Guidance for Industry Process Validation: General Principles and Practices

Dr. Mark Tucker,
F. Hoffman-La Roche, Ltd.

DIA®
www.diahome.org

FDA ALUMNI ASSOCIATION
Serving Those Who Have Served™

Disclosures

- I am currently a Senior Technical Advisor at F. Hoffman -La Roche.
- I worked at the U.S. Food and Drug Administration (FDA) from 1996 - 2002. My last position at FDA was Director, Investigations Branch, in the Los Angeles District.
- The following are my views and not necessarily the views of the Food and Drug Administration Alumni Association (FDAAA), FDA, or Roche.
- Expenses for travel are being paid by Roche.
- FDAAA permits the reuse of these slides for educational purposes with attribution to the creator and FDAAA.

Presentation Overview

- Guidance Background
- GMPs and Process Validation
- Process Validation Stages – the Lifecycle Approach

Background

- Issued January 25, 2011
- Furthers the goals of GMPs for the 21st Century initiative by fostering innovation and advancing science in pharmaceutical manufacturing.
- Aligns Process Validation activities with the **product** lifecycle
  - More rational, scientific and can help improve control and assurance of quality
- Approach aligns with Quality by Design (QbD)

cGMP Regulations for Finished Pharmaceuticals

- Process Validation is an enforceable requirement for finished drug products:
  - 21 CFR 211.100(a)
    - "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.
  - 21 CFR 211.110(a)
    - "… procedures shall be established ***to monitor the output and to validate the performance of those manufacturing processes that may be responsible for causing variability***…

APIs and the FD&C Act

- Process Validation for Active Pharmaceutical Ingredients
  - is enforceable under Statute:
    - 501(a)(2)(b) of the Federal Food, Drug, and Cosmetic Act
  - and outlined in Guidance:
    - ICH Q7A

Process Monitoring

- 211.110(b)
  - Valid ***in-process specifications*** for such characteristics 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. Examination and testing of samples shall assure that the drug product and in-process material conform to specification.

Statistical Analyses

- 1978 Preamble[1] response to comments regarding 211.110(b):
-
  - "Further, after product histories are developed, the Commissioner encourages manufacturers ***to perform statistical analyses on their products and processes with a view to controlling batch-to-batch variability to the maximum extent possible.***"

[1]1978 Preamble, Human and Veterinary Drugs, Good Manufacturing Practice in Manufacture, Processing, Packing, or Holding

Sampling

- 21 CFR 211.165(d):
  - Samples must represent the batch being analyzed. (21 CFR 211 160(b)(3))
  - Meet specifications and appropriate statistical quality control criteria as a condition for batch approval and release. (21 CFR 211 165(d))

More on 211.165….

- Section 211.165 is therefore modified to allow greater latitude in establishing acceptance criteria, ***while retaining the basic requirements that acceptance criteria for sampling and testing, and for acceptance levels, be based on appropriate statistical quality control criteria. The Commissioner is convinced that sound statistical methodology should be applied to the procedures for testing of attributes or variables that impact on the quality of drug products and the evaluation of the results of such testing to determine acceptance or rejection of the lot.*** The uses of AQL and UQL are examples of statistically derived levels for acceptance or rejection. The Commissioner believes that more study must be given to this aspect of manufacturing practice and advises that in the future FDA will invite additional industry comment regarding revision of this section

Data Analysis Requirements

- Section 211.180(e) requires that information and data about product quality and manufacturing history be periodically (at least annually) evaluated to determine the need for changes in specifications or manufacturing or control procedures, and must include:
  - A review of a representative number of batches, whether approved or rejected, and, where applicable, records associated with the batch.
  - A review of complaints, recalls, returned or salvaged drug products, and investigations conducted.

The Questions of Process Validation

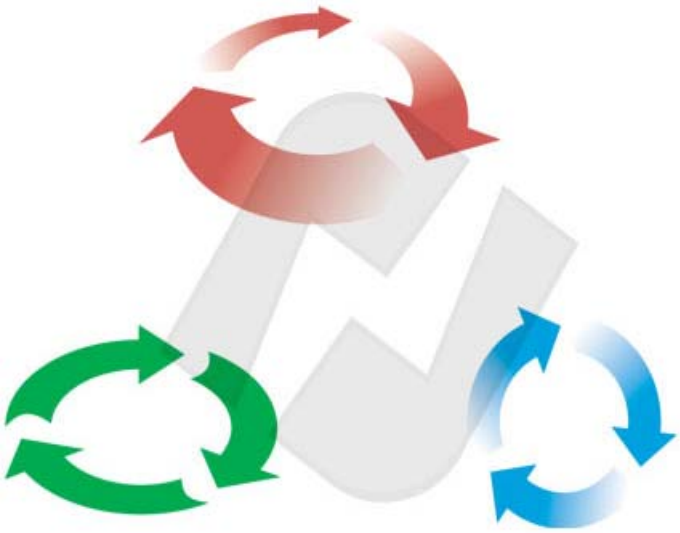
- What scientific evidence assures me that my process is capable of consistently delivering quality product?
- How do I demonstrate that my process works as intended?
- How do I know my process remains in control

The ‘process’ of Process Validation

- 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.

- It is a series of activities taking place over the lifecycle of the product/process.
  - Not a one time event but key milestones.

Lifecycle Approach



- Lifecycle
  - Overall validation is not “completed” but ongoing
  - Necessitates comprehensive process design to understand sources of variability and achieve process understanding
  - Incorporates risk management
  - Recognizes that more knowledge will be gained during commercialization

Process Lifecycle Stages

- Stage 1, Process Design:
  - Lab, pilot, small scale and commercial scale studies to establish process
- Stage 2, Process Qualification (PQ):
  - Facility, utilities and equipment qualified
  - Process Performance Qualification (PPQ)
    - Confirms commercial process design at (or near) scale
- Stage 3, Continued Process Verification:
  - Monitor and assess process during commercialization for:
    - process improvement
    - assurance that process remains in a state of control.

Goals

- Stage 1 - Functional understanding between parameters (material and process) and quality attributes
- Stage 2 – Measurable scientific evidence that
  - product will consistently meet specifications
  - process performance meets acceptance criteria; reproducible
- Stage 3 - Maintain or improve control and reduction in product and process variability

Stage 1: Process Design

- Propose process steps (unit operations) and operating parameters to be studied.
- Identify sources of variability each unit operation is likely to encounter.
- Consider possible range of variability for each input into the operation.
- Evaluate process steps and operating parameters for potential criticality.

Stage 1: Process Design

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

Stage 1: Process Design

- Manufacturers should
  - understand the sources of variation,
  - measure the degree of variation,
  - understand its impact on the process and product quality attributes, and
  - manage the variability in a manner commensurate with risk it represents to the process and product.
  - Develop mechanisms for managing variability
    - is part of the control strategy

Process Design Outputs

- Master production and control records
- Overall control strategy
- Operational limits/ranges
- Specifications

Stage 2: Process Qualification (PQ)

- Process Qualification: provides confirmation that the process design is functional for commercial scale manufacturing.
- Transfer process design knowledge to production, i.e., technology transfer

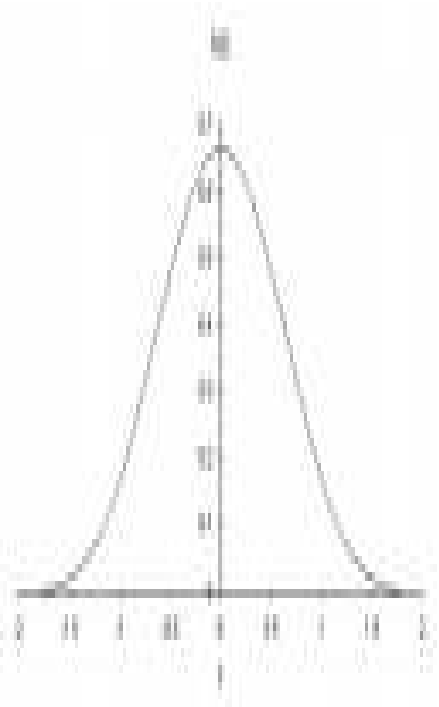
Process Qualification

- Two Aspects
  - Qualification of equipment, utilities and facilities
  - Process Performance Qualification (PPQ)

Facilities, Utilities and Equipment

- Precedes PPQ
- Consider user requirements, use risk analysis to identify studies/ tests needed and chose criteria to assess outcomes
- Plan for handling changes
- Generally engineering with development, production, and quality unit involvement
- Quality Unit reviews/approves the qualification plan(s) and report(s)

Process Performance Qualification (PPQ)



- Performance qualification protocol(s)
  - Protocol considerations must go beyond just a particular number of batches made
  - Criteria, including statistical criteria, that if met, leads to the conclusion that the process consistently produces quality product
  - Can leverage previous experience and knowledge if the data is relevant to the commercial scale process

Performance Qualification

- Typically will include:
  - Commercial batches manufactured with the qualified utilities, facilities, production equipment, approved components, master production and control record, and trained production personnel in place.
  - Usually run at target/nominal operating parameters within proven acceptable range or design space.
  - Extensively tested, i.e., combination of samples analytically tested and increased process control monitoring beyond typical routine QC levels.

Basis for Commercial Distribution

- *"Success at this stage signals an important milestone in the product lifecycle. A manufacturer must successfully complete PPQ before commencing commercial distribution of the product. The decision to begin commercial distribution should be supported by data from commercial scale batches. Data from laboratory and pilot studies can provide additional assurance that the commercial manufacturing process performs as expected."*

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 release of the product."*

Stage 3: Continued Process Verification

- Process Validation during commercial manufacturing
  - *"An ongoing program must be established. 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."*

Trend and Assess Data

- Evaluate periodically (at least annually[1)] to determine the need for changes in drug product specifications or manufacturing and control procedures
- Analyze data gathered from monitoring processes
- Incorporate statistical and/or quantitative measures where appropriate and feasible
- Study OOS and OOT (out of trend) data
- Assess impact of process and product changes over time
- Feedback into design stage for significant process shifts or changes

[1] 21 CFR 211.180(e)

Stage 3: Continued Process Verification

- Pursue gaps in knowledge when discovered
  - Follow up unexpected, unexplained results
- Revisit process design to improve current process robustness
- Conduct in depth root cause analyses when deviations occur.
- Further refine Control Strategy

Changes to the Process

- Statutory and GMP References:
  - FD&C Act Section 506A(b) "**Manufacturing Changes**" post marketing - **requires validation** of the effects of a change on the identity, strength, quality, purity and potency
  - 21 CFR 211.100(a) "…written procedures**, including any changes**, shall be drafted, reviewed and approved…"
  - 21 CFR 211. 180(e) – Annual review to determine whether changes in specifications or manufacturing or control procedures are needed"

Periodic Evaluation

- **Re-validation** – term is not used in the Process Validation Guidance
- Production phase (continual verification) monitoring will evaluate quality indicator data, changes and adverse trends and should be be used to periodically decide if new studies, e.g., conformances batches or other verification experiments, need to be done.

Continuous Processing

- Use of PAT systems to detect input and output variability of the material and react in real time to prevent sub-quality product
- Scale-up issues may not be as relevant as with batch manufacturing.
- Combination of real time detection of material attribute quality (particle size, uniformity) as well as process drift or change in performance (e.g. flow rates, power)
- Monitoring quality on a continuous basis.

Summary

- The lifecycle approach to Process Validation links product/process development to the commercial manufacturing process, and maintains the process in a state-of-control during routine production.

谢谢

Xie xie.

Thank you.

您是否有任何問題？

Nǐ yǒu shé me wèntí ma?

Do you have any questions?