Process Validation
A Lifecycle Approach

Grace E. McNally
Senior Policy Advisor
U.S. Food and Drug Administration
Center for Drug Evaluation and Research
Office of Compliance
Division of Manufacturing and Product Quality

Agenda

1. CGMPs and Process Validation (PV) for drug manufacturing
2. Lifecycle approach: Stage 1 (Process Design), Stage 2 (Process Qualification) and Stage 3 (Continued Process Verification)
3. Comments to the 2008 Draft

Guidance for Industry
Process Validation: General Principles and Practices

1. Further the goals of the CGMPs for the 21st Century Initiative such as advancing science and technological innovation.

2. Update Guidance based on regulatory experience since 1987.
   - Emphasis on process design elements and maintaining process control during commercialization
   - Communicate that PV is an ongoing program and align process validation activities with product lifecycle
   - Emphasize the role of objective measures and statistical tools and analyses.
   - Emphasize knowledge, detection, and control of variability.

Lifecycle approach is more rational, scientific and can improve control and assurance of quality.

Key CGMPs for Process Validaton

211.100(a)

211.42

211.160(b)

211.110(a)

211.63

211.165(c)

211.110(b)

211.68

211.165(d)

211.84

211.180(e)

Regulatory Requirements for Process Validation

- § 211.100(a), "there shall be written procedures for **production and process control designed to assure** that the drug products have the identity, strength, quality, and purity they purport or are represented to possess..."

- Requires manufacturers to design a process, including operations and controls, which results in a product meeting these attributes.

Regulatory Requirements for Process Validation

- § 211.110(a), *Sampling and testing of in-process materials and drug products*, requires that control procedures ". . . 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"**

- Even well-designed processes must include in-process control procedures to assure final product quality.

Regulatory Requirements for Process Validation

- Establishing in-process specifications
- Section 211.110(b) requires that in-process specifications ". . . **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."**
  - analyze process performance and control batch-to-batch variability!

Regulatory Requirements for Process Validation

- CGMP regulations regarding sampling:
  - samples must represent the batch under analysis (§ 211.160(b)(3));
  - **meet specifications and statistical quality control criteria as condition of approval and release** (§ 211.165(d);
  - and the batch must meet its predetermined specifications (§ 211.165(a)).

Regulatory Requirements for Process Validation

- **Control of Components and Drug Product Containers and Closures**

- Sec. 211.84 ((b) - "Representative samples of each shipment of each lot shall be collected for testing or examination. **The number of containers to be sampled, and the amount of material to be taken from each container, shall be based upon appropriate criteria such as statistical criteria for component variability, confidence levels, and degree of precision desired, the past quality history of the supplier**, ..."

Regulatory Requirements for Process Validation

- Section 211.180(e) requires that information and data about product quality and manufacturing experience **be periodically evaluated to determine need for changes in specifications or manufacturing or control procedures.**

- Ongoing feedback about product quality and process performance is an essential feature of process maintenance.

Guidance for Industry

Process Validation: General Principles and Practices

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
Center for Veterinary Medicine (CVM)

January 2011
Current Good Manufacturing Practices (CGMP)
Revision 1

Applicability of PV Guidance

- The 2011 PV Guidance does not specifically apply to validation of sterilization and cleaning processes.
- Other more prescriptive agency guidance on specific unit operations or specific processes should be considered the primary reference.
  - E.g., Aseptic Processing Guidance for Industry: Sterile Drugs Produced by Aseptic Processing should be considered primary guidance

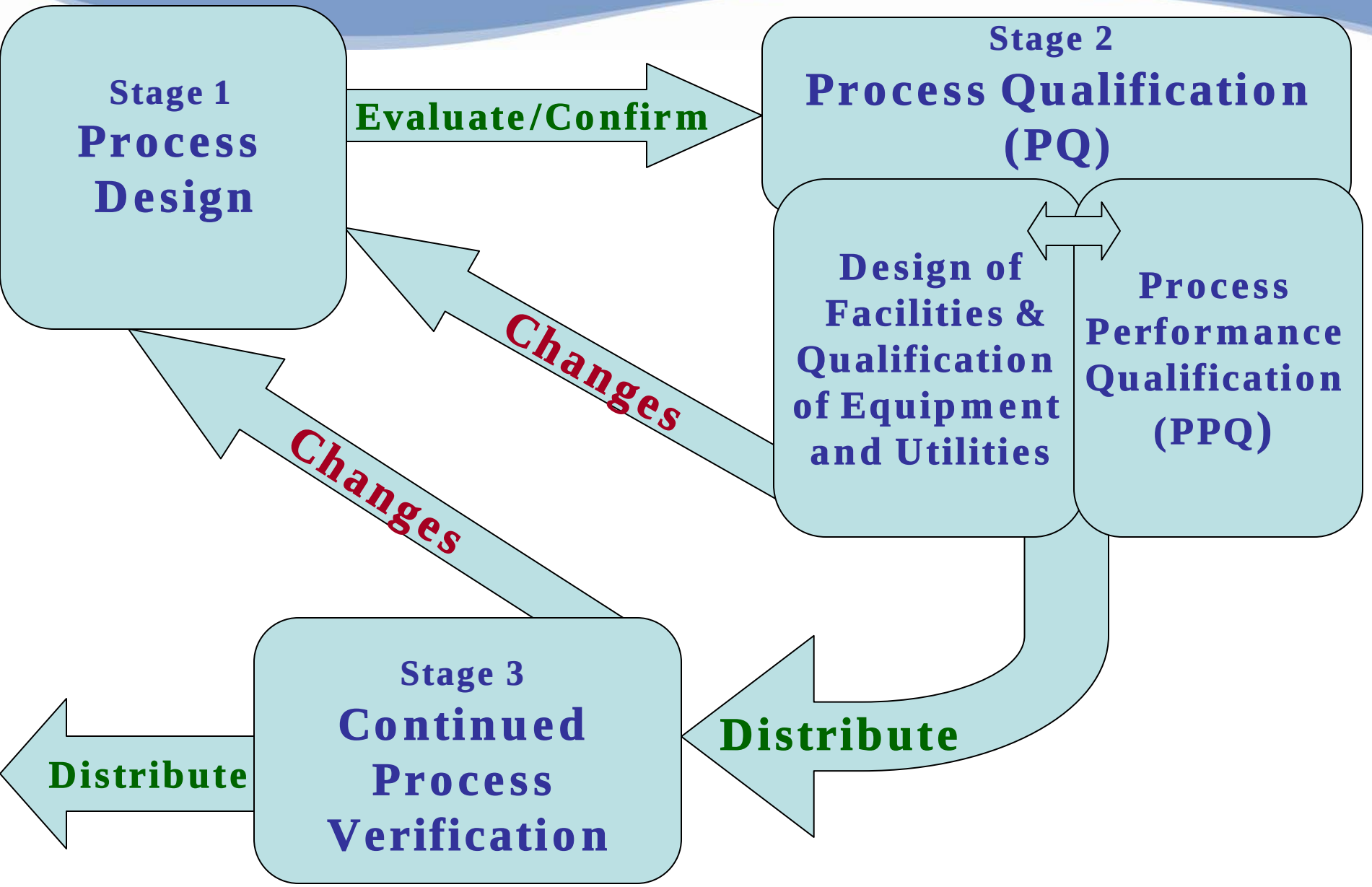
Final PV Guidance

Process validation **is defined as the collection and evaluation of data, from the process design stage through commercial production, which establishes scientific evidence that a process is capable of consistently delivering quality product.**

A series of activities taking place over the lifecycle of the product and process.

- Stage 1 – Process Design: The commercial process is defined during this stage based on knowledge gained through development and scale-up activities.
- Stage 2 – Process Qualification: 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.

Guidance describes activities typical in each stage, but in practice, some activities in different stages might overlap.


Stage 1
Process Design
Evaluate/Confirm
Stage 2
Process Qualification (PQ)
Design of Facilities & Qualification of Equipment and Utilities
Process Performance Qualification (PPQ)
Changes
Changes
Stage 3
Continued Process Verification
Distribute
Distribute

Learning progression

Good planning, expected path

Comprehensive process design, scientific process understanding

Sound, thorough process qualification. Confirms design

Continued Verification, Process learning and improvement

Poor design, planning, process understanding

Poor, minimal design

PQ checklist exercise w/little understanding

Unexplained variation, Product and process problems. Process not in control. **Major learning!** Potentially substandard product on market

Stage 1: Process Design

- *"Focusing exclusively on qualification efforts without also understanding the manufacturing process and associated variations may not lead to adequate assurance of quality."*

- Poor quality drugs on the market, evidenced by recalls, complaints and other indicators, from supposedly "validated" processes pointed to a lack of process understanding and adequate process control. This was an impetus for revising the 1987 Guideline.

Process Design

Process Design

that is minimal, incomplete, lacks depth, method and/or rigor

is risky business!

Pursue gaps in knowledge

- Follow up unexpected, unexplained information during early design studies
- Understand multivariate interactions and scale factors
- Consider cumulative effects of tolerance stacking
- Anticipate and plan for greater input variability at commercial scale from Operators, Equipment, Manufacturing instructions, Environment, APIs and Excipients, Measurement Systems

- Revisit process design if current process is not robust
- Revisit and update earlier risk assessments
- Re-assess original specifications, i.e., - are they appropriate?
- Conduct in-depth Root Cause Analysis

Stage 2: Process Qualification

- Two Aspects

1. Design of facilities and qualification of equipment and utilities

2. Process Performance qualification (PPQ)

Facilities, Equipment and Utilities

- Facilities
  - Proper design of manufacturing facility is required under 21 CFR part 211, subpart C, of the CGMP regulation on Buildings and Facilities
- Activities performed to assure proper facility design and that the equipment and utilities are suitable for their intended use and perform properly
  - Precedes PPQ.

PPQ - Process Performance Qualification

- Protocol(s) include
  - "*Criteria and process performance indicators that allow for a science- and risk-based decision about the ability of the process to consistently produce quality products.*"
  - "*A description of the statistical methods to be used in analyzing all collected data (e.g., statistical metrics defining both intra-batch and inter-batch variability).*"

PPQ - Process Performance Qualification

- Part of the planning for Stage 2 involves defining performance criteria and deciding what data to collect when, how much data, and appropriate analyses of the data.
- Likely consist of planned comparisons and evaluations of some combination of process measures as well as in-process and final product attributes.
- Manufacturer must scientifically determine suitable criteria and justify it.
- Objective measures, where possible.
- May be possible to leverage earlier study data if relevant to the commercial scale.

Basis for commercial distribution

- *"Each manufacturer should judge whether it has gained sufficient understanding to provide a high degree of assurance in its manufacturing process to justify distribution of the product."*

Commercial Distribution

- Decision to commercially distribute product from a given process is the firm's decision based on having reached the (pre-determined) high level of assurance.
- Criteria for high level of assurance is specific to the particular product and process being validated (results of stages 1 & 2) and is judged by the firm.
- Decision must be deliberate, obvious, and firm takes responsibility for it.

Concurrent Release in the PV Guidance

- In the PV guidance, the term "concurrent release" is meant exclusively in terms of the process performance qualification (PPQ) study protocol.
  - It means releasing a lot(s) included in a pre-planned study protocol before the study is completed, data collected and analyzed, and conclusions drawn.

- **PV Guidance definition**

  Concurrent Release: Releasing for distribution a lot of finished product, manufactured following a qualification protocol, that meets the [lot release criteria] standards established in the protocol, but before the entire study protocol has been executed.

Concurrent Release

Why does this matter?

- Under normal circumstances, a firm's decision to begin to commercially distribute product from a particular process is based on having achieved that *high degree of assurance* threshold.
- Unless there are special circumstances (e.g., orphan drugs, short shelf-life radiopharmaceuticals, medically necessary drugs to alleviate short supply) there is no reason to distribute products before that threshold has been reached.
- In these special circumstances, the benefit of having these drugs available to patients is judged to be greater than the risk of a lower degree of assurance.

Recommendation for sampling/monitoring after Stage 2

- *"The increased level of scrutiny, testing, and sampling should continue through the process verification stage as appropriate,* ***to establish levels and frequency of routine sampling and monitoring for the particular product and process.*** *Considerations for the duration of the heightened sampling and monitoring period could include, but are not limited to, volume of production, process complexity, level of process understanding, and experience with similar products and processes."*

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."***

Recommendation for 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.
  - Objective basis to meet CGMPs requirement of "statistically appropriate and representative levels"

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)).

Process Variability

- In order to detect process drift, **normal (common cause) variability** has to be understood and measured where possible.
- Range of input variability a process may encounter in commercial production may not be fully known during the process design stage.
  - E.g., excipients–
  - Laboratory or pilot-scale models that are representative of the commercial process can be used to estimate variability but need to obtain data from commercial manufacturing experience to confirm predictions.

Stage 3- Continued Process Verification

- A strategy for trending and monitoring.
  - What is the goal?
  - For example, determining machine-to-machine variability? within a machine? Batch to batch variability for certain attributes?
  - May need to tailor approaches, use different tools, for different products and processes.
- Obtain expertise applying statistical tools and analysis to manufacturing data.
- Further refine the control strategy.

Stage 3- Continued Process Verification

- *"An ongoing program to collect and analyze product and process data that relate to product quality must be established* ***(§ 211.180(e)).*** *The data collected should include relevant process trends and quality of incoming materials or components, in-process material, and finished products. The data should be statistically trended and reviewed by trained personnel. The information collected should verify that the quality attributes are being appropriately controlled throughout the process."*

"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

- **3. CONFORMANCE TO STANDARDS**

- 3.10. Applicability of Standards
- The manufacturer's specifications, **and good manufacturing practices** generally, are developed and followed to ensure that the article will comply with compendial standards until its expiration date, when stored as directed. Thus, any official article tested as directed in the relevant monograph shall comply.

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

USP 33–NF 28 Reissue General Notices

- 4.10.10. Applicability of Test Procedures
- 4.10.20. Acceptance Criteria
  - The acceptance criteria allow for analytical error, for **unavoidable variations in manufacturing** and compounding, and for deterioration to an extent considered acceptable under practical conditions.
  - .....
  - **An official product shall be formulated with the intent to provide 100 percent of the quantity of each ingredient declared on the label.**

- Manufacturers must determine appropriate sampling and monitoring for their processes.
- Compendial tests are standards that any compendial drug must meet if tested.
- By themselves they are not appropriate for process validation studies.

Legacy Products

- *"Manufacturers of legacy products can take advantage of the knowledge gained from the original process development and qualification work as well as manufacturing experience to continually improve their processes.* ***Implementation of the recommendations in this guidance for legacy products and processes would likely begin with the activities described in Stage 3."***

The Question of Process Validation

- Do I have confidence in my manufacturing process? Or, more specifically, what scientific evidence assures me that my process is capable of consistently delivering quality product?
- How do I demonstrate that my process works as intended?
- How do I know my process remains in control?