PDA Technical Report 60 Revision Process Validation: Principles and Practice

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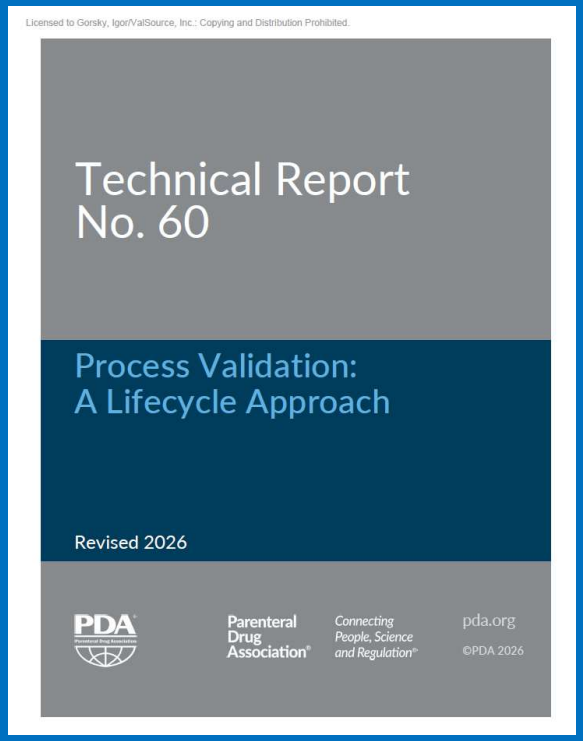

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PDA Technical Report 60 Revision

PDA Technical Report 60 – Little bit of History

- PDA launched the project activities related to the PCMO(Paradigm Change in Manufacturing Operations) in December 2008 to help implement the scientific application of the ICH Q8, Q9 and Q10 series

- The PDA Board of Directors approved this program in cooperation with the Regulatory Affairs and Quality Advisory Board, and the Biotechnology Advisory Board and Science Advisory Board of PDA

- What happened in 2008 – FDA issued first draft of Process Validation Guidance

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Table of Contents

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Why Revision?

- Older Document
  - Original Publishing – 2013 to address FDA Process Validation Guidance (2011)
  - Proposal for revision was drafted in 2020
- There was an eminent need to modernize the document
  - Changes to Regulatory Guidance (Annex 15, Annex 1, ICH Q12, 13 and14)
  - Statistical Methods alignment (PDA issued TR59 after TR60)
  - Quality Risk Management alignment (PDA issued a number of QRM documents after issuance of original version)
  - Other PDA documents relevant to Process Validation alignment
  - Rise of Artificial Intelligence

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Scope

- Pharmaceuticals, sterile and non-sterile
- Biotechnological/biological products, including vaccines
- Blood derivatives products
- ATMP products
- Drug Substances (Active Pharmaceutical Ingredients (APIs))
- Radiopharmaceuticals
- Veterinary drugs
- Drug constituents of combination products (i.e. a combination drug and medical device)

Out of Scope

- Medical devices
- Dietary supplements
- Medicated feed

Audience

- Product and Process Developers
- Process Validation Practitioners
- Quality Risk Management Personnel
- Quality Assurance
- Operations
- Technical Services
- Research and Development
- Compliance and Regulatory Affairs

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Revision Objectives

- This revision was issued to update one of the most important PDA Technical Reports to the current state of the industry

- This revision should be serving newer generations of Process Validation implementers as a practical and compliant guide for interpretation of principles, methods and practices on the subject

- This revision should provide most current examples of implementation practices that illustrate up to date Process Validation ideas and thoughts

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Impactful Changes

- ICH Q12 Principles (EC Changes)
- ICH Q13 Principles (Continuous Manufacturing)
- Artificial Intelligence Discussion
- Complementary to TR59, TR60-2 and TR60-3
- Knowledge Management Enhancement
- Updated Charts and Graphs for Ease of Use
- Performance Qualification

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Glossary (Example Changes)

- **Continuum of Criticality (Removed)**
- **Component (Added)**
- **Data Integrity (Added)**
- **Critical/Non-Critical/Process Parameters**

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Process Development/Process Design (Examples)

- Analytical Methods (Significant Information Added)
- Manufacturing and Technology Considerations
- Scale-Down Models
- Process Validation Summary of Activities

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Process Performance Qualification

- General Enhancements
- Maintaining System in the State of Control (Consolidation and directing to Glossary and Stage 1 Deliverables)
- Performance Qualification (Addition)
- Risk Based Performance Qualification and Number of Batches Science and Risk Based Approach
- Sample Size Methods
- Continuous Manufacturing per ICH Q13 and EMA Annex 15

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Continued (EU: Ongoing) Process Verification

- Introduction of Stages 3a and 3b
- Enhanced View on the Program based on Industry Experience and Expertise with Emphasis on Knowledge, Risk, Responsibility and Documentation
- Data Acquisition Introduction
- Complimentary with PDA TR59 (Statistics)
- Digital twins (digital replica of the process)
- Artificial Intelligence Introduction
- Decision Making
- Regulatory Commitments (ICH Q12) and Established Conditions (EC) Changes

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Process Validation for ATMPs and Vaccines

- **Vaccines**
- **Cell Therapies**
- **Complimentary with PDA TR60-3 (Biopharmaceuticals Process Validation)**

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Process Validation Enabling Systems and Technologies

- Risk Management Enhancements – Text Revision and Editing
- Statistical Analysis (Complimentary to TR59)
- Process Analytical Technology
- Knowledge Management (Enhanced Content):
  - Chart,
  - Roles and Responsibilities
  - Application for all three Stages
  - KM and QRM

Appendices

- Large and Small Molecule Examples were kept
- Statistical Appendices were kept
- Almost 60% Increase in References
- Added Appendices References

Notable Final Notes

- First Draft of Proposal – February of 2020
- Publishing – March of 2026
- 2 members of Original Team joined New team
- 90% of the Team was new volunteers
- Multiple sub-teams
- Representation of WHO

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FDA Process Validation Guidance and PDA TR60

- **The transition was challenging for many manufacturers, particularly in implementing Continued Process Verification (Stage 3) effectively.**
- **While FDA adopted this approach, many manufacturers operating globally still had to adhere to "three-batch" expectations in other markets.**
- **Implementation is ongoing, with companies continuously learning to refine their process understanding over time**
- **Overall, the 2011 guidance was a necessary modernization of pharmaceutical manufacturing that, despite implementation challenges, has resulted in improved product quality and risk management**

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Process Validation: Principles and Practice

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regulatory basis

- Process validation for drugs (finished pharmaceuticals and components) is a legally enforceable requirement under section 501(a)(2)(B) of the Act (21 U.S.C. 351(a)(2)(B)), which states the following:
  - *A drug . . . shall be deemed to be adulterated . . . if . . . the methods used in, or the facilities or controls used for, its manufacture, processing, packing, or holding do not conform to or are not operated or administered in conformity with current good manufacturing practice to assure that such drug meets the requirements of this Act as to safety and has the identity and strength, and meets the quality and purity characteristics, which it purports or is represented to possess.*
- FDA regulations describing current good manufacturing practice (CGMP) for finished pharmaceuticals are provided in 21 CFR parts 210 and 211.

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regulatory basis

- Purpose of regulations is to protect the public and to provide effective products
- 21 CFR 211.100 of GMPs:

  "There shall be written procedures for product and process control designed to **assure** that drug products have identity, strength, quality, and purity they purport or are represented to possess."

- Industry must provide assurance that products are **safe and pure.**
- How is that assurance provided?

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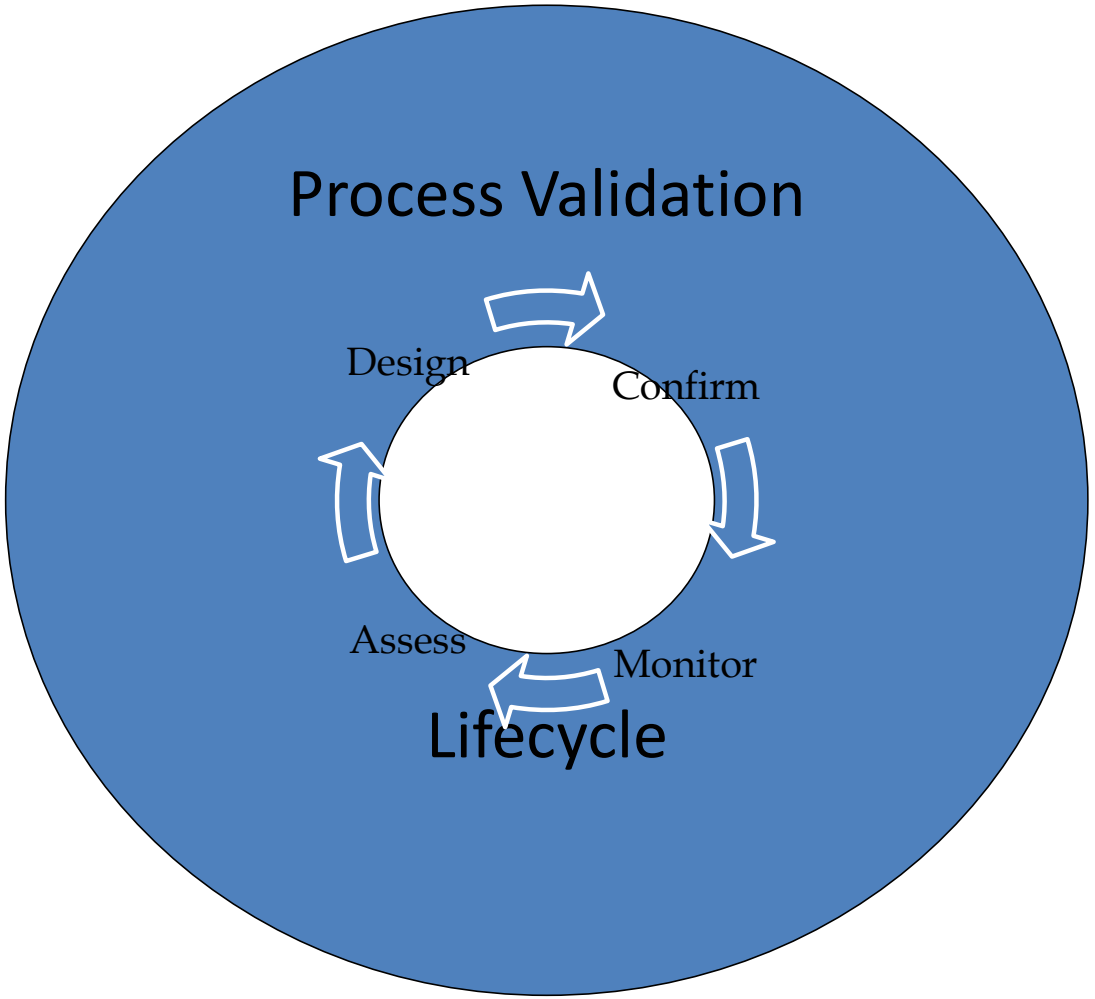
2011 Guidance for Industry - Process Validation: General Principles and Practices

Process Validation:

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.


Process Validation
Design
Confirm
Assess
Monitor
Lifecycle

2011 Guidance for Industry - Process Validation: General Principles and Practices

Series of activities over the lifecycle of the product and process.

In Guidance, PV activities described in three stages. Some activities in different stages might overlap.

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:

- During this stage, 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.

PV, ICH, QbD and CGMPs

CDER's PV guidance tracks well with principles adopted and lifecycle activities described in ICH Q8, Q9 & Q10.

CGMP regulation reflects QbD and ICH concepts of design, risk management, and the product and process lifecycle with language like

- "designed to assure…" [211.100(a)] Design
- "…appropriate specifications" [211.165(d)] or "suitable statistical procedures where appropriate" [211.110(b)] Risk
- "…periodically evaluated to determine need for changes in specifications or manufacturing or control procedures." [211.180(e)]

Lifecycle

Questions to consider……..

- How do I know if my process is in a state of control?
- How sure am I that all dosage units in a batch possess the necessary quality?
- How variable are my inputs?
- How much variation can be tolerated in my outputs?

CGMP on process control, variability and performance

The CGMP regulation makes reference to the ongoing nature of validation, of gaining experience and developing an acceptable history.

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. Examination and testing of samples shall assure that the drug product and in process material conform to specifications."

Key elements

- Control procedures
- Monitor the output
- Performance
- Variability in the characteristics of in-process material and the drug product

- ….derived from previous acceptable process average and process variability estimates (where possible)
- ….determined by…suitable statistical procedures (where appropriate)

Transition from Stage 2 to Stage 3

Process Variability Estimates

- Measure, characterize and understand the common cause variability

Determine the robustness of the process

- How well does it tolerate input variability and result in the consistent output

Goals of the CGMP regulation and PV Guidance

- Measure normal process (common cause variability) over time
  - Begins in stage 1, ramps up in stage 2, fully realized in stage 3
- Evaluate both lot quality and appropriateness of control strategy over time.
  - Can detection methods can find abnormal behavior (special cause variability)
- Where common cause variability is too wide, drive process tighter as appropriate
  - one type of continual improvement

Stage 2 and process performance measures

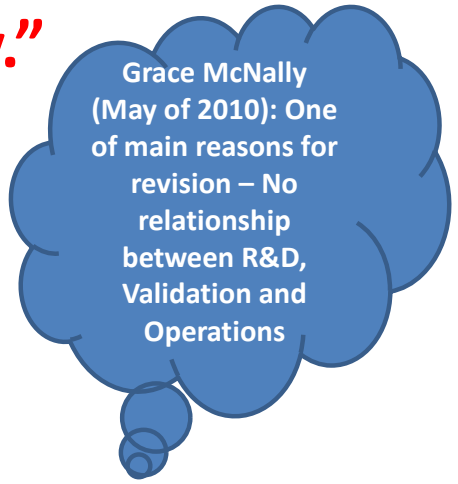
How much is needed and when?

- First things first
  - Limited experience and data will produce conclusions that have less certainty than conclusions based on more data and experience.
- Maintain a sense of proportion
  - PV is a big on-going program with many nested elements.
  - Successful PV is greater than the sum of its parts.

Stage 2

2011 PV Guidance

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



Transition from Stage 2 to Stage 3

- Evaluate the individual batches in the study and as well as the process performance overall
  - Use objective measures and statistical tools, where possible, to inform decisions and make conclusions
  - Be reasonable and scientific
  - Be in line with product/process complexity and understanding
  - Complete investigations before concluding the study
  - Meet your criteria and expectations before declaring the process (initially) qualified to begin distribution

Transition from Stage 2 to Stage 3

- Stage 2:
  - understand the degree of input variability, achieve estimates of output variability.
  - Gain sufficient confidence to begin distribution.
- Stage 3:
  - measuring and characterizing common cause variability (refining earlier variability estimates)
  - checking the 'robustness' of the process as new input variability enters the system.
  - Assessing output variability (common cause) – does it meet the patient and consumers' needs?
  - Evaluating process capability and process performance
  - Assessing control strategy and ability to distinguish between special cause variability and common cause

Different tools for different data types and different questions

- Time ordered data analysis (during the run)
- Batch data analysis (population as a whole)

- Intra batch variability
- Inter batch variability

- Process performance
- Process capability

Statistical Tools

- Average, Standard Deviation,
- %RSD and sample size.
- Time plots
- Control Charts
- Histograms
- Statistical Tolerance Intervals
- Cpk and Ppk

Lynn Torbeck, Principal Statistician
PharmStat, Inc.

Cpk & Ppk

- These are ratios of the specification range to the natural variability of the data.

- Answers the question: *"Is this process capable of meeting its specifications now or in the future?"*

- **Cpk is for short term variability**
- **Ppk is for long term variability**

Lynn Torbeck, Principal Statistician
PharmStat, Inc.

Useful standards…..

- ASTM E2709-10, Standard Practice for Demonstrating Capability to Comply with a Lot Acceptance Procedure.
- ASTM E2281-03, Standard Practice for Process and Measurement Capability Indices.
- ASTM E2474-06, Standard Practice for Pharmaceutical Process Design Utilizing Process Analytical Technology.
- ASTM E2476-09, Standard Guide for Risk Assessment and Risk Control as it Impacts the Design, Development, and Operation of PAT Processes for Pharmaceutical Manufacture.
- ASTM E2629-11, Verification of Process Analytical Technology (PAT) Enabled Control Systems
- ASTM E2500-07, Standard Guide for Specification, Design, and Verification of Pharmaceutical and Biopharmaceutical Manufacturing Systems and Equipment.

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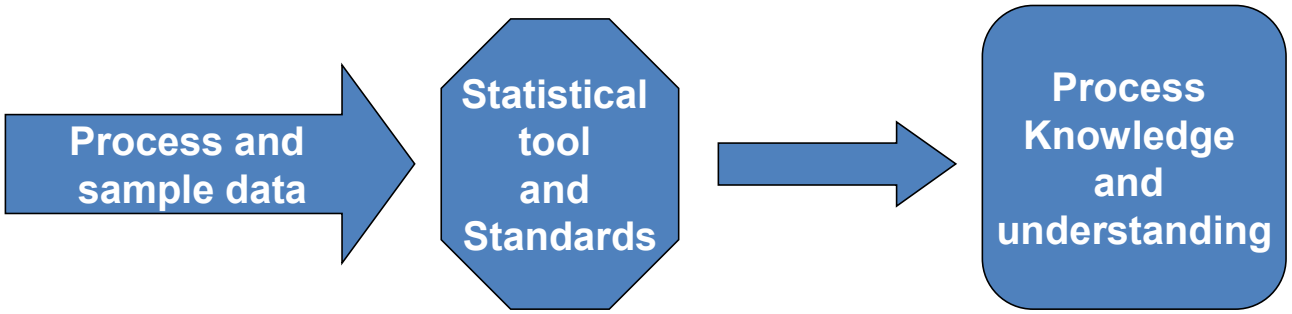
Statistical tools and standards



•**As this institutional knowledge base grows in coverage (range of variables and scenarios) and data density,** it can be mined to determine useful patterns for future development projects. These experimental databases can also support the development of process simulation models, which can contribute to continuous learning and help to reduce overall development time.

2011 Process Validation Guidance

Reference to advanced manufacturing technologies:

"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."

Questions about Quality

- How is quality defined?
  - Risk assessment should establish the confidence level necessary for particular attributes.

- How is quality measured?

Regulatory Guidance


INTERNATIONAL CONFERENCE ON HARMONISATION OF TECHNICAL REQUIREMENTS FOR REGISTRATION OF PHARMACEUTICALS FOR HUMAN USE

ICH HARMONISED TRIPARTITE GUIDELINE

QUALITY RISK MANAGEMENT
Q9

Current *Step 4* version
dated 9 November 2005

This Guideline has been developed by the appropriate ICH Expert Working Group and has been subject to consultation by the regulatory parties, in accordance with the ICH Process. At Step 4 of the Process the final draft is recommended for adoption to the regulatory bodies of the European Union, Japan and USA.


INTERNATIONAL CONFERENCE ON HARMONISATION OF TECHNICAL REQUIREMENTS FOR REGISTRATION OF PHARMACEUTICALS FOR HUMAN USE

ICH HARMONISED TRIPARTITE GUIDELINE

PHARMACEUTICAL DEVELOPMENT
Q8(R2)

Current *Step 4* version
dated August 2009

This Guideline has been developed by the appropriate ICH Expert Working Group and has been subject to consultation by the regulatory parties, in accordance with the ICH Process. At Step 4 of the Process the final draft is recommended for adoption to the regulatory bodies of the European Union, Japan and USA.

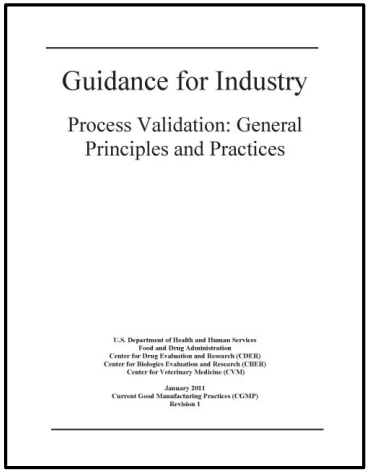

INTERNATIONAL CONFERENCE ON HARMONISATION OF TECHNICAL REQUIREMENTS FOR REGISTRATION OF PHARMACEUTICALS FOR HUMAN USE

ICH HARMONISED TRIPARTITE GUIDELINE

PHARMACEUTICAL QUALITY SYSTEM
Q10

Current *Step 4* version
dated 4 June 2008

This Guideline has been developed by the appropriate ICH Expert Working Group and has been subject to consultation by the regulatory parties, in accordance with the ICH Process. At Step 4 of the Process the final draft is recommended for adoption to the regulatory bodies of the European Union, Japan and USA.


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

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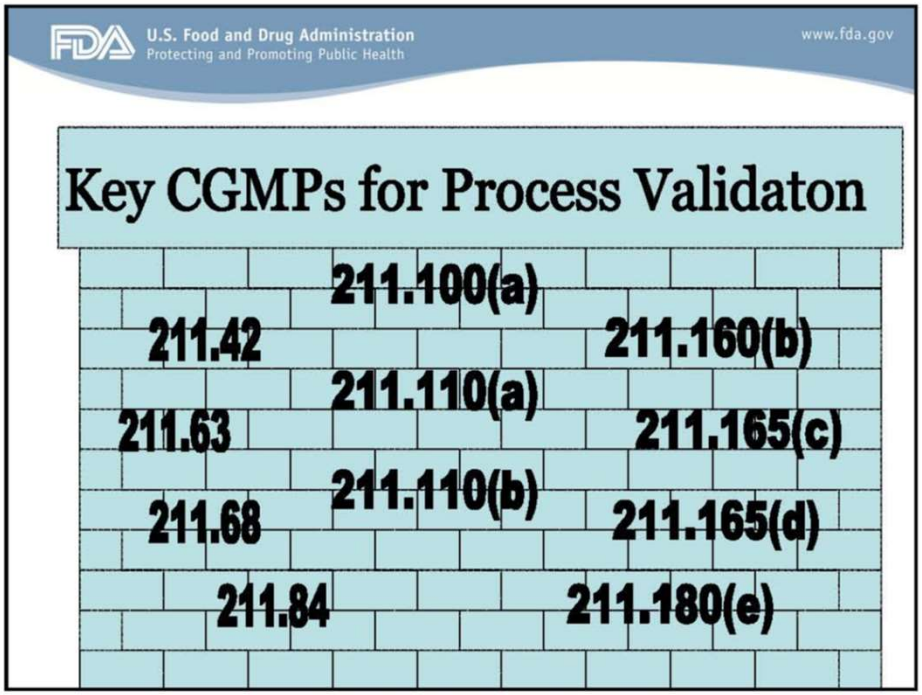
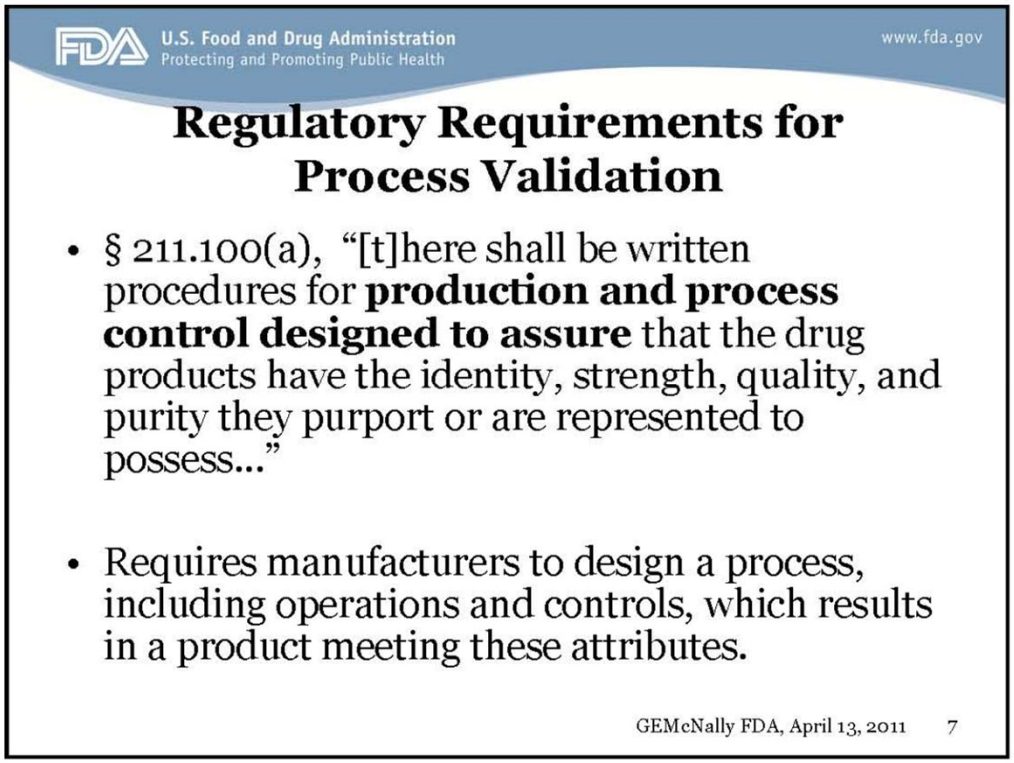
Regulatory Requirements



Regulatory Requirements



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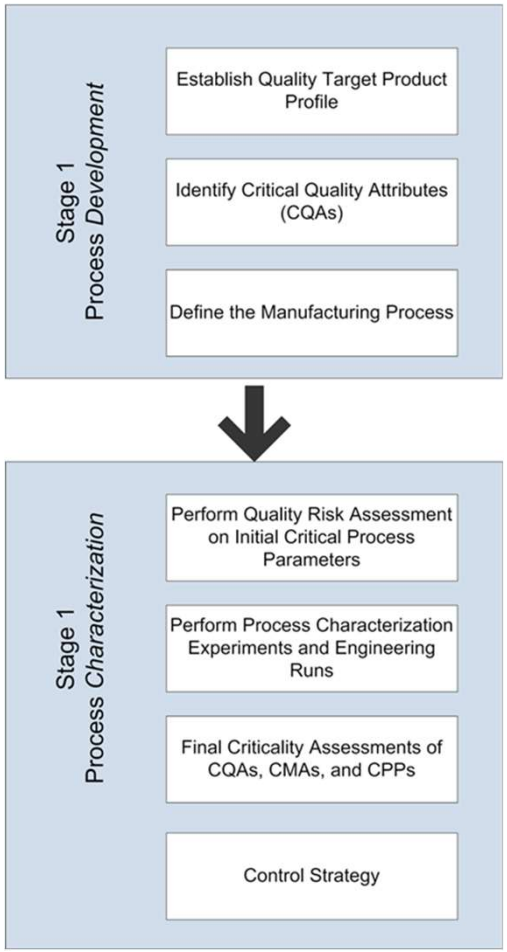
Process Validation Stage 1



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Introduction

- **Scope of Process Design**
  - Activities leading to definition of the commercial manufacturing process and associated control strategy
    - commercial formulation development
    - commercial process development
    - commercial package development

- **Goal of Process Design**
  - To design a process suitable for routine commercial manufacturing
    - control strategy should be "manageable"
    - robust processability and suitable cost
  - Consistently deliver a product that meets its critical quality attributes
    - consistent with the quality target product profile
    - physical, chemical, biological, and microbiological tests that provide assurance of safety and efficacy

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Introduction (Continue)

- **Some considerations for formulation and process selection**
  - Drug substance attributes
    - Solubility
    - Chemical sensitivities (e.g., moisture, heat, etc.)
    - Physical attributes
  - Quality target product profile
    - Desired tablet strength (drug loading)
    - Desired pharmacokinetic profile
    - Desired stability profile
  - Company platform technology
  - Company's manufacturing expertise
  - Production cost

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Process Design Tools

- **Quality Risk Management**
- **Design of Experiments**
- **Process Analytical Technology**
- **Process Modeling**

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Process Validation:
FDA Observations and Warning Letters

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FDA 483 Genzyme Alston

- Ob 4. “Validation of the fill process for low volume products is inadequate in that full size validation runs have not been executed since process and equipment parameter **changes** have been implemented to prevent low fill volumes.”

- Ob 49. The quality group has not approved all as-built drawings and floor plans on site…Prior to May 2009, when floor plans were **changed**, the older floor plan was discarded and it was replaced with the modified floor plan without any review or approval by quality.

FDA 483 McNeil Consumer Healthcare Fort Washington

- Ob 1. “…it (quality unit) neglects review and approval of validation protocols regarding **changes** in product processes and equipment to determine when revalidation is or should be warranted…”

- Ob 2. “The compounding and transfer of the __ batch size suspension to the hold (tank) is not in a "state of control". The firm did not effectively evaluate the **change** in the manufacturing … time to when the batch size was increased from into ___and/or when the hold (tank) size used for a ___ batch was decreased from a ____ tank. (time to shut off agitator)”

FDA Warning Letter Sandoz

Equipment Comparability and Process Capability

- Four (4) tablet products, various strengths
  - Initial process qualification used a single-sided tablet press. During routine production, however, these products were also being manufactured using a double-sided tablet press.
  - Compression using the double sided press was not qualified.
  - Firm's response to the FDA483 attempted to show statistical equivalence between the single and double sides presses.

FDA Warning Letter

Equipment Comparability and Process Capability

- The firm's written response referenced the Cpk values for processes using a double-sided tablet press and the single-sided tablet press.

- FDA evaluation of the FDA483 response
  - The Cpk value alone was not an appropriate metric to demonstrate statistical equivalence. Cpk analysis requires a normal underlying distribution and a demonstrated state of statistical process control. The firm did not address these issues in their response.

  - Statistical equivalence between the two presses could have been shown by using either parametric or non-parametric (based on distribution analysis) approaches and comparing means and variances. Neither of these approaches was employed. Firm did not use the proper analysis to support their conclusion that no significant differences existed between the two compression processes.

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FDA Warning Letter

- Issues –
  - Data did not support proper statistical conclusions
  - Firm did not understand underlying assumptions required to conduct Process Capability calculations
  - Firm did not conduct proper statistical analysis to demonstrate equivalence between two operations.

Different tools for different data types and different questions

- Time ordered data analysis (during the run)
- Batch data analysis (population as a whole)

- Intra batch variability (within in same batch)
- Inter batch variability (same product different batch)

- Process performance (A measure of actual results achieved by following a process)
- Process capability (The range of expected results that can be achieved by following a process)

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