistical rejection of outliers, or extrapolations of results to larger populations, as well as the necessity and appropriate frequency of batch testing, are neither specified nor proscribed by the compendia. First-party (manufacturer), second-party (buyer), or third-party (regulator) compliance testing may or may not require examination of additional specimens, in accordance with predetermined guidelines or sampling strategies

# Specifications and Batch Release

FDA GMPS

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.

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