Process Validation
Developing Guidance

What are we aiming at?

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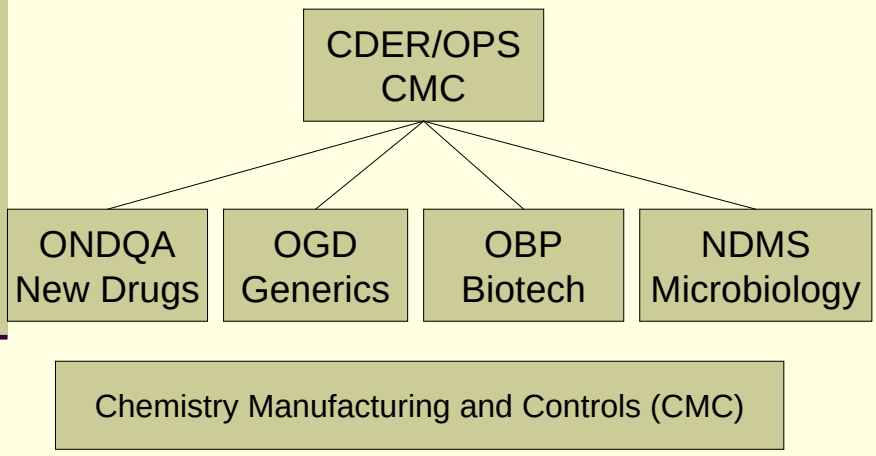

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Process Validation: Enforceable Requirement

- For *finished drug products*:
  - 21 CFR 211.100(a)
    - "written procedures… designed to assure…"
  - 21 CFR 211.110(a)
    - "… procedures shall be established to monitor the output and validate the performance…"
  - 21 CFR 211.113
    - validation of sterilization processes
  - 21 CFR 211.160
    - scientifically sound specifications + sampling

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Process Validation: Enforceable Requirement

- For *Active Pharmaceutical Ingredients*
- Statutory cGMP provision at 501(a)(2)(b) of the Federal Food, Drug, and Cosmetic Act
  - feasible and valuable
- CGMP guidance available - ICH Q7A

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The Questions of Process Validation

- Do I have confidence in my manufacturing process?
  - Confidence based on science & statistically sound
- How will I know if my process does not work as intended?
  - Before distribution
  - After distribution

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Process Validation: A Lifecycle

- Series of activities taking place over the ‘life’ of the product/process
- Overall validation is not “complete” but ongoing
  - Requires comprehensive process design to identify and mitigate significant sources of variability
    - achieve process understanding
- May incorporate risk management
- Recognizes that more knowledge will be gained during commercial distribution

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Lifecycle Approach to Process Validation

- Process Design:
  - The commercial process is defined during this phase based on knowledge gained through development and scale-up activities
    - Lab, pilot, small-scale, and commercial scale studies to establish process
- Process Qualification:
  - The process design is confirmed as being capable of reproducible commercial manufacturing
    - Facility, utilities, and equipment
    - Confirm commercial process design

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Lifecycle Approach to Process Validation

- Continued Process Verification (Commercialization):
  - Ongoing assurance is gained during routine production that the process remains in a state of control
    - Monitor, collect information, assess
    - Maintenance
    - Continuous verification
    - Process improvement

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Process Design

- Studies to identify multivariate interactions
- Studies to understand effects of scale
- Establish mechanisms to limit or control variability based on experimental data

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Process Design

- Designed experiments
- Lab scale, small scale, pilot scale studies
- Representative models
- Commercial scale - some aspects of certain processes can only be studied at commercial scale

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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

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Process Design Outputs

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

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Process Qualification

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

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Process Qualification

- Two Aspects
  1. Design of facilities and qualification of equipment and utilities
  2. Performance qualification

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Facilities, Utilities & Equipment

- Consider user requirements along with risk analysis to identify studies/tests needed and acceptable outcomes
- Plan for handling deviations and changes
- Engineering with Development, Production, and Quality Unit involvement
- Quality Unit reviews/approves the qualification plan(s) and report(s)

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Performance Qualification Protocol

- Written, specifying manufacturing conditions, controls, testing, and expected outcomes
  - Including operating parameters, processing limits, and component (raw material) inputs, data to be collected and when and how to be evaluated
  - Tests to be performed (in-process, release, characterization) and acceptance criteria for each significant processing step
  - Sampling plan, including sampling points, number of samples, and the frequency of sampling for each unit operation and attribute
    - The number of samples should be adequate to provide sufficient statistical confidence of quality both within a batch and between batches

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Performance Qualification Protocol

- Criteria that provide for a rational conclusion whether the process consistently produces quality products.
  - Description of the statistical methods to be used in analyzing data (e.g., statistical metrics defining both intra-batch and inter-batch variability).
  - Provision for addressing deviations and handling of nonconforming data. Data should not be excluded from further consideration in terms of performance qualification without a documented, science-based justification.
- Design of facilities and the qualification of utilities and equipment, personnel training and qualification, and verification of material sources
- Status of the validation of analytical methods used
- Review and approval by appropriate departments and the quality unit

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Successful Performance Qualification

- Confirms the process design
- Demonstrate that the commercial manufacturing process performs as expected
- Signals an important milestone in the product lifecycle
- Must be completed before a manufacturer commences commercial distribution of drug product

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Process Qualification

- Decision to “release the process” for routine commercial manufacturing
- Combination of Process Design work and Process Qualification work is basis for decision to go to market

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Product Distribution

- Before any batch from the process is commercially distributed for use by consumers, a *high degree of assurance* in the performance of the manufacturing process, that it will consistently produce APIs and drug products, is needed.

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High Degree of Assurance

- Is obtained by providing objective information and data from laboratory-, pilot-, and/or commercial-scale studies
  - to demonstrate that the commercial manufacturing process is capable
    - of consistently producing acceptable quality products
    - within commercial manufacturing conditions
    - including those conditions that pose a high risk of process failure

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Process Monitoring

- Verifies process is in control
- Adds assurance of product quality
- Reveals need or opportunities for improving
  - process
  - control strategy

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Trending and Assessing Data

- Evaluate periodically (at least annually per 21 CFR 211.180(e)) 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 made over time
- Feedback into design stage for significant process shifts or changes

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Input Variability

- Mechanisms for managing variability is part of the control strategy
- cGMP choices are
  - slow feedback/control (SPC)
    - greater loss potential
  - rapid feedback/control (PAT)
    - greater efficiency...

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Successful Validation

- Depends on information and knowledge from product and process development
  - is the basis for establishing an approach to control that is appropriate for the manufacturing process.
- Manufacturers should:
  - Understand the sources of variation
  - detect the presence and degree of variation
  - understand the impact of variation on the process and ultimately on product attributes
  - control the variation in a manner commensurate with the risk it represents to the process and product

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Process Control Strategy

- Process knowledge and understanding is the basis for establishing an approach to process control for each unit operation and the process overall
- Strategies for process control can be designed to reduce input variation, adjust for input variation during manufacturing (and so reduce its impact on the output), or combine both approaches
- Process controls address variability to assure quality of the product

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Process Control Strategy

- Controls can consist of material analysis and equipment monitoring at significant processing points designed to assure that the operation remains on target and in control with respect to output quality.
- Special attention to control of the process through operational limits and in-process monitoring is essential
  - (1) where the product attribute is not readily measurable due to limitations of sampling or detectability
  - (2) when intermediates and products cannot be highly characterized and well-defined quality attributes cannot be identified.

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Process Validation & PAT

- A manufacturing process that uses PAT may warrant a different performance qualification approach.
- Such a process is one that is designed to measure in real time the attributes of an in-process material and then adjust the process in a timely control loop so the process maintains the desired quality of the output material.
- The process design phase and the process qualification phase should have as a focus the measurement system and control loop.
- Regardless, the goal remains the same: establishing scientific evidence that the process is reproducible and will consistently deliver quality APIs and products.

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Commercial Production

Validation in Production

- Activities to continually assure that the process remains in a state of control

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Monitoring

- Timely monitoring of critical operating and performance parameters
- Monitoring of product characteristics (e.g., stability, product specifications)
- Monitoring adequacy of personnel training and material, facility/equipment
- Investigate problems for root cause and implement corrective action

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Establish Process History

- Measurements of process variability
  - only have estimates for new processes
- Measurements of process performance over time

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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 specification or manufacturing procedures are needed*”

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Periodic Evaluation

- Re-validation – not using this term in the revised Process Validation Guidance
- Production phase monitoring
  - evaluate quality indicator data, changes and adverse trends
  - periodically decide if new studies, e.g., conformances batches or other verification experiments, need to be done.
- Retrospective (no longer exists)

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Process Validation

- “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.”

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