Connecting People, Science and Regulation

# ICH Q7 Chapter 12 & 19.6: Process Validation

PDA - PIC/S
ICH Q7 Training 01/2014



## Disclaimer

- **The slides set is based on the training sessions developed and performed by the members of the ICH Q7 Expert Working Group (EWG) on ICH Q7 2001/2002**
- **The slides regarding the Q8,Q9,Q10 implementation have been developed by members of the ICH Q-IWG originally prepared and presented by Stephan Rönninger and Jacques Morenas**
- **The slides have been updated 2012 and represents the views of the PDA / PIC/S committee for the purposes of a general training for regulators and industry**

***We focused on elements in ICH Q7 where further explanation and/or clarification is useful.***

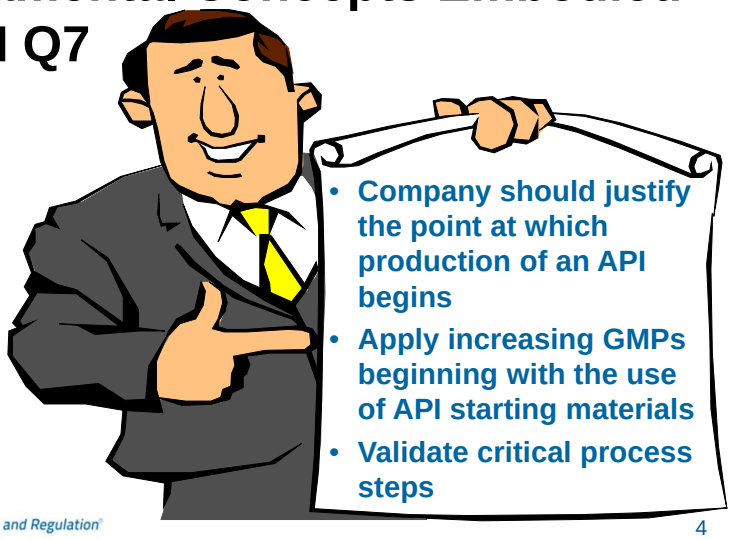
## Content

- **General about Validation**
- **Validation Policy** *(12.1)*
- **Validation Documentation** *(12.2)*
- **Qualification** *(12.3)*
- **Process Validation** *(12.4)*
- **Process Validation Program** *(12.5)*
- **Periodic Review of Validated Systems** *(12.6)*
- **Validation of APIs Used In Clinical Trials** *(19.6)*





## Fundamental Concepts Embodied in ICH Q7



- **Company should justify the point at which production of an API begins**
- **Apply increasing GMPs beginning with the use of API starting materials**
- **Validate critical process steps**

# Validation Drug Products vs. APIs

| Drug (medicinal) Product | API |
|---|---|
| **Validate all manufacturing steps, such as**<br>- Cleaning<br>- Weighing<br>- Measuring<br>- Mixing<br>- Blending<br>- Filling<br>- Packaging and labeling | **Validate critical processing steps**<br>- Determined to impact the quality and purity of the API |

- *There need to have a clarification which steps are critical*
- *There should be a scientific justification excluding specific steps consider that this is not necessarily a regulatory filing issue*
- *Not validating a step does not mean that there is no control*



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# Processing steps where validation may be applicable

## Examples of typical critical steps

- **Point where significant impurities may be introduced into or removed from the process**
- **Point after which no significant impurities will be removed from the process**
- **Point at which all essential structural elements of the API are present**
- **Steps that effects the physical characteristics of the API**

## 12.1 Validation Policy

- **Should extend to those operations determined to be critical to the quality/purity of API**
- **Critical parameters/attributes are normally identified during the development stage or from historical data, along with ranges necessary for reproducible operations** *(12.11)*



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## 12.1 Validation Policy

- **Includes** *(12.11)*
  - Defining the API in terms of its critical attributes
  - Identifying process parameters that could affect the critical quality attributes of the API
  - Determining the range for each critical process parameter used during routine manufacturing

# Definitions on Validation

- **As defined in ICH Q7**
  - 'Establishing documented evidence which provides a high degree of assurance that a specific process will consistently produce a product meeting its pre-determined specifications and quality attributes.'*(12.40)*
- **As defined in ICH Q8(R2)/Q11**
  - Continuous Process Verification
    An alternative approach to process validation in which manufacturing process performance is continuously monitored and evaluated



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# Validation / Qualification

- **Significant items, including significant changes, which should be qualified**
  - Premises
  - Facilities
  - Equipment or

  **Respectively validated**
  - Processes

  **which may affect the quality of the product**

# Objective of Process Validation

## Generate evidence of consistency

- **Traditional approach**
  - A Manufacturing processes: Repeatability
- **Enhanced approach**
  - A Manufactruing processes: Capable and Robust

◆ *Over the time the enhanced approach should be the norm and applied also for existing processes*





# About Validation and related terms

| Traditional Process Validation | Continuous Process Verification |
|---|---|
| **Outcome:** Repetition possible | **Outcome:** A robust process is functioning |
| **Achieved by:** + usually 3 validation batches + additional sampling | **Achieved by:** + ongoing monitoring + risk control actions, if applicable |

## Potential Considerations on Process Validation

| | 'Process Validation' | | |
|---|---|---|---|
| Approach | **Traditional approach to process validation** | | **Continuous Process Verification (CPV)** |
| | Empirical; Usually based on traditional development | | Enhanced risk and science-based |
| Life cycle approach | Emphasis on limited number of batches | | 'Continuous process verification' throughout product lifecycle |
| Focus | Repeatability | | Robustness |
| Use of statistical tools | Trending | | Monitoring & Trending |
| Documentation | a) Protocol, Report<br>b) Manufacturing batch record & additional sampling / testing for validation batches | | a) Protocol, Report, Annual Product Review<br>b) Integrated into routine workflow c) Manufacturing batch record facilitating additional knowledge and CAPA |
| State of control | Validated at 'set point. Variability more likely. Very limited information about extrems | | A demonstrated 'state of control' maintained. Variability minimized. |
| Relationship to control strategy | Additional quality attribute monitoring for valid. batches:<br>a) Additional testing<br>b) Additional samples<br>c) Document process parameters | | Ongoing enhanced CQA & CPP monitoring |
| Process improvement | Reactive: Opportunity for process improvement based on periodic review and deviation control, which may not be timely and validation activities need to be repeated | | Proactive: Opportunity for continual process improvement and review of the validation activities according to risk. |
| Sample size | An increase sample size for validation batches. | | Number of samples optimised during lifecycle in response to process knowledge. |
| Change management | Reactive approach. | | Proactive approach. |
| Number of batches for PV | Fixed; additional monitoring for limited number and by a case by case basis | | All; includes process performance from all relevant batches/scales used during development as well as ongoing monitoring at commercial scale |

Process Validation typically occurs between these extremes

Based on ICH Q-IWG, 2011



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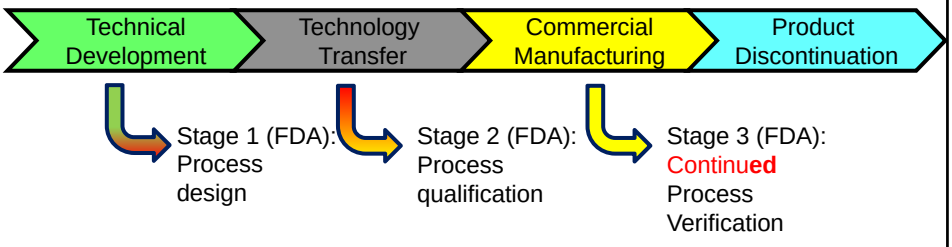
## Enhanced Validation

- **As of ICH Q10: 'Continuous process verification'**

**A life cycle approach**

e.g. see 'Process Validation: General Principles and Practices' (FDA 2011)



## Validation and QRM

- **QRM principles should be used**

**1. To identify the scope, extent and focus of the validation**

Use QRM tools such as e.g. Risk ranking and filtering / FMEA, Fishbone diagram, HACCP

**System approach**

**2. To support continuous process verification**

a) Retrospective trending using the traditional approach (e.g. X-bar charts, histograms)

b) Prospective monitoring the process performance (e.g. process capability assessments or EWMA, CuSum charts)

**Product approach**





## Ranges for Process Parameters

- **Necessary because variability is inherent in manufacturing processes**
- **Most often set during process development**
- **Limits not normally tested at plant scale due to economic and safety reasons**
- **Ranges in commercial batch production are often tighter than the acceptance ranges**

## Determining ranges for Process Parameters

- **Historical data from manufactured batches are used**
- **Experiments are often conducted in the laboratory or pilot plant to determine the effect of changes in control variables on the API**
  - Effect of raw material purity on API's impurity profile
  - Effect of reactor's temperature on degradants
  - Effect of cooling rate on polymorphs



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## 12.2 Validation Documentation

- **Validation protocol should be reviewed / approved by the quality unit(s) and other designated units** *(12.20)*
- **Protocol should specify** *(12.21)*
  - Critical process steps
  - Acceptance criteria
  - Type of validation to be conducted
  - Number of process runs

## 12.2 Validation Documentation

- **Validation report should include** *(12.22)*
  - Cross reference to the protocol
  - Summary of results
  - Explanation of process deviations
  - Appropriate conclusions
  - Recommendations
  - Variations from the validation protocol should be justified and documented *(12.23)*
- *An additional plan how to effect ongoing process verification*
- *A periodic report e.g. as part of product quality review or a separate document*





## 12.3 Qualification

- **Before initiating process validation, appropriate qualification of critical equipment and ancillary systems should be completed** *(12.30)*
  - URS = User requirements specification
  - DQ = Design Qualification
  - IQ/OQ and PQ = Installation, operational and performance

## 12.4 Process Validation

- **Normally performed for all API processes: Prospective Validation** *(12.42)*
  - *An exception may be for atypical API*
- **Validation of API process should be completed before commercial distribution of the final drug product manufactured from that API** *(12.42)*
  - *When implementing the continuous process verification approach the appropriate steps of the life cycle must be completed*



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## 12.4 Process Validation

- **Concurrent Validation** *(12.43)*
  - *now called 'concurrent release' (US-FDA)*
    - Can be conducted when data from replicate production runs are unavailable because
    - Only a limited number of API batches have been produced (e.g., clinical or orphan drugs)
    - API batches are produced infrequently (e.g., limited market demand, complex multi-step processes)
    - API batches are produced by a validated process that has been modified

# 12.4 Process Validation

- **Concurrent Validation** *(12.43)*
  - Batches can be released and used in production of drug products for commercial distribution based on thorough monitoring and testing of the API batches
- **Exception for *well established processes* used without significant changes to API quality due to changes in** *(12.44)*
  - Raw materials, Equipment, Systems, Facilities
  - Production process



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# 12.4 Process Validation

- **Retrospective Validation may be used where** *(12.44)*
  - Critical quality attributes and critical process parameters have been identified
  - Appropriate in-process acceptance criteria and controls have been established
  - Impurity profiles have been established for existing API
  - Process/product failures attributed mostly to operator error or sporadic equipment failures unrelated to equipment suitability, not process variability
- *Based on this historical concept current expectation is that companies no longer make use of this approach as their sole evidence of validation and should be moving towards CPV*

# 12.5 Process Validation Program

## How many Validation Batches?

- **Depends on the complexity of process or magnitude of process change being considered** *(12.50)*
- **For prospective and concurrent validation** *(12.50)*
  - Three consecutive, successful production batches should be used as a guide
  - Additional batches may be needed in some instances to show process consistency

◆ *For continuous process verification all batches are in the scope*





# 12.6 Periodic Review

- **Systems and processes should be periodically evaluated to verify that they are still operating in a valid manner** *(12.60)*

◆ *Using the enhanced CPV approach these is automatically fulfilled*

- **No need for revalidation if significant changes have not been made and a quality review confirms that the system or process is consistently producing material meeting specifications** *(12.60)*

## 19.6 Validation of APIs Used In Clinical Trials

- **Process validation normally inappropriate because of** *(19.60)*
  - Process changes during API development
  - Production of a single or limited number of API batches
- **Combination of controls, calibration, and where appropriate, equipment qualification, ensures API quality during the development phase** *(19.60)*



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## 19.6 Validation of APIs Used In Clinical Trials

- **Process validation should be conducted in accordance with Section 12 when batches are produced *for commercial use, even when such batches are produced on a pilot or small scale*** *(19.61)*

◆ *Using the enhanced CPV approach the requirements for the development (& transfer) life cycle stage apply*

## Key Message

- **Risk and science based approach**
  - An understanding of processing go a long way towards determining what aspects of an operation are critical
- **Goal: Generate evidence of consistency**
- **Validation Master Plan**
  - The key elements of a qualification and validation program of a company should be clearly defined and documented





## Acknowledgement

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Parenteral Drug Association
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