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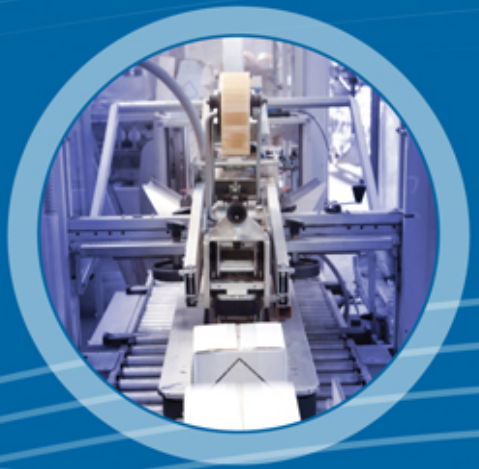
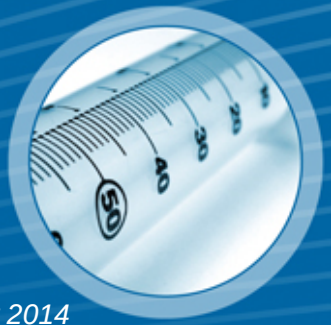
ICH Q7 Chapter 12 & 19.6:
Process Validation





PDA - PIC/S ICH Q7 Training

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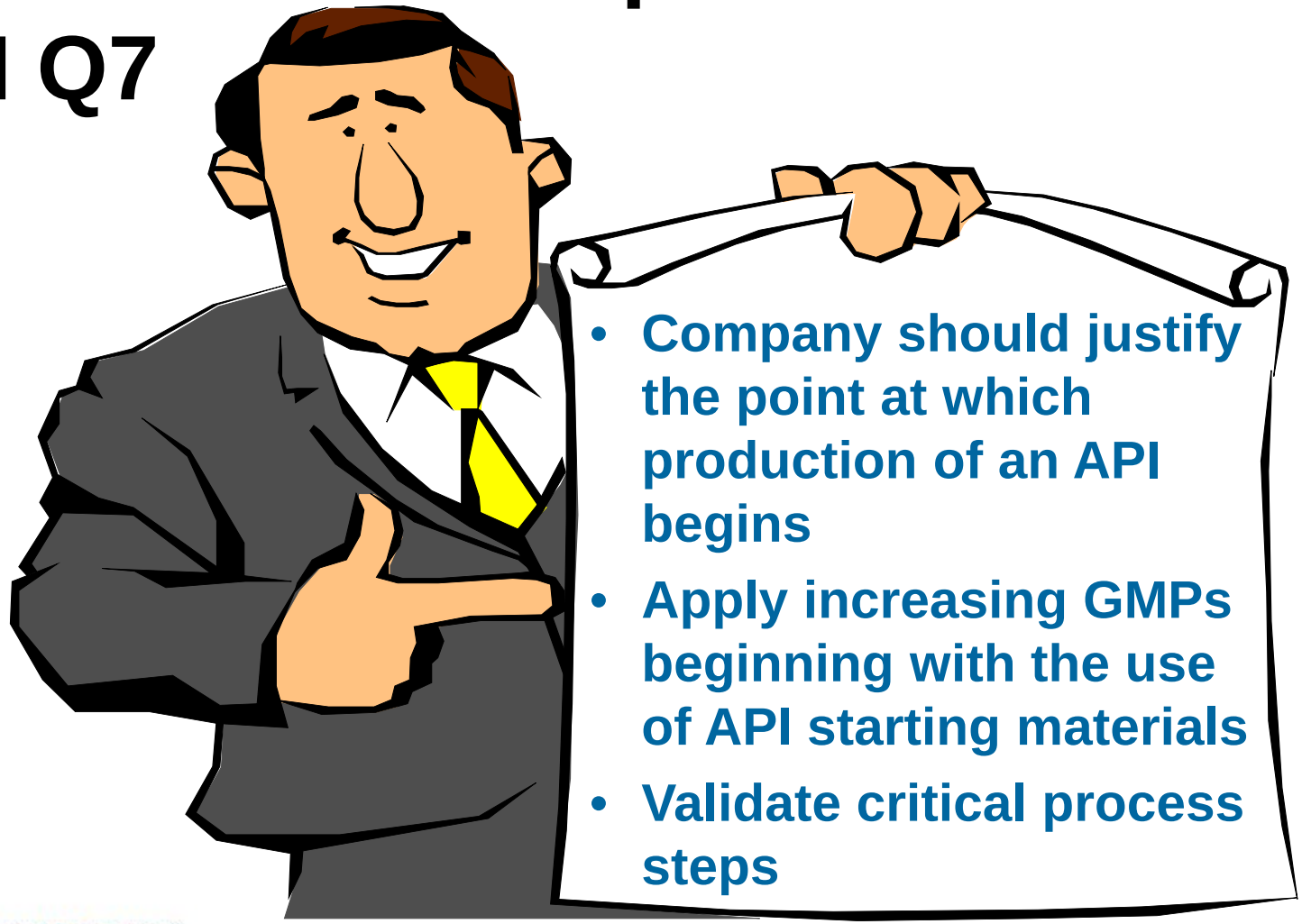
Fundamental Concepts Embodied in ICH Q7



- 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

Validate all manufacturing steps, such as

- Cleaning
- Weighing
- Measuring
- Mixing
- Blending
- Filling
- Packaging and labeling

API

Validate critical processing steps

- 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*

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)*

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

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** (according to ICH Q7)
  - Manufacturing processes: Repeatability
- **Enhanced approach** (according to ICH Q11[Q8(R2)] see ICH Q-IWG)
  - Manufacturing processes: Capable and Robust
  - *Over the time the enhanced approach should be the norm and applied also for existing processes*
  - *ICH Q8-Q11 all make reference to the "product lifecycle" . Under this model, "continuous process verification" (ICH Q8), rather than a separate or "enhanced" activity, is part of the change management for continual improvement throughout product lifecycle.*

About Validation and related terms

Traditional Process Validation [e.g. ICH Q7]

Outcome:
Repetition possible

Achieved by:
+ usually 3 validation batches
+ additional sampling

Continuous Process Verification [e.g. ICH Q11/Q8, Q10, Q-IWG]

Outcome:
A robust process is functioning

Achieved by:
+ ongoing monitoring
+ risk control actions, if applicable

Potential Considerations on Process Validation

	'Process Validation'	Process Validation typically occurs between these extremes	
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 b) Manufacturing batch record & additional sampling / testing for validation batches		a) Protocol, Report, Annual Product Review 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: a) Additional testing b) Additional samples 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

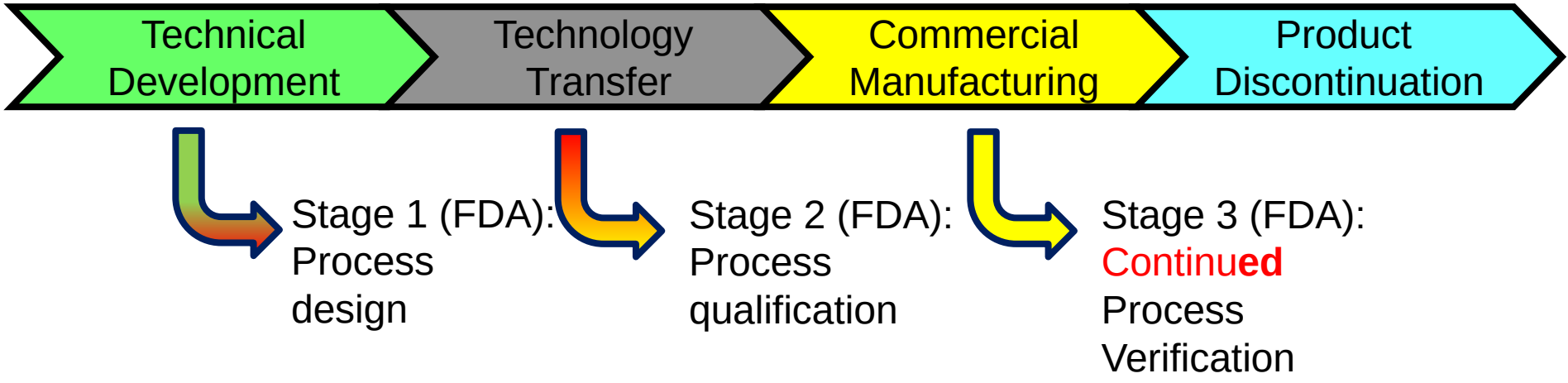
Based on ICH Q-IWG, 2011

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

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)*
- **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*

12.4 Process Validation

- **Concurrent Validation** *(12.43)*
  - *now called 'concurrent release'* (Guidance for Industry – Process Validation: General Principles and Practices, *US-FDA, 2011)*
    - 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
  - *It is expected to use concurrent validation only rarely*

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

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 (ICH Q11 and respectively ICH Q8(R2); see also ICH Q-IWG points to consider)*

◆ *In general risk Management principles (ICH Q9), specified and/or acceptable number of batches will depend on many parameters and could be decided on a case-by-case basis*

Q7 Expectations for PV (12.5/12.6)

- # of process runs should depend on the complexity of the process or magnitude of the process change
- 3 consecutive batch approach is mentioned only as a GUIDE, not expectation for all cases: additional process runs may be warranted to prove consistency of process
- Critical parameters should be controlled and monitored
- Impurity profile controlled and monitored
- All changes that could affect the production and controls should be evaluated
- Validation Report-Cross Referenced With Protocol

SLIDES 28-40

Focused on FDA's Guidance on Process Validation Also Applicable to APIs

What is CPV ?
Stage 3- Continued Process Verification

"…continual assurance that the process remains in a state of control (the validated state) during commercial manufacture."

"A system or systems for detecting unplanned departures from the process as designed is essential to accomplish this goal."

Stage 3- Continued Process Verification

- "*An ongoing program to collect and analyze product and process data that relate to product quality must be established*

- *The data collected should include relevant process trends and quality of incoming materials or components, in-process material, and finished products.*

KEY OBJECTIVE OF CPV-S3

SYSTEM(S) IN PLACE

Collect Information

Relevant Data (meaning of data?)

Analyze*

NOTE: impact of unplanned deviations, data used related to process performance, problems, actions taken to correct, did it prevent recurrence, and is the process under control

Helpful Questions: Stage 3 CPV

1. **How and what data should be collected to assure process continues to be in control? Intra lot and inter lots.**

Q. WHAT DATA WOULD YOU EXPECT A FIRM TO COLLECT?

2. What is the information collected telling us?

3. What does the below mean to company?

- Repeated incidents of impurities, increase in # peaks
- Many “minor”, changes
- # of lab investigations (analyst…)
- # process deviations
- # rejects
- # of lots reprocessed, # process changes
- Lots returned, complaints, recalls,

4. How involved or knowledgeable is the quality unit about the trends and process variability?

5. Who evaluates the CAPA implemented ?

6. Who evaluates recurrence or repeated problems?

7. Who is reviewing the information/data and reaching conclusions about its meaning?

8. Would collecting and analyzing trends be a way to provide assurance, why?

9. How about process/product stability/process capability?

10. Procedures should describe how the firm intends to do trending and assessments?

11. Should know the process so well that they should avoid overreaction to individual events, but must AVOID failing to detect unintended process variability.

CPV-S3

12. How about raw material supplier qualifications, why is this important to assure continuous control?

13. When is the assessment of complaints, OOS, process deviations, uninspected variations, changes…. performed ? At the end of the year, or is it a continuous process?

CPV-S3

14. Does the firm continue to monitor and sample process parameters, and the quality attributes, as established during process qualification until sufficient data are available to levels and frequency or routine sampling and monitoring?

15. How are changes to process monitoring done, and who is involved/decides?

16. How are process improvements implemented and who is involved?

17. Process Variability Periodically Assessed?

“What does periodically mean?”

18. How and who manages process changes?

19. Who maintains facilities, utilities and equipment?

Stage 3- Continued Process Verification

- 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.”
- On-going programs to evaluate and assure the state of control of the process

Regulatory Expectation

FIRMS MUST HAVE:

Systems to detect and manage process variability: complaints, process deviations, OOTs, OOS, process yield variations, batch record reviews, review of test data/raw material/in-process and finished test results…how and who collects and analyzes trends, who investigates complaints…

"It met specifications, so my process continues to be in control"

- Conclusions from sampling and testing are probabilistic.
- Interplay between sample size, process variability, confidence desired and probability.
- The outcome from conducting a single USP/compendium/approved method test cannot be assumed for all the untested units in the batch.

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)*

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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