

GMP

APIC Active Pharmaceutical
Ingredients Committee

QUALIFICATION OF EXISTING EQUIPMENT

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GMP**APIC** *Active Pharmaceutical
Ingredients Committee*

1. Acknowledgement

This document was prepared by a Task Force consisting of representatives from various companies within the Active Pharmaceutical Ingredients industry that participate in the API Committee of CEPIC. We thank all the members mentioned below for their efforts, cooperation, creativeness, constructive comments and endurance. Without these elements this document would not have reached its present status.

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2. Introduction

Detailed guidance for the qualification of new equipment is given in existing guidelines (see References). However APIC recognized there is only limited guidance with respect to the qualification of existing equipment. Therefore APIC has prepared a document to reflect current thinking of the API manufacturing industry on this matter.

It is not unusual to find that an existing facility has a mixture of new fully qualified equipment (DQ, IQ, OQ, PQ) and partially qualified / unqualified equipment.

Through many years of use, it can usually be shown that facilities, systems, equipment and utilities can function to varied requirements. Nevertheless, cGMPs necessitate that, items which have impact on the quality of the intermediate or API, should be qualified. Formal qualification is the basis for the related activities such as validation associated with new product introduction or validation of existing processes. It forms the starting point for future change control. Qualification should provide documented verification that the parameters defined as critical for operation and maintenance are adequately controlled. It is essential that the qualification is practical and achievable, adds value to the project and is concentrated on the critical elements of the system. It is recommended that a risk assessment approach is used to define the depth of qualification. There should always be a reasonable proportionality between risk for the product quality, the amount of measures to be taken and documentation to be prepared (.e.g. stage of manufacture, regulatory status and intended use).

GMP**3. Scope**

This guide is intended for use by manufacturers of Active Pharmaceutical Ingredients (APIs) and API intermediates that use existing facilities, systems, equipment and utilities.

This guide is applicable to all stages from the API Starting Material onwards, which can influence product quality. However earlier stages could be considered.

4. Regulatory requirements

The ICH Q7a (see Reference 1) requirement is that facilities, systems, equipment and utilities are properly qualified and maintained to assure data and product integrity.

Additional guidance is provided by PIC/S: *“While it is not possible to undertake the details of an Installation Qualification for established equipment nor the detailed approach for an Operational Qualification, nevertheless there should be data available that support and verify the operating parameters and limits for the critical variables of the operating equipment. Additionally, the calibration, cleaning, preventative maintenance, operating procedures and operator training procedures for the use of the equipment should be documented and in use as standard operating procedures (SOPs).” (see Reference 3).*

5. Guidance**5.1 Risk Assessment**

This section describes the principle of Risk Assessment (RA) as applied to plant qualification.

The next section (5.2 “Procedure”) describes the recommended activities required to qualify existing equipment – including when to use the RA process.

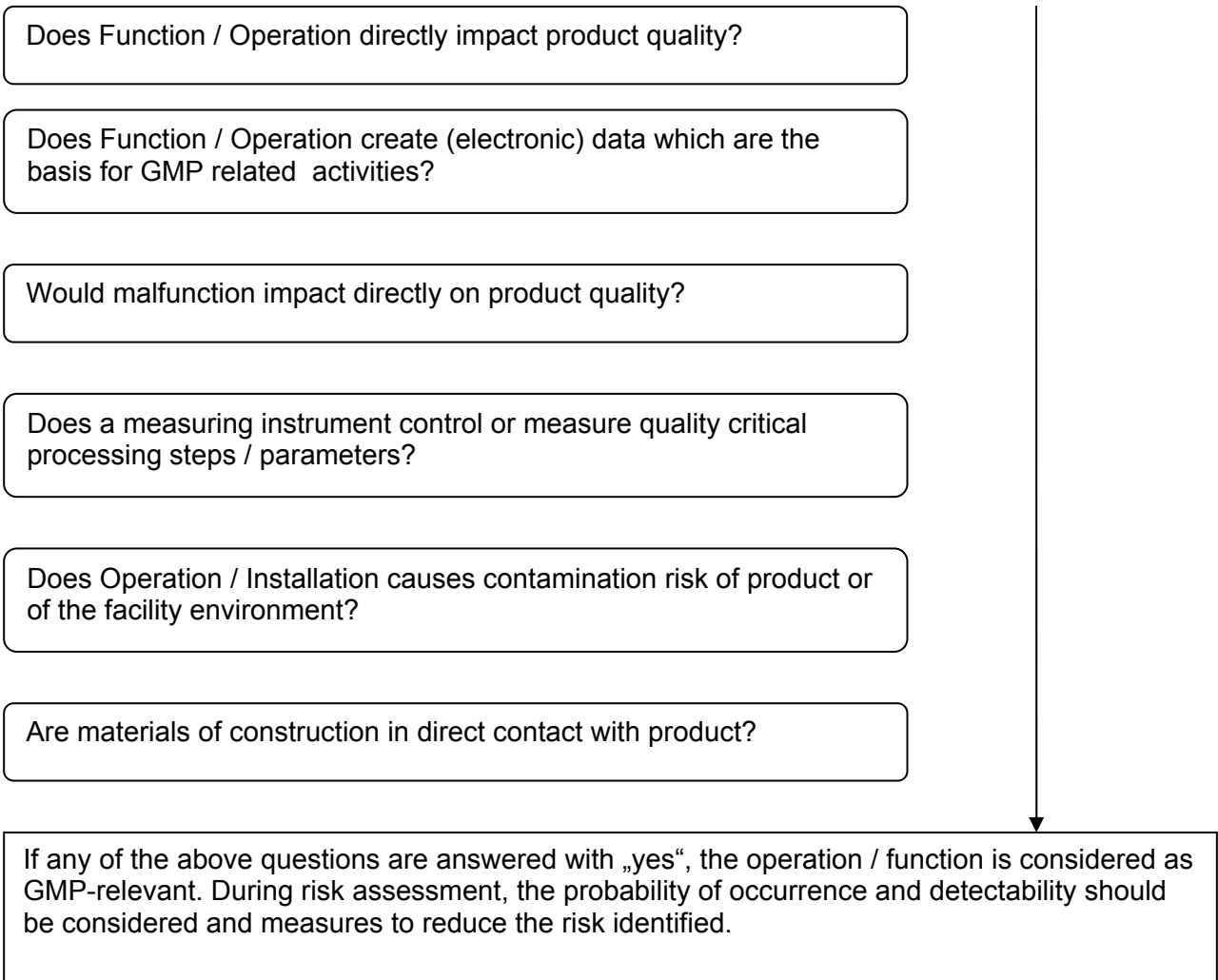
RA is a formal and systematic approach to identify GMP risks related to equipment and supporting systems. It is a very helpful tool that can be applied to plant, equipment and systems which have been in use for many years.

It is recommended that the manufacturing instructions are used in combination with general GMP requirements (e.g. design, documentation, risk for contamination, usage in final dosage form etc.) as the basis for the risk assessment. Each manufacturing step can be assessed individually with respect to critical operations / activities (e.g. stirring speeds, temperature ranges, pressure, hygroscopy, open product handling etc.). Process descriptions, development reports, product quality reviews and process validation reports can assist in identifying the quality critical operations and parameters.

Risk Assessment can be carried out using different approaches e.g. HAZOP, FMEA, decision tree etc. Equipment risk assessment can be performed by equipment train or by individual processing units (individual reactor, individual centrifuge, etc.) and supporting systems. A grouping strategy of similar/identical processing units can be used.

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Unit operations or functions could be assessed according to the following scheme:



An example for a technical GMP risk assessment is given below:

- Objective of the risk assessment
 - Identification of potential risks related to products, preventive / corrective actions and checks related to qualification.
- Scope
 - Identification of processing unit and location.

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- General
 - Description of the processing unit (size, configuration, supporting systems (heating / cooling / vacuum / nitrogen / solvents etc.), type of products produced (e.g. APIs, API intermediates, drug product application, etc.), possible connections with other processing units (like filters, centrifuges, supporting systems, containers, gases, water systems, waste gases etc.),
- System boundaries
 - Description of what will be addressed during the risk assessment.
- Related documents / baseline documents for risk assessment
 - P&IDs, engineering documents, SOPs, deviations.

The risk assessment can be performed using a template, where typical working steps / activities for the processing units are listed (including instrumentation and control systems).

An example is given below for a reactor:

- stirring
- crystallisation
- supporting systems
- heating / cooling
- charging / discharging
- evacuation
- sampling
- etc.

Additionally, materials of construction with direct product contact are assessed and critical measuring and control devices are identified that need to be calibrated.

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5.2 Procedure

It is recommended that the following activities are carried out during qualification of existing equipment:

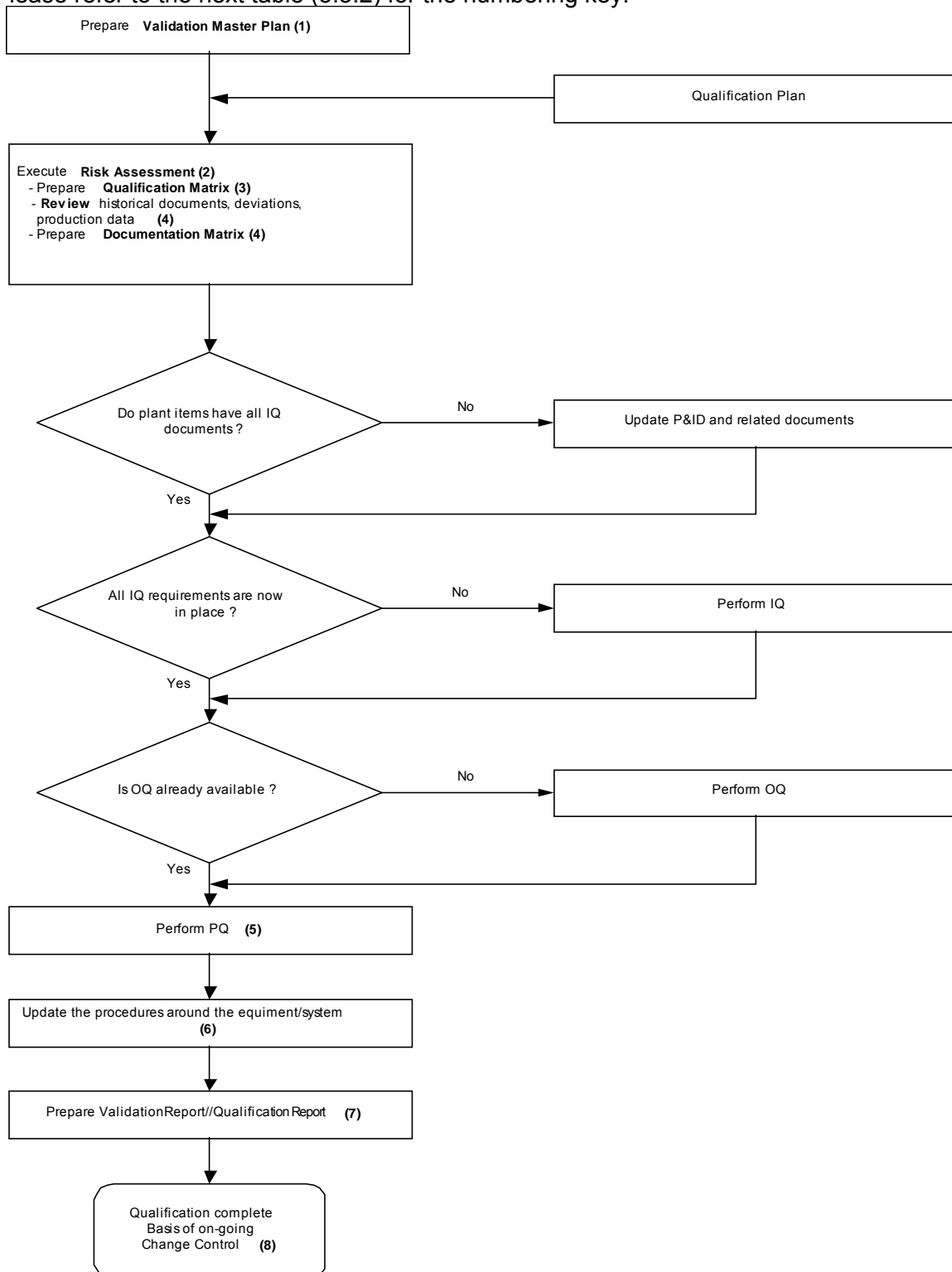
1. Collect flow diagrams and matrixes which can be useful in providing an overview and monitoring tool. A flow scheme for the introduction of a new product into an existing plant is shown (see 5.3.1).
2. Refer to the table (see 5.3.2) which indicates the activities in the qualification.
3. Prepare a Validation Master Plan (VMP) and/or Qualification Plan (QP) (see Definitions). A section of the Validation Master Plan should cover the qualification of plant and equipment [see Reference 4].
4. Collect, review and update related documentation to the equipment (procedures, change control, historical production data, process deviations). This activity may be done using a documentation matrix (example) as shown in 5.3.3.
5. Execute the Risk Assessment Process to identify which items of equipment require qualification (see 5.1). The Risk Assessment Process will be carried out on every system or sub-system.
6. Prepare a Qualification Matrix for IQ (see 5.3.4.1).
7. Update the detailed line diagram of the plant by checking it against the physical plant. The existing Installation Qualification (IQ) and engineering files should be reviewed and updated.
8. Prepare a further Qualification Matrix to review the accuracy and range of equipment/ instruments and identify items requiring OQ and PQ (see 5.3.4.2).
9. Perform the OQ and PQ to complete the qualification.
10. Ongoing change management should be implemented after reporting and approval of all activities in the VMP and/or QP.

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5.3 Tables and flow charts

5.3.1 Flow Scheme

Please refer to the next table (5.3.2) for the numbering key.



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5.3.2 Table

Flow Scheme of Activities in the Qualification

| | Activity | Examples | Document |
|---|--|--|--|
| 1 | Define qualification scope including systems and equipment | | VMP (QP) |
| 2 | Execute Risk Assessment (RA) | | RA matrix |
| 3 | Set-up of a Qualification Matrix with all systems, components | | Qualification Matrix (IQ) |
| 4 | Review historical documents and production data | <ul style="list-style-type: none"> - Datasheet(s) / Technical Description / Certificates (e.g. material of construction) - Drawing(s) - Parts list(s) - Installation instructions - Operating instructions - Maintenance instructions and records - Calibration instructions and records - Copy of supplier's proposal, order and order confirmation - Commissioning and test plans - Electrical diagrams - Batch records and analytical results and plant parameter data | Engineering Files and Documentation Matrix |
| | Collect and review all historical deviations, changes related to equipment/systems and failures if available | <ul style="list-style-type: none"> - Deviation Reports - Change Reports - Complaint Files | Process Validation and Production Campaign Reports Evaluation Report Annual Product Review |
| | Reviewing the available procedures around the equipment/system | <ul style="list-style-type: none"> - Maintenance, calibration procedures | SOP's and working instructions |
| 5 | Review the qualification/accuracy of equipment and implement OQ/PQ | OQ, PQ | Qualification Matrix (OQ, PQ) |
| 6 | Updating the available procedures around the equipment/system | Maintenance, calibration and operating procedures. | SOP's and working instructions |
| 7 | Prepare Validation Report / Qualification Report | | Validation Master Report (or equivalent reports) |
| 8 | Have basis for on-going Change Control | | |

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5.3.3 Example of Documentation matrix

Equipment identification _____

Location _____

Manufacturer _____

Model _____

Serial number _____

| Document type | Required (YES/NO) | Availability (YES/NO) | Document nr | Comments |
|---|-------------------|-----------------------|-------------|----------|
| User Requirement | | | | |
| P&ID and Lay-out | | | | |
| Manufacturing Drawing | | | | |
| Wiring Diagram | | | | |
| Operating Manual | | | | |
| Technical Specification | | | | |
| Factory Acceptance Tests | | | | |
| Site Acceptance Tests | | | | |
| Operating Procedure | | | | |
| Maintenance Procedure | | | | |
| Instruments Calibration | | | | |
| Qualification Protocol | | | | |
| Inspection Report (Safety Requirement) | | | | |
| Materials certification | | | | |
| Cleaning/Sanitation | | | | |
| Training | | | | |
| Supplier Audit | | | | |
| Hardware Design/ Functional Specification | | | | |
| Software Design /Software Specification | | | | |
| Traceability Matrix (UR>FS>Test) | | | | |

Further information to be considered are the following:

- a) operating time
- b) analytical trends
- c) maintenance history
- d) deviations/non-conformities
- e) systems under change control
- f) equipment logbook

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5.3.4 Example of Qualification matrix

5.3.4.1 IQ

| Plant Items / no. | Quality Impact? | | | IQ Required / doc. No. |
|------------------------|-----------------|----------|-----------|------------------------|
| | Direct | Indirect | No Impact | |
| | Y / N | | | |
| Reactor RE1.3.x | Y | N | N | Y |
| Reactor RE1.4.x | Y | N | N | Y |
| Centrifuge CE2.4.x | Y | N | N | Y |
| Dryer DR3.3.x | Y | N | N | Y |
| Chilling Unit CU4.2.x | N | Y | N | N |
| Waste Receiver WR5.7.x | N | N | Y | N |

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5.3.4.2 OQ/PQ

| Plant Items / Operations / no. | Parameters | | | Test by OQ / doc. No. | Test by PQ / doc. No. |
|-----------------------------------|-------------|-----------|----------|--------------------------------|--------------------------------|
| | Type | Range | Accuracy | | |
| Reactor RE4.3.x | Temperature | -20/180°C | ± 2°C | Y | Y |
| Reactor RE4.4.x | Vacuum | 50m bar | ± 20mbar | N | Y |
| Weigh Scale WS10.3.x | Weight | 0/1500Kg | ±1.0 Kg | N* | N |
| Weigh Scale WS10.4.x | Weight | 0/2000 Kg | ± 1.0 Kg | N* | N |
| Solvent Meter SM14.6.x | Volume | 130L | ±2.0L | N* | N |
| Reactor RE2.1.x | Temperature | 20/180°C | ± 2°C | Y | Y |

* The weigh scale and solvent meter has still to be calibrated.

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6. References

1. Good Manufacturing Practice Guide for Active Pharmaceutical Ingredients. ICH Harmonized Tripartite Guideline. 2000 (Q7a)
2. I.S.P.E. Pharmaceutical Engineering Guide for New and Renovated Facilities, Vol. 5 Commissioning and Qualification, March 2001
3. PIC/S Recommendations on “Validation Plan, Installation and Operational Qualification, Non-Sterile Process Validation, Cleaning Validation”, August 2001.
4. EC Guide to GMP, Annex 15 ‘Qualification and Validation’.

7. Appendices

1. Glossary and Abbreviations

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1. Glossary and Abbreviations

Active Pharmaceutical Ingredient (API)

Any substance or mixture of substances intended to be used in the manufacture of a drug (medicinal) product and that, when used in the production of a drug, becomes an active ingredient of the drug product. Such substances are intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease or to affect the structure and function of the body.

Computer System

A group of hardware components and associated software, designed and assembled to perform a specific function or group of functions.

Concurrent Validation

The validation carried out during routine production of products intended for sale

Critical

Describes a process step, process condition, test requirement, or other relevant parameter or item that must be controlled within predetermined criteria to ensure that the API meets its specification.

Direct impact system

The performance of this type of system has a direct and measurable effect (= impact) on the quality of the product. A system determined to be a direct impact system must be designated as such and maintained per approved procedures.

Design Qualification (DQ)

Documented verification that the proposed design of the facilities, systems and equipment is suitable for the intended purpose.

FMEA

Failure mode and effect analysis.

HAZOP

Hazard and Operability studies.

Installation Qualification (IQ)

Documented verification that the equipment or systems, as installed or modified, comply with the approved design, the manufacturer's recommendations and/or user requirements.

Operational Qualification (OQ)

Documented verification that the equipment or systems, as installed or modified, perform as intended throughout the anticipated operating ranges.

GMP**Performance Qualification (PQ)**

Documented verification that the equipment and ancillary systems, as connected together, can perform effectively and reproducibly based on the approved process method and specifications.

Process Validation (PV)

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.

Prospective Qualification

Documented evidence that the equipment and ancillary systems, will consistently function according to pre-determined acceptance criteria. It should be finished before the process validation starts.

Retrospective Qualification

The qualification process (of existing equipment) is carried out when the routine production is already started.

Prospective Validation

The validation is carried out before routine production of products intended for sale.

Retrospective Validation

The validation of a process for a product that has been marketed based upon accumulated manufacturing, testing and control batch data.

Risk Assessment (RA)

A comprehensive evaluation of the risk and its associated impact.

System

A number of integrated steps, functions and items of equipment that must be considered as a unit in order to assure supply of consistent, uniform and high quality components for the manufacturer of a product.

Unit

A part of a processing system that has the ability to carry out independent processing.

Validation

A documented program that provides a high degree of assurance that a specific process, method, or system will consistently produce a result meeting pre-determined acceptance criteria.

Validation Master Plan (VMP)

A high level document, which establishes an umbrella validation plan for the entire project and is used as guidance to the project team for resource and technical planning.

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Qualification Plan (QP)

A high level document which defines the activities associated with the qualification of equipment and may be a part of the VMP.