Qualification and Validation – a review of PIC/S Annex 15

Presented by Marc Fini

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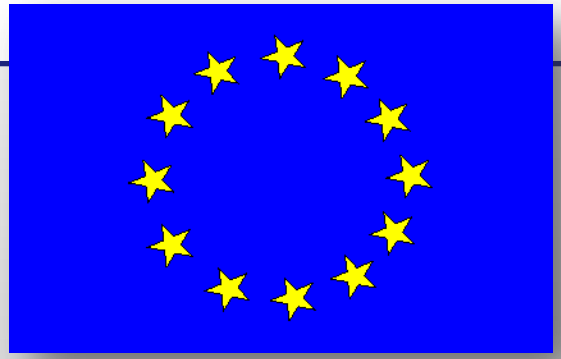
What is validation?

Process Validation

- The documented evidence that the process, operated within established parameters, can perform effectively and reproducibly to produce a medicinal product meeting its predetermined specifications and quality attributes.

EMA Guideline on Process Validation, 2012



What is validation?

Process Validation requires 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 characteristics

USFDA Guideline General Principles of Process Validation, May 1987

What is validation?

Process Validation

- The 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 products

US FDA Guidance for Industry Process Validation 2011

What is validation?

The qualification and validation process should establish and provide documentary evidence that:

- The premises, the supporting utilities, the equipment and the processes have been designed in accordance with the requirements of GMP.
- This normally constitutes Design Qualification.

What is validation?

The qualification and validation process should establish and provide documentary evidence that:

- The premises supporting utilities and the equipment have been built and installed in compliance with their design specifications.
- This constitutes Installation Qualification.

What is validation?

The qualification and validation process should establish and provide documentary evidence that:

- The premises, supporting utilities and the equipment operate in accordance with their design specifications.
- This constitutes Operational Qualification.

What is validation?

The qualification and validation process should establish and provide documentary evidence that:

- A specific process will consistently produce a product meeting its predetermined specification and quality attributes.
- This constitutes Performance Qualification

What is validation?

- A high degree of assurance, there can be no 100% guarantees
- Documented, verifiable evidence is one key deliverable of validation
- A demonstration that the process is robust and repeatable
- Meeting pre determined acceptance criteria

Qualification and validation

ANNEX 15

QUALIFICATION AND VALIDATION

PRINCIPLE

1. This Annex describes the principles of qualification and validation which are applicable to the manufacture of medicinal products. It is a requirement of GMP that manufacturers identify what validation work is needed to prove control of the critical aspects of their particular operations. Significant changes to the facilities, the equipment and the processes, which may affect the quality of the product, should be validated. A risk assessment approach should be used to determine the scope and extent of validation.

Activity

Analyse the principle of Annex 15 and highlight the key terms

Qualification and validation

"…that manufacturers identify what validation work is needed to prove control of critical aspects of their particular operations."

- Significant changes should be validated
- Risk assessment approach

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Planning for validation

All validation activities should be planned

One mechanism for capturing validation planning is a Validation Master Plan (VMP)

- VMP is a summary document
- A VMP needs to be clear, concise and brief
- large scale projects may require a separate VMP

What are the features of a good project plan?

?

Planning for validation

VMP components should include:

- Validation policy
- Organisational structure for the validation effort
- A summary of what is being validated
- The documentation format for protocols and reports
- Planning and scheduling the validation effort
- Deviation management and Change control describing how deviations and changes will be managed
- References

Planning for validation

The validation policy

- How does the organisation handle validation?
- What validation approach will be used?
- How will the extent of validation work be determined?
- How will control of critical aspects be determined?

Planning for validation

Organisational structure for the validation effort:

- Who are the Subject Matter Experts (SMEs)?
- Who will own the validation project?
- How will end users be represented?

Validation projects can become complex and troublesome and managers with excellent people skills, in conjunction with SMEs, may add great value

Planning for validation

The organisational structure for the validation effort should not be limited to the same people every time.

- SMEs will change depending on the project.

Validation projects are about knowledge accumulation, so where a SME is outside of your organisation, develop a strategy to acquire knowledge.

Planning for validation

Ultimate ownership of the validation project is critical and someone of the appropriate authority needs to be identified.

- This person will have review and approval responsibilities for all validation documentation, deviations and changes.
- The owner should not automatically be the area manager of the department most affected.

Planning for validation

How will the end users be represented?

- The input from end users, during the planning phase can ensure a smoother hand over to routine operations

Planning for validation

A summary of what is being validated	This should not be a cursory exercise but an effort to document and comprehend the process flow of the system being validated
The documentation format for protocols and reports	These documents are critical and will be a legacy of the validation effort Cross referencing of these documents must be controlled

Planning for validation

Planning and scheduling

- Consider a current state and future state diagram. This can assist to identify potential compliance issues.
- The validation flow must be documented.
- Does the project feature gateways? For example IQ must be completed before commencing OQ.

Planning for validation

Change control and deviation management.

- Consider using the change control and deviation management processes that already exists in the organisation instead of stand alone processes just for the validation project.

- A risk based approach with appropriate justifications is core to GMP compliance.

Documentation

Written protocols that specify Qualification and Validation processes.

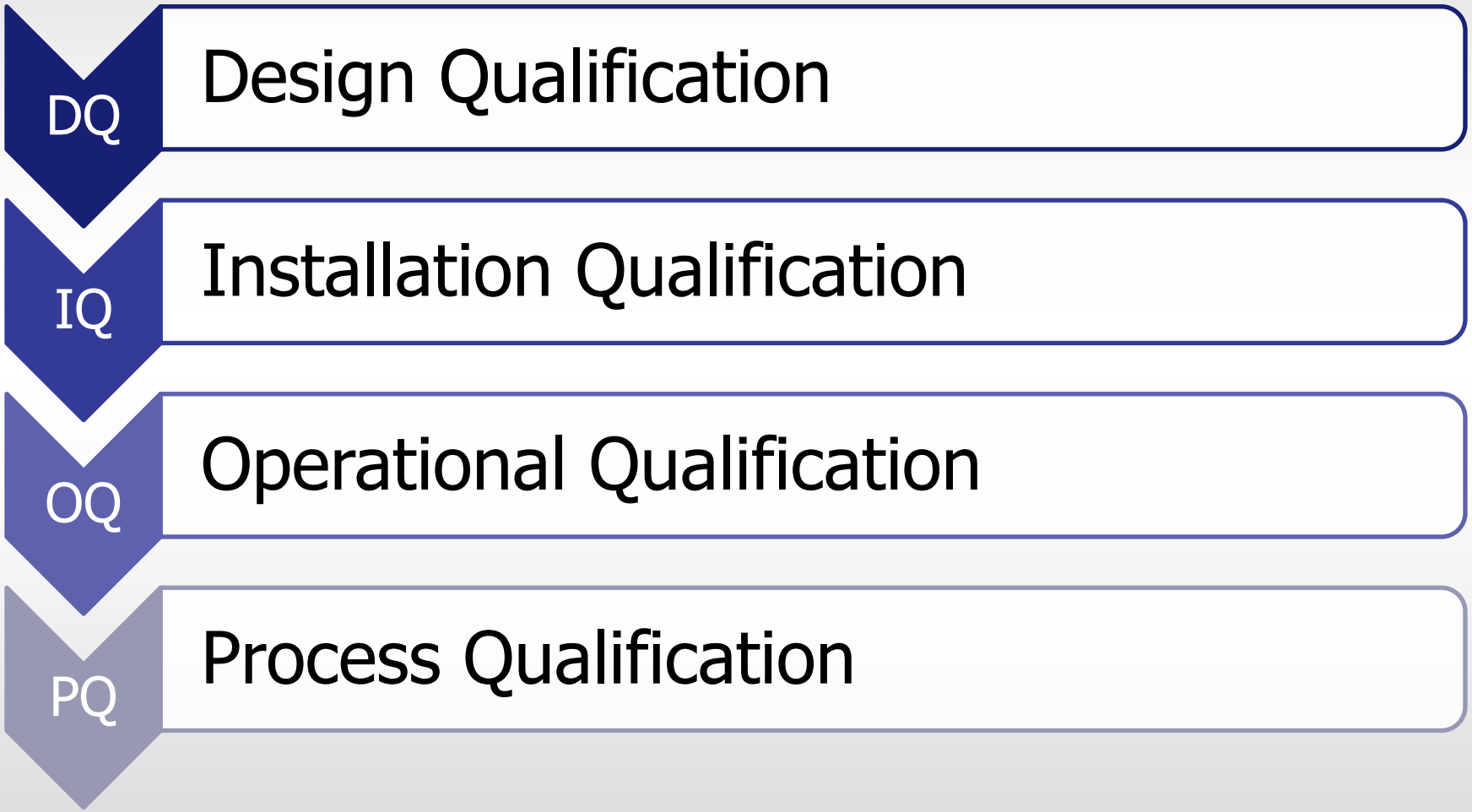
- The review, approval and control of protocols must maintain Good Documentation Practice requirements.
- Acceptance criteria must be detailed before validation work commences.

Documentation

Validation reports must cross reference the protocol and include:

- A summary of the results obtained.
- All changes and deviations to the protocol and reference any other documents justifying the changes and deviations and their impact to the validation effort.
- Conclusions drawn from the validation activities.

Qualification



Design Qualification

To verify that the design of the system complies with GMP.

Design reviews (DR):

- These can provide a comprehensive review of the overall system and should be used to identify and remediate issues.

- A DR should not be a desk based activity, instead wherever possible, a hands on review of the system.

Installation Qualification

An IQ should include but not be limited to the following:

- Installation of equipment according to current engineering documentation and specifications.
- Collation of supplier documentation.
- Calibration requirements.
- Verification of materials of construction.

Operational Qualification

The OQ should include:

- Tests developed from system knowledge
- Tests that include "worst case" conditions or upper and lower operating limits

Operational Qualification

The OQ outcomes should allow:

- Finalisation of calibration procedures
- Finalisation of operating and cleaning procedures
- Development of training methodology for the system
- Preventative maintenance programs to be established
- A formal release for the next phase of the project

Where does training fit in?

- Consider the impact of training within the validation context
- When do you consider training and the requirements for competent personnel to be established?
- In general, training is a deliverable of the OQ phase, however if knowledge is an outcome of validation having skilled, competent resources earlier in the validation lifecycle may provide ongoing benefits

Process Qualification

Process Qualification follows successful IQ and OQ and should include at least:

- Where possible, tests using production materials or justified substitutes.
- Tests including upper and lower limits.
- PQ is referred to as a 'dress rehearsal' for routine production, so the entire system is under review.

Prospective validation

This is the preferred method of validation where a process or system is validated before routine commercial manufacture

Prospective validation

Some key considerations for prospective validation:

- Consider the manufacture of a series of batches under routine conditions.
- The number of batches should generate enough data for analysis.
- "It is generally considered acceptable that three consecutive batches/runs….would constitute a validation of the process."

Batch sizes for process validation should be the same size as routine commercial batches.

Concurrent validation

This refers to distribution of the product before process validation is complete.

This is only acceptable in certain circumstances and should not be standard practice.

A formal justification to perform concurrent validation must be documented and approved by authorised people.

Retrospective validation

This is a least preferred option

Retrospective validation is only acceptable for well-established processes.

- Performing retrospective validation after changes have been made is not acceptable.
- Change management is a critical quality system component and changes must be approved before they are implemented.

Retrospective validation

The advantage of retrospective validation is the availability of historical data, including:

Retrospective validation

Batches reviewed for retrospective validation should be a true reflection of batches during the review period chosen.

- This includes failed batches.
- Generally data from 10 to 30 consecutive batches should be reviewed.

Cleaning validation

Cleaning validation is to ensure the effectiveness of a cleaning procedure.

- Consider the process of manufacture to determine cleaning strategies.
- The sensitivity of methods is very important to detect residues or contaminants.

Cleaning validation

Generally only product contact surfaces need to be validated.

Consider the time between use and cleaning and the time between storage of components and reuse.

A worst case approach may be acceptable

- Generally, three consecutive cleaning applications are considered appropriate

Validation summary report

At the conclusion of the validation exercise, a validation summary report will bring together all the aspects of the validation and allow conclusions to be drawn regarding the suitability and overall compliance with the validation plan.

Change control

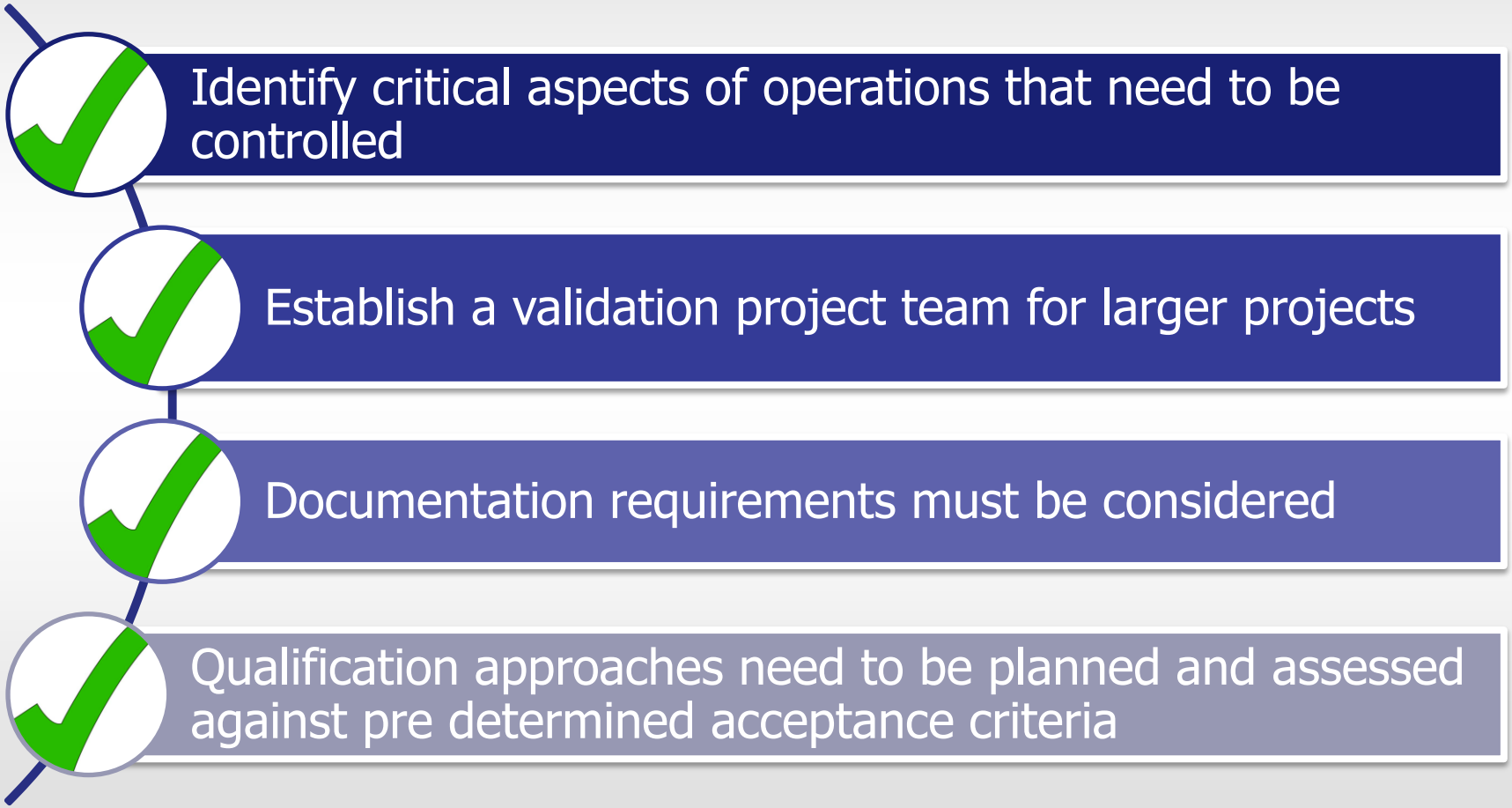
44. All changes that may affect product quality or reproducibility of the process should be formally requested, documented and accepted. The likely impact of the change of facilities, systems and equipment on the product should be evaluated, including risk analysis. The need for, and the extent of, re-qualification and re-validation should be determined.

Revalidation

A periodic review to ensure systems remain valid is required.

- This could become part of your product quality review program.
- Where there have been no "significant" changes then a review with evidence may be appropriate.

Summary



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