Chapter 5
Qualification and Validation

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Qualified equipment and *validated processes* ensure satisfactory, safe, and reproducible outcomes and allow personnel to achieve, within the limits of the precision of the process, the same output when starting with the same input. Any change of equipment, utilities, or process should be formally documented and the impact on the validation status or control strategy assessed (change control [Fig. 5.1]).

A process is validated by establishing objective evidence that the process consistently produces an expected endpoint or result that meets predetermined acceptance criteria. Process validations can be performed prospectively or concurrently.

The transplant program or facility should have a specific SOP or document (validation master plan – VMP) related to qualification and validation, detailing which validation studies are mandatory, how to perform them, and in what format. The design of the validation study should be adequate to determine if the process reproducibly achieves the purpose for which it is intended.

In this SOP/VMP, the following items should be addressed:

- Scope of validation and critical processes to be validated
- Activities included in the validation plan, methods, and tools to be used to verify the reproducibility of results
- Activities to perform in the qualification of materials/supplies, facilities, equipment, and verification of personnel training

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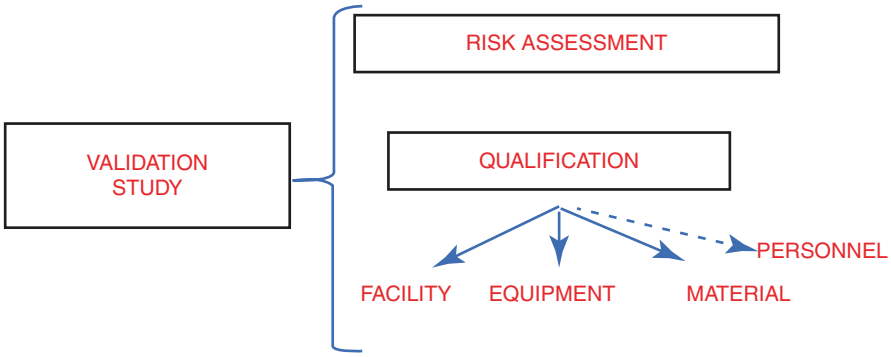

Fig. 5.1 Validation study including risk assessment and qualification

- Collection and analysis of data, tests to be performed, number of samples to be tested, range of acceptable results
- Collection and documentation of results
- Conclusions and approval of validation study
- Duration of validation and criteria for revalidation
- Change control management

The responsibility for the validation SOP/VMP lies with the director of the transplant program. However, responsibility is shared with the quality manager, who has the key role of deciding on the methodological tools to be used for qualification and validation by the professionals involved in this process. The quality manager is responsible for organizing and monitoring training and ensuring the competencies of the personnel involved in the validation studies as well as organizing training on change control and risk management. Finally, the quality manager verifies the implementation of and compliance with the validation SOP/VMP.

The result of each validation study must be reviewed and approved by both the quality manager and the transplant program director or facility director (collection, processing, or clinical) and/or by the individuals deemed responsible according to national pharmaceutical law.

All transplant program personnel should be involved in the validation studies. This can be achieved by establishing a dedicated validation team with representatives from across the transplant program. Professionals involved in the qualification and validation steps should have specific training in the relevant area and in the processes to be validated. They should collaborate with the quality manager and, if required, external experts; for example, when qualifying equipment, this may necessitate the involvement of the hospital maintenance office and the manufacturer.

A risk assessment should be performed for each validation study to assess how critical the process is and to define the level of risk.

Qualification of the facility, equipment and material, and verification of personnel training are included in the validation study (Fig. 5.1).

Validation Process (Fig. 5.2)

Identification of critical processes to be validated JACIE defines some minimal mandatory validations, though every transplant program should decide whether additional processes are critical to their activities and might therefore merit formal

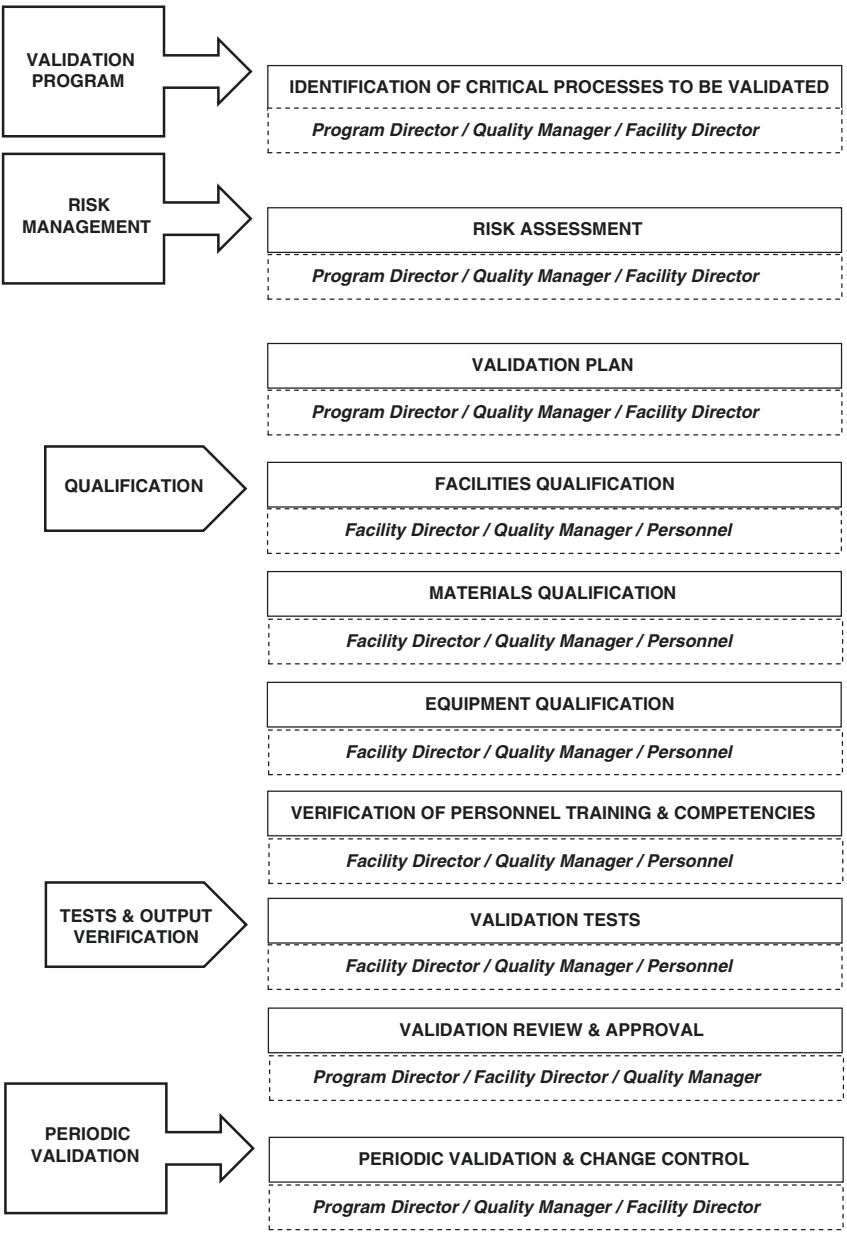

Fig. 5.2 Steps to carry out a validation study and responsibilities

validation. A process is considered critical if it impacts on the quality and/or safety of cellular products.

The minimal Validation studies required by the JACIE Standards are as follows:

- Apheresis collection
- Bone marrow collection
- Processing and cryopreservation
- Labeling
- Storage
- Distribution (included transportation and packaging)

Risk assessment Evaluation of the level of risk and activities that might mitigate this risk (see Chap. 18 on Risk Management).

Validation plan For each critical process requiring validation, the facility should produce a validation plan that includes the following:

– Rational for validation: refer to standards, applicable laws, critical nature of process, etc.
– Results of risk analysis: the facility should define the type of validation exercise based on the perceived level of risk
– The expected endpoint or result
– The different phases of validation, assignment of roles, the output for each phase and methodologies to be adopted
– List of variables to be qualified: facilities, materials, equipment, and personnel
– Method for qualification of facilities, materials, equipment, and personnel
– Operating standards (process parameters, SOP, etc.): to guarantee satisfactory ongoing supply of the process and to maintain the validation status over time
– Evidence of validation
– Validation protocol: method for collection of data and analysis, timeline, expected output, presentation of results, deviations management
– Validation documentation: registration forms, database, etc., to guarantee documented evidence of the results of the validation process
– Validation cycle planned for revalidation and requalification of equipment

Qualification: facilities, material, equipment, personnel Each component that could influence the results of the process should be qualified. Qualification of facilities, for example, is based on the verification of suitability of the rooms for the proposed activities, verification of environmental conditions, access for authorized staff, certification, etc. Qualification of materials is based on the verification of the manufacturer's certification, integrity of packaging, expiration date, etc.

Qualification stages for equipment, facilities, utilities, and systems according to [1] are listed in Fig. 5.3:

1. User requirements specification (URS)
2. Design qualification (DQ)

3. Installation qualification (IQ)
4. Operational qualification (OQ)
5. Performance qualification (PQ)
6. Requalification

Competencies The competency of personnel to perform the activities related to the process undergoing validation should be verified and, if insufficient, specific training should be arranged. The validation team should check that there are SOPs for all the processes involved in the validation study and, if unavailable, need to generate such policies; registration forms need to be available to ensure that every step of the process can be clearly traced.

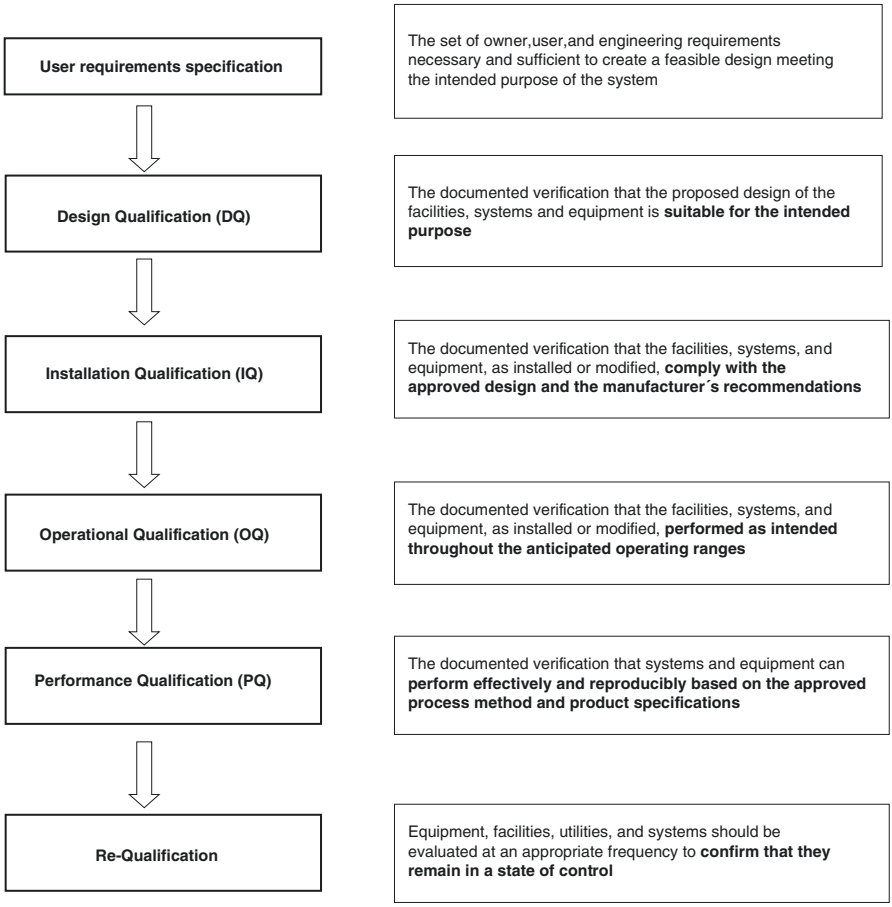

Fig. 5.3 Qualification stages for equipment, facilities, utilities, and systems

Validation tests Based on the validation plan, an adequate number of tests should be performed. The number of tests required to consider the process validated will vary, based on the frequency of the respective activity, level of risk, precision, range of acceptable or expected results, etc. The rationale and the established number of tests should be documented. The validation study should include the parameters to be verified, the expected results, the criteria and acceptance range, and the method for verification (test, visual assessment, document-based, etc.)

Validation review and approval Following completion of the validation, all data analyzed, the output and results should be included in a final validation report; the quality manager and the transplant program director and/or facility director should review the report and confirm with their dated signature that the process is validated and that it may be used for clinical purposes.

Periodic validation The transplant program or facility shall decide on the length of the validation cycle. This decision should be based on various factors, including the level of risk, the internal control process, equipment wear, and other components. The basis for this decision shall be described and documented.

Change control If a significant change is introduced in the process, it should be revalidated. A change control analysis is required before starting the validation study to predict the possible impact of the change on the process (Fig. 5.4).

Example of Documents and Registration Forms for Validation

Validation Master Plan (VMP)

General SOP or other document that describes how to perform a validation study.

Validation Study

A specific SOP or document that describes how to perform validation of a specific process. It contains the specifications of the process (phases, components to be qualified, expected output, prerequisites and performances, type and range of evidence required to confirm that the process is validated).

- Data collection and analysis form
- Qualification form for materials/supplies
- Qualification form for facilities

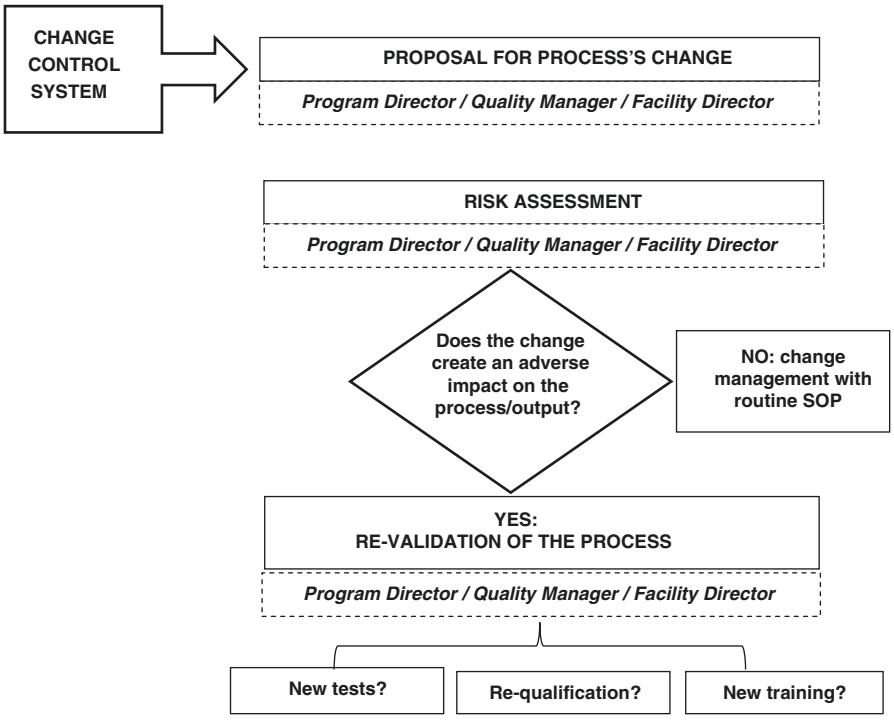

Fig. 5.4 Change control flowchart

- Qualification form for equipment
- Validation final report
- Change control report

Computerized systems used in the manufacture of medicinal products should also be validated according to the requirements of EU-GMP Annex 11; these are not included in this chapter, for details see reference [2].

Glossary

Change Control A formal system by which qualified representatives of appropriate disciplines review proposed or actual changes that might affect the validation status of facilities, systems, equipment, or processes. The intent is to determine the need for action to ensure and document that the system is maintained in a validated state.

Process validation The documented evidence that the process, operated within established parameters, can be performed effectively and reproducibly to

produce a medicinal product/cellular therapy product meeting its predetermined specifications and quality attributes

Qualification The establishment of confidence that equipment, supplies, and reagents function consistently within established limits.

Quality assessment The actions, planned and performed, to evaluate all systems and elements that influence the quality of the product or service.

Quality assurance The actions, planned and performed, to provide confidence that all systems and elements that influence the quality of the product or service are working as expected or exceed expectations individually and collectively.

Quality risk management A systematic process for the assessment, control, communication, and review of risks to quality across the lifecycle.

Quality Conformity of a product or process with pre-established specifications or standards.

Verification The confirmation of the accuracy of something or that specified requirements have been fulfilled. Verification distinguish from validation in that validation determines that the process performs as expected whereas one verifies that the products of a process meet the required conditions.

References

1. EudraLex. Volume 4. EU guidelines for good manufacturing practice for medicinal products for human and veterinary use Annex 15: qualification and validation. http://academy.gmp-compliance.org/guidemgr/files/2015-10_annex15.pdf.
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