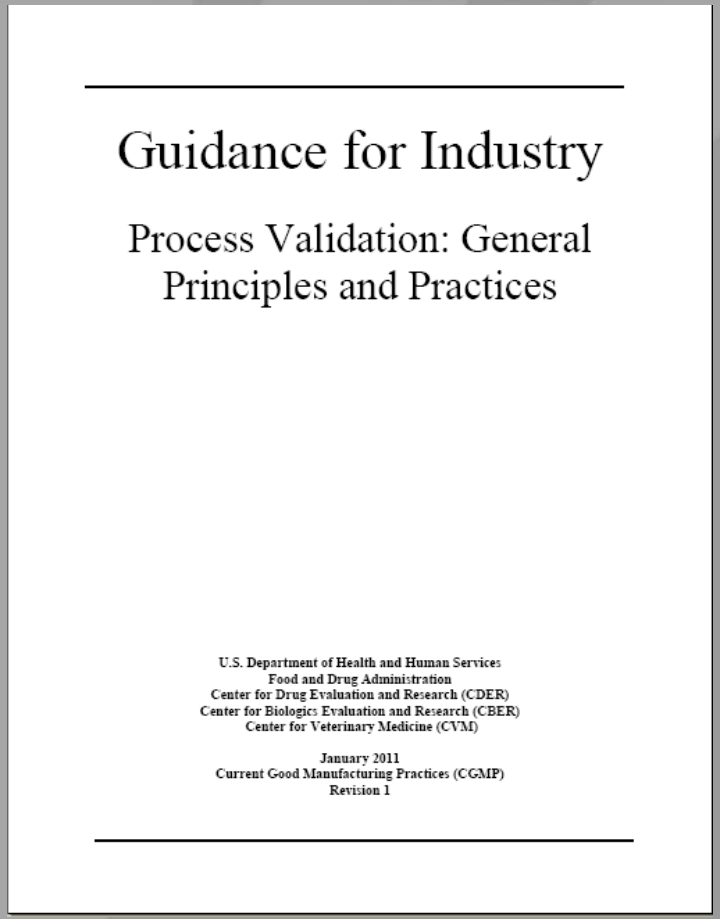
Guidance for PV

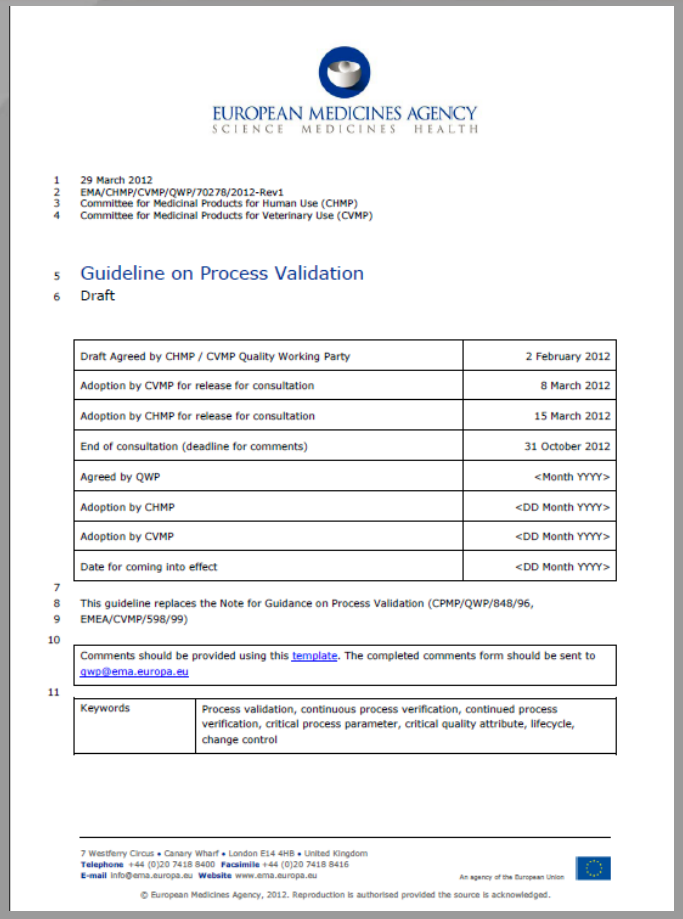


Guidance for Industry

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



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

29 March 2012
EMA/CHMP/CVMP/QWP/70278/2012-Rev1
Committee for Medicinal Products for Human Use (CHMP)
Committee for Medicinal Products for Veterinary Use (CVMP)

Guideline on Process Validation

Draft

Draft Agreed by CHMP / CVMP Quality Working Party	2 February 2012
Adoption by CVMP for release for consultation	8 March 2012
Adoption by CHMP for release for consultation	15 March 2012
End of consultation (deadline for comments)	31 October 2012
Agreed by QWP	<Month YYYY>
Adoption by CHMP	<DD Month YYYY>
Adoption by CVMP	<DD Month YYYY>
Date for coming into effect	<DD Month YYYY>

This guideline replaces the Note for Guidance on Process Validation (CPMP/QWP/848/96, EMEA/CVMP/598/99)

Comments should be provided using this template. The completed comments form should be sent to qwp@ema.europa.eu

Keywords	Process validation, continuous process verification, continued process verification, critical process parameter, critical quality attribute, lifecycle, change control

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Agenda

- What is it?
- Why change the paradigm?
- The new principles of Quality Assurance
- Life Cycle Approach
- Three Stages of Process Validation
  - Process Design Focus
  - Process Performance Qualification
  - Continued Process Verification
- Summary

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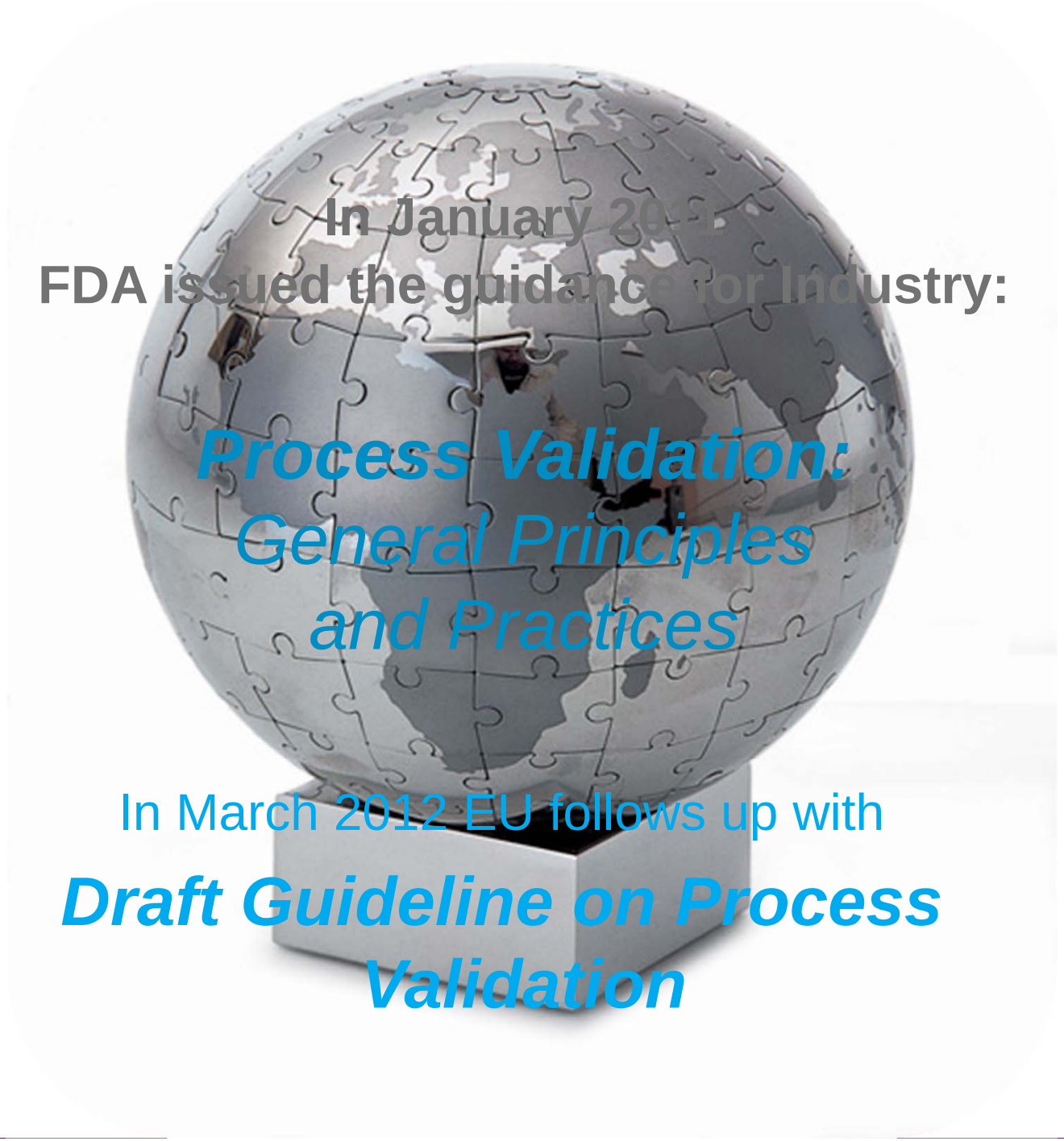

In January 2011

FDA issued the guidance for Industry:

Process Validation:
General Principles
and Practices

In March 2012 EU follows up with

Draft Guideline on Process Validation

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What do the Guides Promote?

- **Modern manufacturing principles**
- **Real time process improvement**
- **Innovation**
- **Sound science**
- **Risk Management**
- **Lifecycle assessment**

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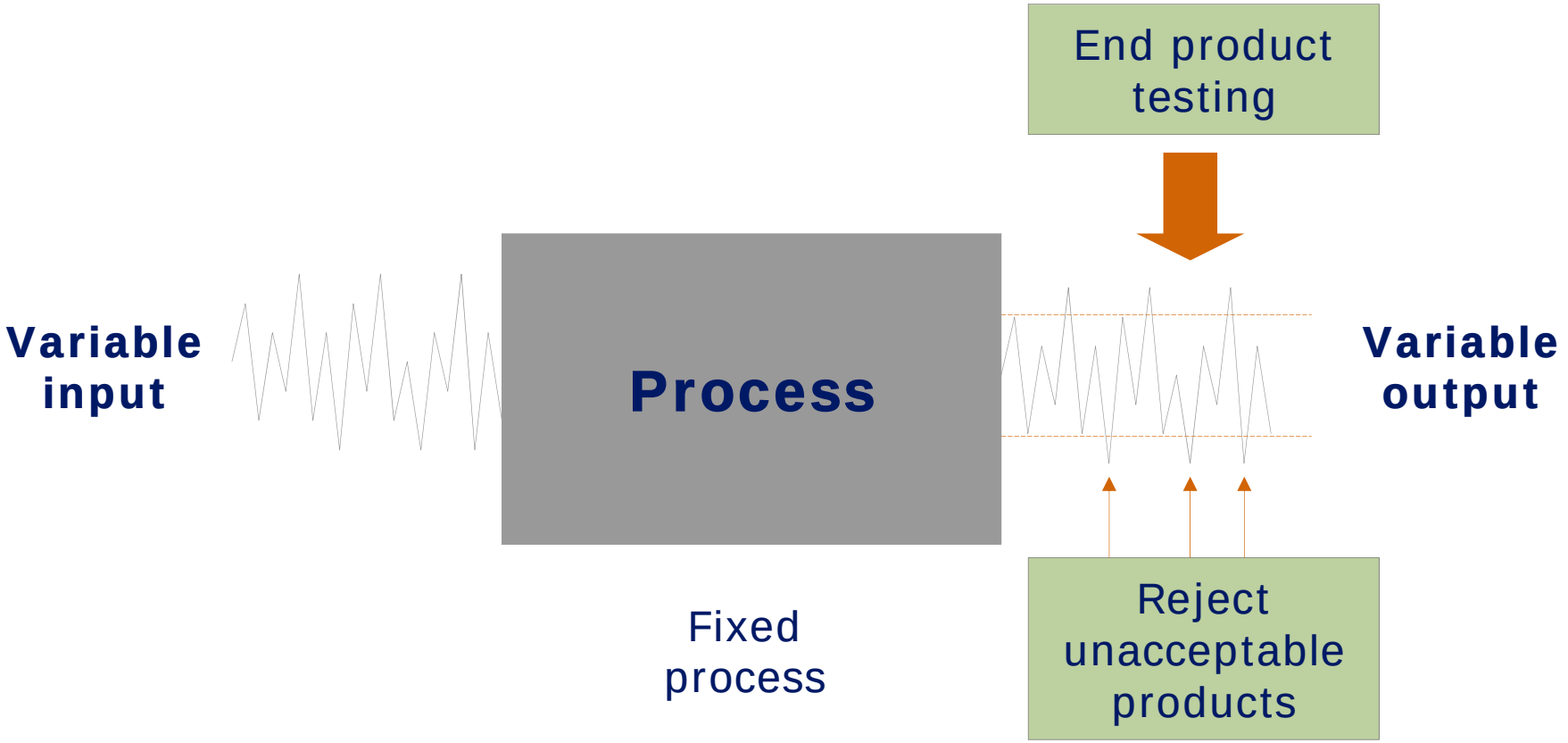
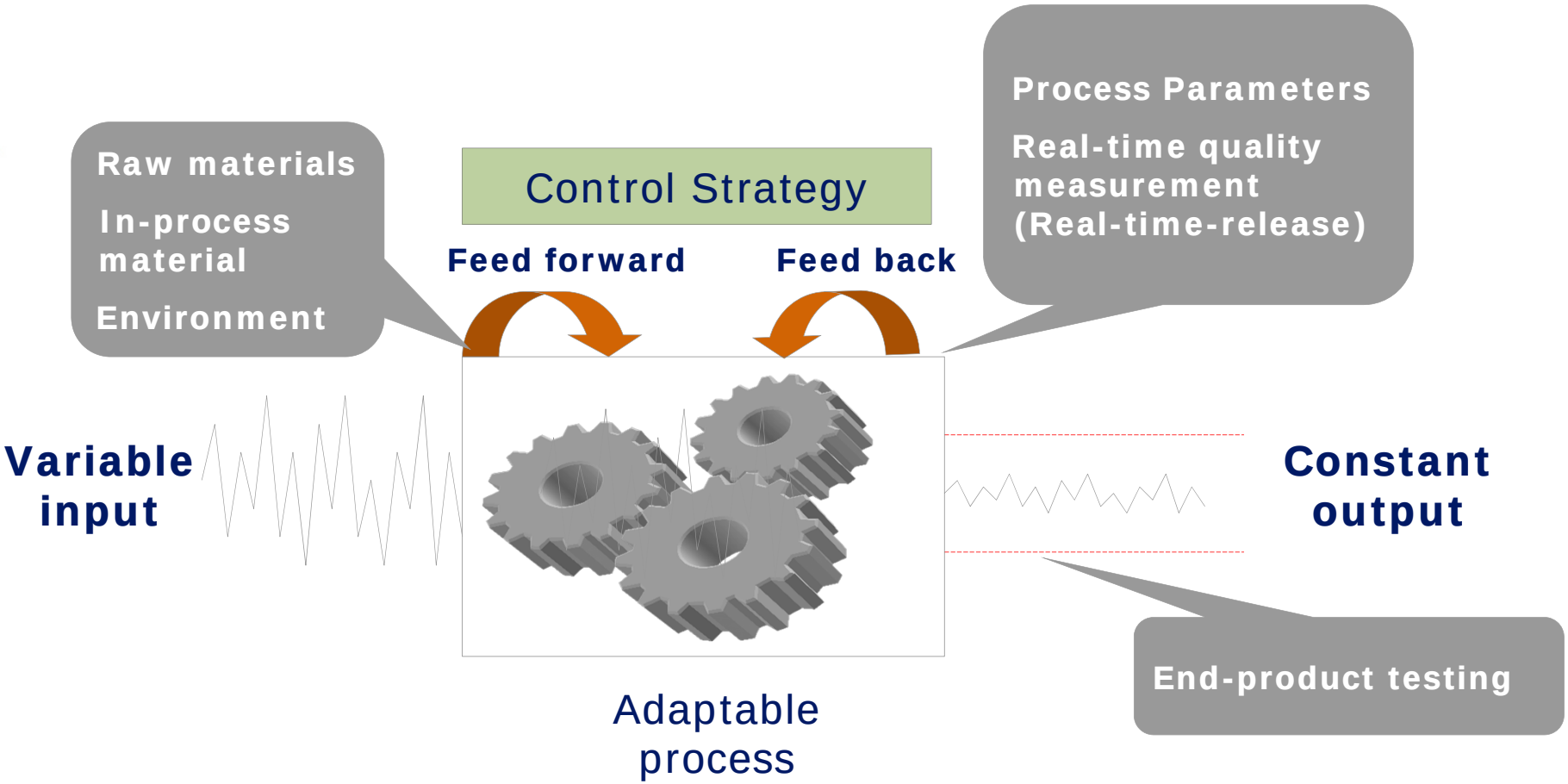
Where We Come From…



…And Where We Are Going…



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The (new?) Principle of Quality Assurance

...the principle incorporates the understanding that the following conditions exist:

- **Quality**, safety, and efficacy **are designed or *built*** into the product.
- Quality **cannot be** adequately **assured** merely **by in-process and finished-product inspection or testing**.
- Each step of a **manufacturing process is controlled** to assure that the finished product meets all design characteristics and quality attributes including specifications.

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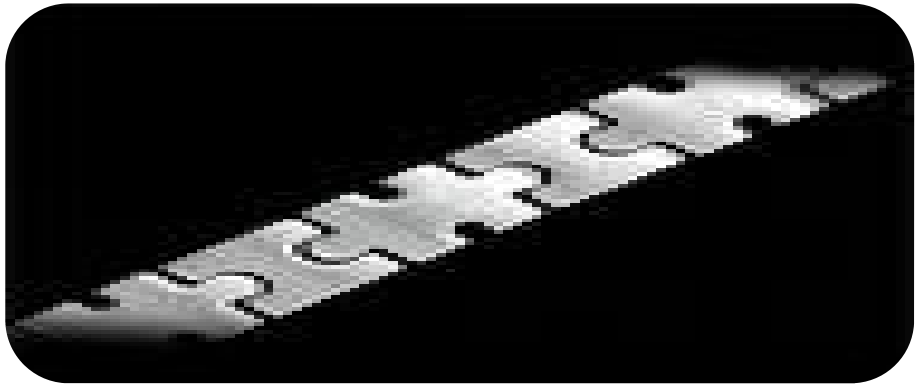
Product quality in the context of process validation means that product performance is consistent from batch-to-batch and unit-to-unit.

The Comparison

FDA

- FDA asking for more scientific arguments.
- *Three is* NOT *a magic number.*
- Apply a Life Cycle approach.
- 10 fold rule

The 2011 guide collects several stand-alone activities in to one context: ***Process Validation***.



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The Comparison

EMEA

- enhancement of process understanding.
- *Still use (minimum) three batches as a rule.*
- Apply a Life Cycle approach.
- Include Risk Assessment.
- 10 fold rule with approval
- Continuous Verification as an alternative.

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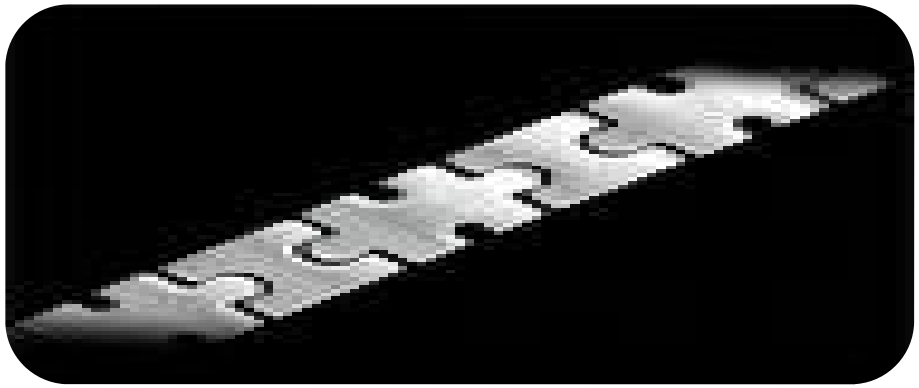

Process Validation is defined as the collection and evaluation of data, from the ***process design stage throughout production,*** which establishes scientific evidence that a process is capable of consistently delivering quality products.

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Process Validation During the Product Life Lifecycle Approach

- Overall validation is not *completed* but **on-going**.
- 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.

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Lifecycle approach links product and process **development** to the **commercial manufacturing** process, and maintains the process in a state-of-control during **routine production**.

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The PV puzzle – The 3 stages

1. ***Process Design:*** The commercial process is defined during this stage based on knowledge gained through development and scale-up activities. (A combination of lab, pilot, small scale and commercial scale studies).

2. ***Process Qualification:*** During this stage, the process design is confirmed as being capable of reproducible commercial manufacturing. Including qualification of the facility, utilities and equipment.

3. ***Continued Process Verification:*** Maintenance, continuous verification, and process improvement. On-going assurance that routine production process remains in a state of control. Assessed by collecting and monitoring information during commercialization.

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Process Design

Performing the Process Design

Process Knowledge **Product Knowledge** **Understanding**

- During the process design study, large amounts of knowledge will be generated.
- All activities and studies must be documented.
- Risk assessment of the process (selecting parameters).
- Design of Experiments (DOE)
- Modeling (predicting and confirming the process/parameter behavior).

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Process Design (continued)

Establish a Control Strategy

Process knowledge and understanding is the basis for establishing an approach to process control for each unit operation and the process overall.

The control strategy covers:

- The overall strategy for process control
- The commercial production and control records
- The operational limits

The Control Strategy should be carried forward to the next stage (PQ) for confirmation.

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STOP
Evaluate your current Design Phase

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Process Design
Where are we today?

- What type of information is gathered during the design phase?
- How does this information help to ensure that product is produced consistently every time?
- How well do you know your process / product?
- What's in the Technology Transfer Package?

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Process Design – Stage 1 output:

- Verification/determination of the limits for the *critical process parameters.*
- The limits/process boundary have been validated.
- Knowledge of process variable is gained, enabling the **establishment of control strategy**.

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Process Qualification

Successful completion of this stage is necessary before commercial distribution.

The process qualification stages covers:

- Design of the facility
- Qualification of the equipment and utilities
- Performance qualification

For all activities during the *Process Qualification* – cGMP procedures must be followed.

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Process Qualification (continued)

- The Qualification should demonstrate that the **utilities and equipment** are suitable for their intended use.
- Risk management can be used to prioritize activities and to identify the level of effort during the qualification.
- It must be verified that the utility systems and equipment operates in accordance with the process requirements in all anticipated operating ranges.
- The qualification should include challenging of the equipment functions, e.g., interventions, stopping and start-up, as expected during routine production.

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Process Qualification (continued)

- Three is ***not*** a magic number…The past and the present and the future. You **no longer** get three as a magic number.
- The approach to PQ should be based on the **overall** product and process **understanding**.
- The PQ lots should be manufactured under normal conditions by personal expected to routinely perform each step.
- The manufacturer should judge whether it has gained sufficient understanding to provide a HIGH degree of assurance in its process to ***justify*** commercial distribution of the product.

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STOP
Evaluate your current Process Qualification Phase

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Process Qualification
Where are we today?

- Do I have confidence in my manufacturing process?
- 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?

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Process Qualification – Stage 2 output:

A successful PQ will confirm the process design and demonstrate that the commercial manufacturing process performed as expected.

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Continued Process Verification

The goal of this stage is to **continually** assure that the process remain **in a state of control during commercial manufacture.**

- In **1987** it is was called Revalidation or Requalification.
- Today a more broad focus should be applied.
- An ongoing program must be established to collect and analyze ***product and process data***.
- The information collected should verify that the critical quality attributes are being controlled throughout the process.

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Continued Process Verification

Once established, the **equipment qualification** status must be maintained through:

- Routine monitoring
- Maintenance
- Calibration procedures

And the data should be assessed periodically to determine whether re-qualification should be performed.

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Continued Process Verification

On-going Sampling is part of the program:

- ***In the first phase of commercial production.***
  Continued monitoring and/or sampling at the level established during the process qualification stage.

- ***In the second phase of commercial production.***
  When sufficient data is available to generate significant variability estimates and the variability is known.
  - sampling and/or monitoring should be adjusted to a statistically appropriate and representative level.

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Continued Process Verification

Process Optimization

Data gathered during Stage 3 might suggest ways to improve and/or optimize the process.

The information and data about

- product performance
- manufacturing experience

should be periodically reviewed to determine whether any **changes to the established process are warranted**.

- Modifications may warrant additional process design and process qualification activities.

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STOP
Evaluate your current Continued Process Verification Phase

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Continued Process Verification
Where are we today?

- How do I know my process remains in control?
- What type of data is being collected?
- How often is this data reviewed?
- How do I react to trends in the data?
- What type of sample plan is in place?

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Continued Process Verification – Stage 3 is on-going

- Collection and evaluation of information and data about the performance of the process, will allow **detection of process *drift***.
- On-going feedback about product performance is an **essential feature** of process maintenance.

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The New Paradigm – Where Are We Going?

With the new paradigm there is an increased focus on assuring process robustness and a process in control.

- ***The control strategy*** is focusing on the process parameters. If the control strategy is outside the process limits, the *Critical Quality Attributes* of the product can be affected thereby creating a hazard for the patient.

- The QbD concept, when fully implemented, allows ***real-time release*** instead of release testing – a well known concept, for sterilization processes, here called *Parametric released*.

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The New Paradigm – Where Are We Going? (continued)

With the new paradigm there is an increased focus on continually assuring that the process remains in at state of control.

- An on-going program - ***Continues Process Verification*** – must be established, where the purpose is to verify the critical quality attributes are being controlled throughout the process.
- The program should included relevant process trends, quality of incoming materials, in-process material, etc.
- Data should be ***statistically trended*** and review by trained personnel (SMEs).

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Summary
FDA Process Validation DRAFT

1. Process Design

- Select utilities and equipment
- Verify build and installation
- Verify operation in all operating ranges
- Challenge in routine production:
  loads performance of interventions

2. Process Qualification (PQ)

•Combines qualified equipment and trained personnel with commercial manufacturing process, control procedures and components to produce commercial batches

3. Continued Process Verification

•Continually assure that the process remains in a state of control.

•Continued monitoring at the level established during PQ until significant data is available to generate significant variability estimates.

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The Process validation Guide

The guide is available on-line form the CDER website.

http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070336.pdf

http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2012/04/WC500125399.pdf

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Thank You

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