



EUROPEAN COMMISSION
ENTERPRISE DIRECTORATE-GENERAL

Single market, regulatory environment, industries under vertical legislation
Pharmaceuticals and cosmetics

Brussels, July 2001

Working Party on Control of Medicines and Inspections

Final Version of Annex 15 to the EU Guide to Good Manufacturing Practice

Title: **Qualification and validation**

.

First discussion in drafting group	
Discussion at the working Party on Control of Medicines and Inspection for release for consultation	16 September 1999
Pharmaceutical Committee	28 September 1999
Released for consultation	30 October 1999
Deadline for comments	28 February 2000
Final approval by Inspector's working party	December 2000
Pharmaceutical Committee (for information)	April 2001
Date for coming into operation	September 2001

Note that this document is based in the PICS/S recommendations

Table of Contents

	Page
1. Qualification and Validation	3
2. Planning for Validation	4
3. Documentation	4
4. Qualification	5
5. Processs Validation.	6
6. Cleaning Validation	7
7. Change Control	8
8. Revalidation	9
9. Glossary	10

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.

PLANNING FOR VALIDATION

2. All validation activities should be planned. The key elements of a validation programme should be clearly defined and documented in a validation master plan (VMP) or equivalent documents.
3. The VMP should be a summary document which is brief, concise and clear.
4. The VMP should contain data on at least the following:
 - (a) validation policy;
 - (b) organisational structure of validation activities;
 - (c) summary of facilities, systems, equipment and processes to be validated;
 - (d) documentation format: the format to be used for protocols and reports;
 - (e) planning and scheduling;
 - (f) change control;
 - (g) reference to existing documents.
5. In case of large projects, it may be necessary to create separate validation master plans.

DOCUMENTATION

6. A written protocol should be established that specifies how qualification and validation will be conducted. The protocol should be reviewed and approved. The protocol should specify critical steps and acceptance criteria.
7. A report that cross-references the qualification and/or validation protocol should be prepared, summarising the results obtained, commenting on any deviations observed, and drawing the necessary conclusions, including recommending changes necessary to correct deficiencies. Any changes to the plan as defined in the protocol should be documented with appropriate justification.
8. After completion of a satisfactory qualification, a formal release for the next step in qualification and validation should be made as a written authorisation.

QUALIFICATION

Design qualification

9. The first element of the validation of new facilities, systems or equipment could be design qualification (DQ).
10. The compliance of the design with GMP should be demonstrated and documented.

Installation qualification

11. Installation qualification (IQ) should be performed on new or modified facilities, systems and equipment.
12. IQ should include, but not be limited to the following:
 - (a) installation of equipment, piping, services and instrumentation checked to current engineering drawings and specifications;
 - (b) collection and collation of supplier operating and working instructions and maintenance requirements;
 - (c) calibration requirements;
 - (d) verification of materials of construction.

Operational qualification

13. Operational qualification (OQ) should follow Installation qualification.
14. 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.
15. The completion of a successful Operational qualification should allow the finalisation of calibration, operating and cleaning procedures, operator training and preventative maintenance requirements. It should permit a formal "release" of the facilities, systems and equipment.

Performance qualification

16. Performance qualification (PQ) should follow successful completion of Installation qualification and Operational qualification.
17. PQ should include, but not be limited to the following:
 - (a) tests, using production materials, qualified substitutes or simulated product, that have been developed from knowledge of the process and the facilities, systems or equipment;

- (b) tests to include a condition or set of conditions encompassing upper and lower operating limits.
18. Although PQ is described as a separate activity, it may in some cases be appropriate to perform it in conjunction with OQ.

Qualification of established (in-use) facilities, systems and equipment

19. 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.

PROCESS VALIDATION

General

20. The requirements and principles outlined in this chapter are applicable to the manufacture of pharmaceutical dosage forms. They cover the initial validation of new processes, subsequent validation of modified processes and re-validation.
21. Process validation should normally be completed prior to the distribution and sale of the medicinal product (prospective validation). In exceptional circumstances, where this is not possible, it may be necessary to validate processes during routine production (concurrent validation). Processes in use for some time should also be validated (retrospective validation).
22. Facilities, systems and equipment to be used should have been qualified and analytical testing methods should be validated. Staff taking part in the validation work should have been appropriately trained.
23. Facilities, systems, equipment and processes should be periodically evaluated to verify that they are still operating in a valid manner.

Prospective validation

24. Prospective validation should include, but not be limited to the following:
- (a) short description of the process;
 - (b) summary of the critical processing steps to be investigated;
 - (c) list of the equipment/facilities to be used (including measuring/monitoring/recording equipment) together with its calibration status
 - (d) finished product specifications for release;
 - (e) list of analytical methods, as appropriate;
 - (f) proposed in-process controls with acceptance criteria;
 - (g) additional testing to be carried out, with acceptance criteria and analytical validation, as appropriate;
 - (h) sampling plan;

- (i) methods for recording and evaluating results
- (j) functions and responsibilities;
- (k) proposed timetable.

25. Using this defined process (including specified components) a series of batches of the final product may be produced under routine conditions. In theory the number of process runs carried out and observations made should be sufficient to allow the normal extent of variation and trends to be established and to provide sufficient data for evaluation. It is generally considered acceptable that three consecutive batches/runs within the finally agreed parameters, would constitute a validation of the process.
26. Batches made for process validation should be the same size as the intended industrial scale batches.
27. If it is intended that validation batches be sold or supplied, the conditions under which they are produced should comply fully with the requirements of Good Manufacturing Practice, including the satisfactory outcome of the validation exercise, and with the marketing authorisation.

Concurrent validation

28. In exceptional circumstances it may be acceptable not to complete a validation programme before routine production starts.
29. The decision to carry out concurrent validation must be justified, documented and approved by authorised personnel.
30. Documentation requirements for concurrent validation are the same as specified for prospective validation.

Retrospective validation

31. Retrospective validation is only acceptable for well-established processes and will be inappropriate where there have been recent changes in the composition of the product, operating procedures or equipment.
32. Validation of such processes should be based on historical data. The steps involved require the preparation of a specific protocol and the reporting of the results of the data review, leading to a conclusion and a recommendation.
33. The source of data for this validation should include, but not be limited to batch processing and packaging records, process control charts, maintenance

log books, records of personnel changes, process capability studies, finished product data, including trend cards and storage stability results.

34. Batches selected for retrospective validation should be representative of all batches made during the review period, including any batches that failed to meet specifications, and should be sufficient in number to demonstrate process consistency. Additional testing of retained samples may be needed to obtain the necessary amount or type of data to retrospectively validate the process.
35. For retrospective validation, generally data from ten to thirty consecutive batches should be examined to assess process consistency, but fewer batches may be examined if justified.

CLEANING VALIDATION

36. Cleaning validation should be performed in order to confirm the effectiveness of a cleaning procedure. The rationale for selecting limits of carry over of product residues, cleaning agents and microbial contamination should be logically based on the materials involved. The limits should be achievable and verifiable.
37. Validated analytical methods having sensitivity to detect residues or contaminants should be used. The detection limit for each analytical method should be sufficiently sensitive to detect the established acceptable level of the residue or contaminant.
38. Normally only cleaning procedures for product contact surfaces of the equipment need to be validated. Consideration should be given to non-contact parts. The intervals between use and cleaning as well as cleaning and reuse should be validated. Cleaning intervals and methods should be determined.
39. For cleaning procedures for products and processes which are similar, it is considered acceptable to select a representative range of similar products and processes. A single validation study utilising a "worst case" approach can be carried out which takes account of the critical issues.
40. Typically three consecutive applications of the cleaning procedure should be performed and shown to be successful in order to prove that the method is validated.
41. "Test until clean". is not considered an appropriate alternative to cleaning validation.

42. Products which simulate the physicochemical properties of the substances to be removed may exceptionally be used instead of the substances themselves, where such substances are either toxic or hazardous.

CHANGE CONTROL

43. Written procedures should be in place to describe the actions to be taken if a change is proposed to a starting material, product component, process equipment, process environment (or site), method of production or testing or any other change that may affect product quality or reproducibility of the process. Change control procedures should ensure that sufficient supporting data are generated to demonstrate that the revised process will result in a product of the desired quality, consistent with the approved specifications.
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

45. Facilities, systems, equipment and processes, including cleaning, should be periodically evaluated to confirm that they remain valid. Where no significant changes have been made to the validated status, a review with evidence that facilities, systems, equipment and processes meet the prescribed requirements fulfils the need for revalidation.

GLOSSARY

Definitions of terms relating to qualification and validation which are not given in the glossary of the current EC Guide to GMP, but which are used in this Annex, are given below.

Change Control

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

Cleaning Validation

Cleaning validation is documented evidence that an approved cleaning procedure will provide equipment which is suitable for processing medicinal products.

Concurrent Validation

Validation carried out during routine production of products intended for sale.

Design qualification (DQ)

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

Installation Qualification (IQ)

The documented verification that the facilities, systems and equipment, as installed or modified, comply with the approved design and the manufacturer's recommendations.

Operational Qualification (OQ)

The documented verification that the facilities, systems and equipment, as installed or modified, perform as intended throughout the anticipated operating ranges.

Performance Qualification (PQ)

The documented verification that the facilities, systems and equipment, as connected together, can perform effectively and reproducibly, based on the approved process method and product specification.

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.

Prospective Validation

Validation carried out before routine production of products intended for sale.

Retrospective Validation

Validation of a process for a product which has been marketed based upon accumulated manufacturing, testing and control batch data.

Re-Validation

A repeat of the process validation to provide an assurance that changes in the process/equipment introduced in accordance with change control procedures do not adversely affect process characteristics and product quality.

Risk analysis

Method to assess and characterise the critical parameters in the functionality of an equipment or process.

Simulated Product

A material that closely approximates the physical and, where practical, the chemical characteristics (e.g. viscosity, particle size, pH etc.) of the product under validation. In many cases, these characteristics may be satisfied by a placebo product batch.

System

A group of equipment with a common purpose.

Worst Case

A condition or set of conditions encompassing upper and lower processing limits and circumstances, within standard operating procedures, which pose the greatest chance of product or process failure when compared to ideal conditions. Such conditions do not necessarily induce product or process failure.
