

1. Purpose

The purpose of this guideline is to provide requirements for the Validation of Facilities and Systems and to outline recommendations on how to achieve compliance.

2. Scope

This guideline can be applicable to any Operations site, function and departments undertaking work, or providing support services, required to meet Good Manufacturing Practice (GMP).

The guideline applies to all Facilities and Systems used in the manufacture and control of registered stages of Drug Product or Active Pharmaceutical Ingredient (API) for validation or sale.

The guideline applies to all projects involving the introduction of, or significant change to, any Facility or System that potentially impacts on product quality. NB: Where this guideline refers to product quality, consideration should also be given to product safety and efficacy.

3. Definitions

3.1 System

A collection of components organized to accomplish a specific function or set of functions.

3.2 Component

A constituent part or aspect of something more complex. In programming and engineering disciplines, a component is an identifiable part of a larger program or construction. A component provides a particular function or group of related functions.

3.3 Commissioning

The process of verification that new or modified assets can meet their design intent, while bringing them from a constructed state into beneficial operation, as defined by the acceptance criteria and agreed with the Project Sponsor.

3.4 Design Qualification

The documented verification that the proposed design of the facilities, systems and equipment is suitable for the intended use.

3.5 Installation Qualification

Documented verification that all physical aspects of a facility or system, which

Manual 069 The validation of facilities and system that required for Good Engineering Practice (sometimes referred to as ~~Enhanced~~ Documentation~~+~~). Validation Documentation should complement (and not repeat) that which is created through Good Engineering Practice. In addition to being approved by a technical/engineering representative they should also be approved by QA.

4. Responsibilities

Each site shall have in place procedures for the validation activities detailed in this guideline. The procedures shall identify the responsibilities associated with the technical and QA approvals of Validation Documentation. As a minimum these should be:

Technical Approvals:

To ensure that all the engineering and operational aspects have been considered and, where appropriate, that the work has been performed in accordance with the approved program / protocol.

QA Approvals:

That all cGMP and regulatory requirements have been considered, met and documented as appropriate.

It is the responsibility of each site to appoint a person accountable for validation for each project. For large projects, this may be a full-time validation manager.

5. Guideline

5.1 Validation Lifecycle for Facilities and Systems

This guideline applies to all types of Facilities and Systems. The validation lifecycle model is illustrated at Appendix 1. The lifecycle phases indicated in the appendix follow the same sequence as those for computerized systems.

The relationship between computerized system validation requirements and the requirements of this guideline should be explained within each individual Validation Master Plan (VMP) or Validation Plan (VP) in the context of the validation being planned.

5.2 Validation Master Plan (VMP)

A VMP is a strategic document, which shall be approved at an early stage in the project that identifies the elements to be validated. It is recommended that these elements are identified by conducting a Systems Impact Assessment.

5.2.1 Systems Impact Assessment (SIA)

A Systems Impact Assessment is the process of determining which Systems should be subject to qualification, part of a risk-based approach to validation.

The assessment is made by evaluating the impact that a System has on the quality of the product. The Systems should each be categorized as one of the

The URS shall be prepared, commented on and approved as a minimum by technical and QA representatives.

The URS shall be approved prior to purchase of the equipment, and thereafter shall be subject to formal change control.

For projects involving the introduction of a new drug product or substance, the URS should relate to the best information available from Development reports and reviews.

5.5 Supplier Selection

Typically, the Supplier Selection process will consist of up to five stages:

- " Supplier's Proposal
- " Supplier Audit
- " Supplier Selection
- " Contract Negotiation
- " Order Placement

The decision on whether or not to audit a supplier should be supported by existing Supplier Information such as Supplier Audit Reports / Questionnaires and Supplier Performance Reviews. The rationale should be recorded in the relevant validation document. Limitations of supplier capabilities, measures to minimize the risk of these limitations and recommended approach should be identified.

Any Supplier Audit Reports acquired or prepared as part of the supplier selection process, should be referenced within the relevant validation document (e.g. DQ report).

5.6 Functional Specification (FS)

The FS shall define how the System meets the operational, performance, regulatory, engineering and EHS requirements defined in the URS. It should be comprehensive and reflect the intended functional use of the System.

Requirements associated with product quality - as identified in the URS (see 5.4, above) - shall be clearly identified (e.g. in tabular form, numbered and prioritized) and shall be capable of verification during subsequent qualification.

The FS shall be prepared, commented on and approved as a minimum by technical and QA representatives. Ordinarily, it should be prepared by the supplier of the System. The approval may effectively be achieved by inclusion of the FS at DQ report approval.

Other document types may specify system function. If other types of document are used they should be identified.

Manual 069 The validation of facilities and system or part of an earlier document, e.g. VP.

5.8.1 Components Impact Assessment (CIA)

A risk assessment shall be conducted to determine which components of a direct impact system shall be subject to qualification. The approach to the assessment will depend upon factors such as system or equipment size, complexity, maturity availability of (and access to) vendor design specifications, and locally established practices.

It is recommended that a component impact assessment is conducted with reference to Appendix 3: Examples of Factors Which Can Determine Impact on Product Quality.

The CIA, as a part of the risk assessment, is made by evaluating the impact that a component of a System has on the quality of the product. The components should each be categorized as one of the following:

- “ Direct Impact Component (can also be called critical component)
- “ Indirect Impact Component (can also be called non-critical component)
- “ No Impact Component (can also be called non-critical component)

Only Direct Impact Components are subject to qualification, though all components are subject to Good Engineering Practice.

Indirect Impact Components can affect the performance or operation of a Direct Impact Component and therefore:

- “ Any interfaces need to be carefully assessed
- “ It should be ensured that Direct Impact Components could detect or prevent a product quality-threatening problem with an Indirect Impact Component linked to it.

In the instance when a component can be used as both a Direct and Indirect Impact Component, the requirements of the Direct Impact Component shall take precedence to ensure compliance to cGMPs.

The components within the Direct Impact Systems, Indirect Impact systems and in some cases also No Impact systems should all be assessed for criticality. This is suggested to ensure that systems previously judged to be Indirect Impact or No Impact in the early, high-level assessment have not subsequently acquired a critical function.

The assessment should document the components of the System and the rationale as to which of its components should or should not be qualified. This rationale should be developed by a multi-disciplinary team (e.g. user representative, engineering representative, process engineer, validation manager, QA representative). The use of detailed drawings will enable system boundaries to be identified.

It is recommended that the output from the assessment is recorded in the DQ

The results of the OQ should comprise the original completed OQ Program / Protocol with its check sheets, etc., marked up with the results observed, comparisons with the pre-determined acceptance criteria, references to any documents (e.g. commissioning records, justification reports) retained elsewhere, signed and dated by the persons involved, together with any relevant attachments, such as additional raw data and deviation reports.

The OQ should be satisfactorily completed before the start of PQ. There could be some items that may not be complete and these require a technical judgment before delaying the start of PQ. The rationale for commencing PQ prior to satisfactory completion of OQ should be formally documented and approved. This is valid even if combined OQ / PQ programs / protocols are to be executed.

The completed OQ results should be presented as a report or a number of completed OQ results combined into a summary report.

The OQ Report shall be prepared, commented on and approved by the persons identified in the VP.

5.11 Performance Qualification (PQ)

5.11.1 Performance Qualification Program / Protocol

PQ follows IQ/OQ. Although described below as a separate activity, it is acceptable to include PQ testing as part of the OQ exercise. The PQ is the final qualification activity prior to performing Process Validation (PV). PQ assesses that the equipment and ancillary systems, as connected together can perform effectively and reproducibly. The PQ is performed using production materials, qualified substitutes or simulated product and subject to processing conditions encompassing upper and lower operating limits or worst case conditions. PQ bridges OQ, with its emphasis on demonstrating equipment function, and PV with its emphasis on process capability and consistency. PQ takes OQ one step further due to the requirement to include production materials, qualified substitutes or simulated product.

A properly executed OQ and PQ means that PV can be conducted using routine process conditions. There are no specific requirements for the number of runs to be performed in PQ. One of the goals of PQ is to demonstrate consistency. Multiple runs or trials, especially for the critical elements of PQ, should be included.

The PQ Program / Protocol shall verify that all aspects of a Facility or System which can affect product quality perform effectively and reproducibly based on the approved process method and specifications. The activities comprising PQ will have been identified in the VP.

The PQ Program / Protocol should be kept specific to product quality related

5.13 Process Validation (PV) and Cleaning Validation (CV)

For appropriate process and cleaning validation please refer to Manual 035, 036 037, 038 & 040

5.14 Validation Report (VR)

A Validation Report(s) shall be produced, corresponding to each of the project VP\$, confirming that all validation activities identified in the VP have been completed and that any anomalies have been satisfactorily resolved.

The VR shall be prepared, commented on and approved by the persons identified in the VP.

5.15 Validation Master Report (VMR)

Where a project specific VMP has been prepared, a corresponding VMR shall be produced, confirming that all validation activities identified in the VMP have been completed and that any anomalies have been satisfactorily resolved.

The final approval for use within the GMP regulated process/processes needs to be demonstrated through a clear statement in the VMR or through other documentation.

Final approval of the VMR will mark the completion of the validation project. However, approved completion of certain elements of the exercise, with supporting documents, may permit beneficial operation to commence prior to VMR approval. As a minimum, all IQ, OQ and PQ work, including any computer validation work must be complete, with approved reports, and CV and PV must be complete, with approved reports. It is recommended that a formal review, with documented output, is conducted to record the status of the facility prior to commencement of beneficial operation (manufacture of product ultimately for sale).

6. Appendices

6.1 Appendix 1: Validation Life Cycle Model

6.2 Appendix 2: Example Commissioning and Qualification Activities

6.3 Appendix 3: Examples of factors which can determine impact on product quality

6.2 Appendix 2: Example Commissioning and Qualification Activities

The following list is an example of the possible commissioning and qualification activities to be undertaken:

1.	Design Qualification	DQ
2.	Factory acceptance testing (FAT)	Commissioning
3.	Loop continuity checks	Commissioning
4.	Hazardous area inspections	Commissioning
5.	Equipment and systems inspections	Commissioning and IQ
6.	Functional loop tests	Commissioning and OQ
7.	Trip and alarm tests	Commissioning and OQ
8.	Instrument calibration	Commissioning and IQ
9.	Equipment IQ	IQ
10.	Site acceptance testing (SAT)	Commissioning
11.	Control loop tuning/tests	Commissioning and OQ
12.	Phase tests	Commissioning and OQ
13.	Equipment OQ	OQ
14.	Operation tests	Commissioning and OQ
15.	Recipe tests (water trials)	Commissioning and OQ/PQ
16.	Equipment PQ	PQ

NB: Only Direct Impact Systems / Components are subject to qualification.