IAEA
International Atomic Energy Agency

This learning material has been prepared by Prof. David Schlyer (Brookhaven National Laboratory) and the Technical Officers in charge are Mr Amirreza Jalilian (Primary) and Ms Aruna Korde (Alternate) from the Radioisotope Products and Radiation Technology Section, Department of Nuclear Sciences and Applications, IAEA.

Radiopharmaceutical Production

Equipment Validation



Equipment Validation

- Validation is a Quality Assurance process of establishing and documenting that a piece of equipment satisfies its intended requirements.

- Validation of equipment includes the qualification of the equipment which entails *Design Qualification* - DQ, *Installation Qualification* - IQ, *Operational Qualification* - OQ and *Performance Qualification* - PQ. Validation also includes training, SOPs on operation, cleaning, maintenance, calibration, etc.

- A great deal of further information can be found at:
- Link to EU validation
- Link to draft FDA methods validation
- Link to FDA bioanalytical methods validation

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Validation Overview

It is a good idea to have some definitions of the terms we will be using. Here are some common ones.

- Validation – Usually applies to a process. It is the overall action of proving, in accordance with the principles of GMP, that any process, equipment, material, activity or system actually results in a test or process that will perform as the user has specified.
- Qualification – Usually applies to equipment. It is the stepwise action of proving that any particular premises, systems and/or piece of equipment will actually lead to the expected results (Qualification is a part of validation. Validation will include other parts such as SOPs for all the operations associated with the equipment and training on the use of the equipment).

Other definitions

- Validation is defined by the World Health Organization as “the collection and evaluation of data, beginning at the process development stage and continuing through the production phase, which ensure that the manufacturing processes - including equipment, buildings, personnel and materials - are capable of achieving the intended results on a consistent and continuous basis.”
- Validation is defined by the FDA as “establishing documented evidence which provides a high degree of assurance that a specific process will consistently produce a product meeting its pre-determined specification and quality attributes.”

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Validation Overview

- From the above definitions, we can say that Validation is the establishment of documented evidence that a system does what it is supposed to do. There are three key points to take from these definitions:

  1. The evidence must be documented. (The results of the validation must be recorded).
  2. Validation applies to all aspects of manufacturing which could influence product quality and safety, including e.g. process development, materials, personnel and equipment).
  3. It should demonstrate that the system does what is expected of it.

- Validation of equipment is carried out against a set of criteria that are defined in advance. These criteria are detailed in the validation plan.

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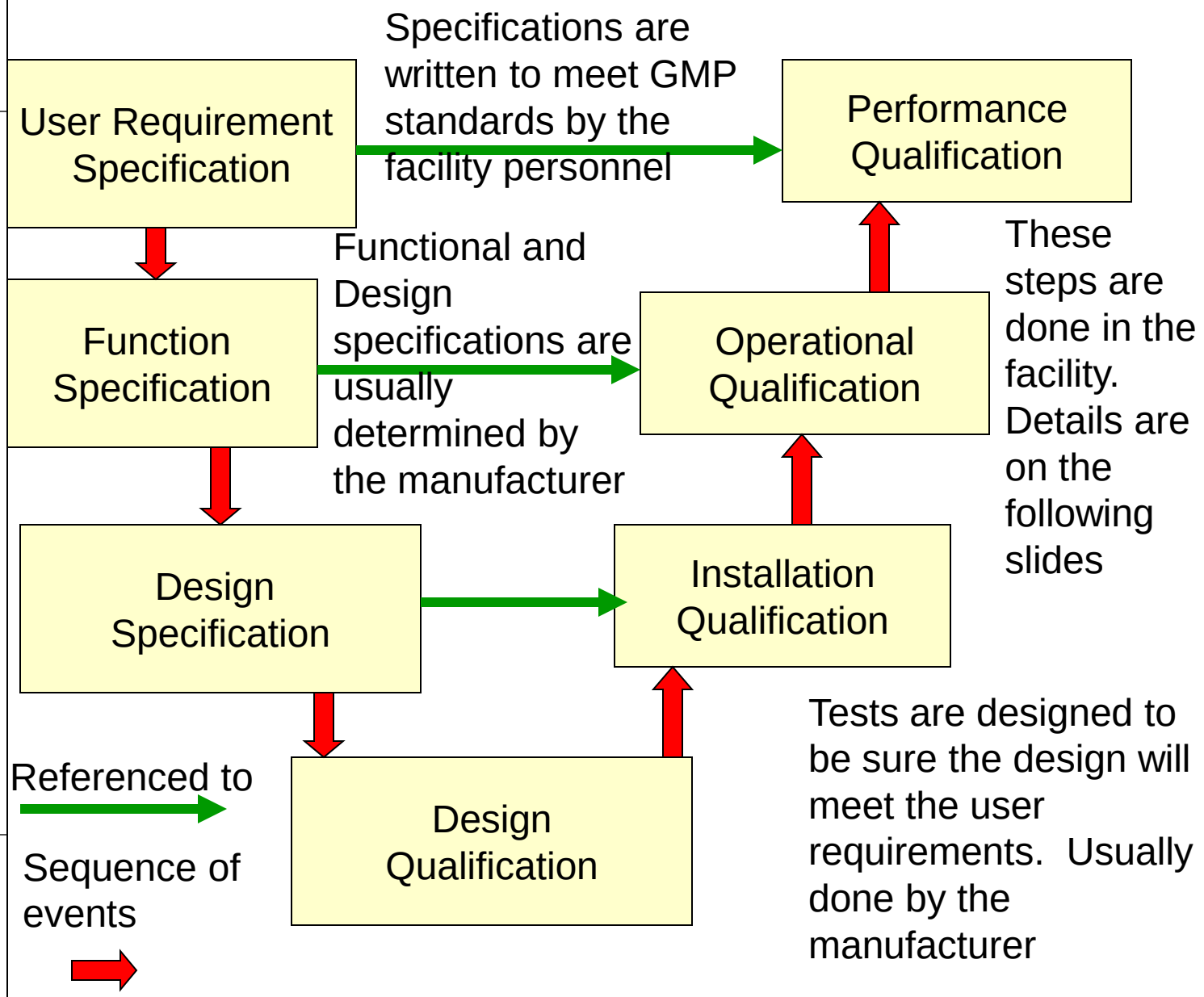
Qualification Overview

- Equipment Qualification is a subset of Validation. Qualification starts with user specifying the design and functions of the equipment, that is, how it must perform. For example, in the case of radiopharmaceutical quality control, the data the equipment must acquire or the functions it must perform are well laid out in the relevant pharmacopeia and it is only necessary to write specifications to meet these standards.
- A design specification is derived from the user functional and operational specifications.
- From the design specification, we can generate a sets of tests to ensure that the equipment meets the design specifications. This is known as the **design qualification (DQ)**. Normally this is done by the manufacturer knowing which tests and operations are being used.
- The **installation qualification (IQ)** ensures that the equipment is installed correctly. It includes checking of the delivered system to be sure it has all the necessary parts and is installed correctly.
- The **operational qualification (OQ)** ensures that the equipment operates as specified. It is the functional testing of the system and associated software.
- The **performance qualification (PQ)** ensures that the equipment performs the tests operations that it needs to perform reliably and accurately. It includes performing an analysis method which will be used in the product manufacture or analysis.
- A flow diagram of these operations and how they are linked is given on the next slide

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Qualification Overview



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Validation Timeline

Validation includes the qualification as shown above, but also a final report, SOPs, training and maintenance of the equipment over time. A validation timeline is shown below including the maintenance and revalidation of the equipment at later times

Vendor's Site	Owner's site			
Before Purchase	Before Use			After Use
Structurally Validated Products DQ	Functional Validation Installation Qualification IQ	Operational Performance Qualification OQ	PQ	Maintenance OQ PQ
System Suitability During Use				

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Qualification Overview

In simplified terms, starting with the Design Qualification, the initial qualification process is as follows:

- Design Qualification - Equipment has been **designed** in accordance with GMP and meet the user requirements/design specification needs.
- Installation Qualification – Each piece of equipment has been **built** and **installed** in accordance with GMP, has all the necessary components and meets user specifications. This may be as simple as making sure it has the correct power connections and is in a suitable location.
- Operational Qualification - Equipment is **operating** in accordance with GMP and meets its operational specifications. This is determined by performing a series of operational tests and documenting the results of the tests to ensure all the specifications are met.
- Performance Qualification - Equipment **performs** the operation or test for which it was designed consistently in accordance with GMP at installation and over a period of time. This usually requires documented retesting at regular intervals



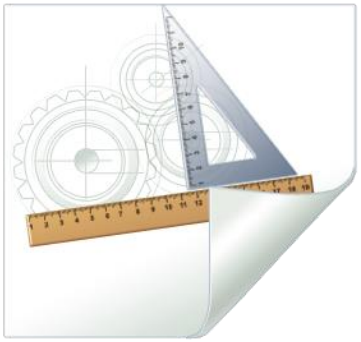
Validation and Qualification

- **VALIDATION INCLUDES QUALIFICATION**
- **Qualification of established (in-use) facilities, systems and equipment includes the steps in the previous slides.**
- Evidence should be available to 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 and records should be documented. Once these additional items are completed, a validation report can be generated for the piece of equipment.

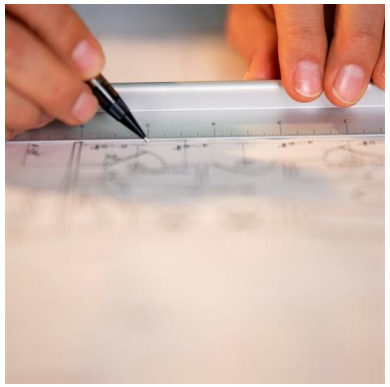
- Each of the specific steps in the qualification are given in the next few slides.

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Design Qualification



- In the usual situation, the facility or user prepares specifications for a piece of equipment. These specifications are reviewed and documented by competent persons to ensure that the designed equipment, if built, will satisfy all the detailed specified requirements.
- The Design Qualification is the only document that is going to confirm that the design will work. It must be carried out by qualified people who can challenge the design performance.
- as shown in the qualification overview and is searching for a manufacturer and is offered equipment off - the - shelf. A DQ can be used to verify whether the off-the-shelf item will fully deliver the functionality detailed in the Design Specification, and conform to the requirements specified GMP guidelines.





Design Qualification

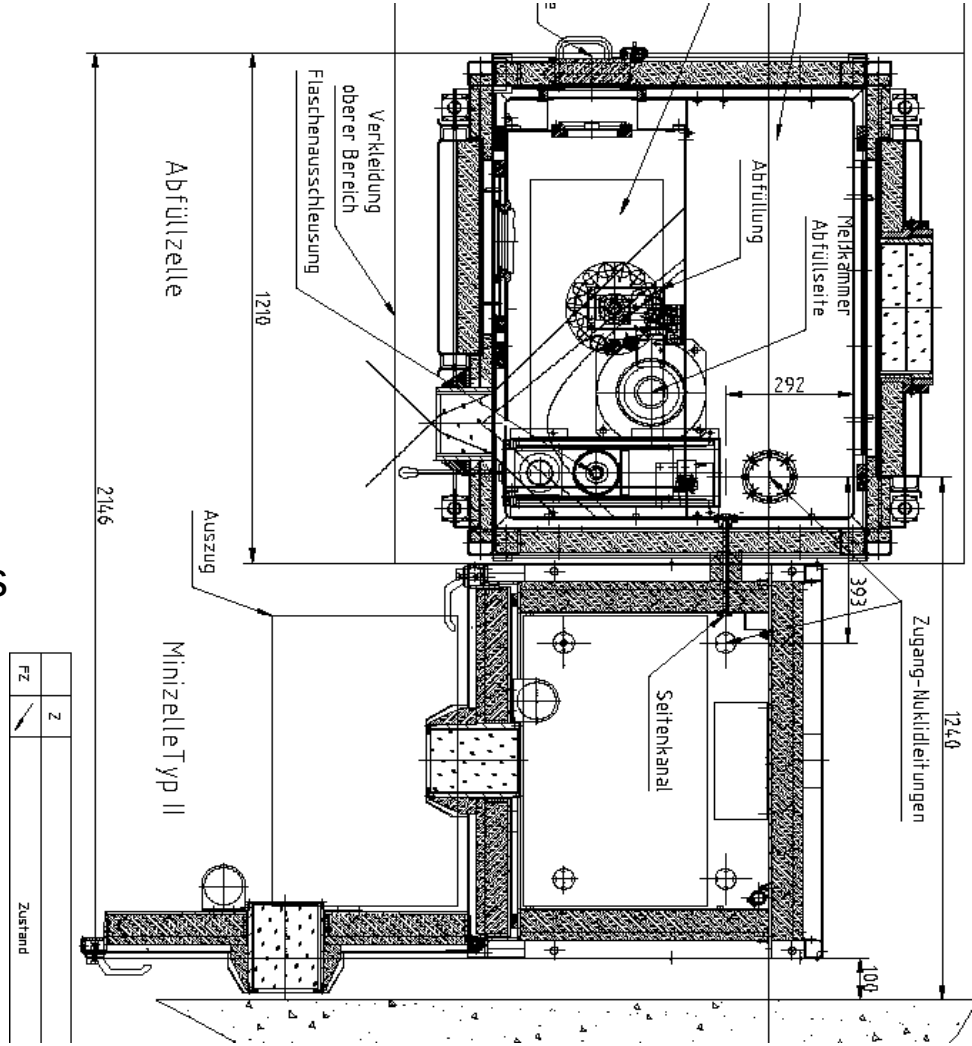
The scope of the DQ must include but is not limited to:

- Verification that the design will achieve the user specifications.
- Verification that the design is compliant with GMP.
- Verification that the design complies with the Validation Master Plan.
- Verification that the utility services required are available and validated.
- Verification that all the required support documentation is specified.
- Verification that the system can be calibrated
- Verification that the system can be maintained.
- Verification of operation staff training requirements.
- Verification that the system will operate in a manner safe to both product and staff.
- Verification that the system conforms to all applicable national standards and guidelines, for example UL listed.

All this information should normally be supplied by the manufacturer.

DQ – Design Qualification

- As an example, let's choose a isolator for the production and dispensing of FDG.
- This should be:
- Class A shielded isolator
  - For dose dispensing in aseptic conditions
- Class C hot-cell
  - For FDG synthesis





Installation Qualification

- The Installation Qualification (IQ**)** execution verifies that the equipment, and its ancillary systems or sub-systems are present and have been installed in accordance with installation drawings and or specifications. It further details a list of all the GMP requirements, that are applicable to the installation. These requirements must all be satisfied before the IQ can be completed and the OQ commenced.
- Installation qualification (IQ) should be performed on new or modified facilities, systems and equipment and documentation may be obtained from the supplier.
- Documented records of qualification and validation, have in the past often not been given sufficient consideration by equipment suppliers and or pharmaceutical companies. As a consequence, companies have not always had sufficient information about the equipment to provide the documented evidence inspectors expected. It is essential, therefore to ensure at the start of any validation project, that the correct information and documentation has been specified and will be available during the validation execution phase.
- IQ should include, but not be limited to the following:
  - installation of equipment, piping, services and instrumentation checked to current engineering drawings and specifications;
  - collection and collation of supplier operating and working instructions and maintenance requirements;
  - calibration requirements;
  - verification of materials of construction.

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Installation Qualification

The scope of the **IQ** testing should include the following:

- Verification that all components parts are present, in place and integrated.
- Verify installation is as specified in the installation instructions or manual.
- Verify supply voltages conform with requirements.
- Verify that the equipment complies with National electrical codes
- Verify that all alarms and visual displays are operational and correct.
- Verify that if appropriate, the correct versions of software are used.
- Identify and verify that serial numbers and model number of all equipment or component parts is as listed in the installation documentation.
- Review all calibration certificates for the equipment.
- Verify that the ambient conditions are appropriate for the operation of the equipment.
- Verify that the documentation provided by the manufacturer will allow maintenance of the system.

IQ – Installation Qualification

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Ensure voltages are correct
Ensure power is supplied to all equipment
Verify operation of lights and display
Ensure floor loading is even, etc.





Operational Qualification

- Operational qualification (OQ) should follow Installation qualification.
- The Operational Qualification includes a review of the operating manual and verification that all functional aspects of the equipment are performing as intended throughout all anticipated operating ranges. (This is a good time to start writing the SOPs pertaining to the equipment.)
- Operational Qualification documentation can often be obtained from the manufacturer. This documentation has the operational tests clearly laid out with the expected results. Filling out this form and recording all the results is usually sufficient as operational qualification documentation.
  - This material is usually an extra charge from the manufacturer, but is the most straightforward way of ensuring that the documentation will be acceptable to the agency governing adherence to GMP principles.
- OQ should include, but not be limited to the following:
  - (a) tests that have been developed from knowledge of processes, systems and equipment;
  - (b) tests to include a condition or a set of conditions encompassing upper and lower operating limits, sometimes referred to as “worst case” conditions.
- The completion of a successful Operational qualification should permit a formal "release" of the equipment.

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Operational Qualification

- The scope of the OQ testing/inspections must include but is not limited to:
- Testing of alarms.
- Testing of interlocks and permissive conditions.
- Testing of database or data storage integrity.
- Testing of report generation and event chronicle.
- Verification of the functionality of the equipment.
- Challenge of software, where required;
- Review of system functionality to verify compliance with GMP regulations.
- Testing of security levels to prevent unauthorized access;
- Testing to verify and document Power loss Recovery.
- Testing of all interfaces between separate pieces of equipment (for example between equipment and data loggers);
- Testing for Electromagnetic interference and compatibility.

- **Operational Qualification is essentially acceptance testing and should serve as the basis for final payment.**

OQ – Operational Qualification

Equipment is operating correctly in the environment of the isolator

Make sure the pressure differential is within specification







Performance Qualification

- Performance Qualification (PQ) is performed after successful completion of the **Installation qualification (IQ)** and **Operational Qualifications (OQ)** . The testing verifies that the performance specified in the Design Specification is being delivered.

- The PQ represents the final qualification of your equipment or system. This incorporates a range of testing to simulate your production process options and provide assurance that your systems and your operating documentation, are capable of subsequent process validation activities. It is used to establish and/or confirm :
  - Definition of performance criteria and test procedures.
  - Selection of critical parameters, with predefined specifications.
  - Determination of the test intervals, e.g.,
    (a) - Everyday.
    (b) - Every time the system is used.
    (c) - Before, between and after a series of runs.
  - Define corrective actions on what to do if the system does not meet the established criteria.

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