



## GOOD MANUFACTURING PRACTICES FOR PHARMACEUTICAL PRODUCTS

### Annex: Guidelines on the Validation of Manufacturing Processes

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#### INTRODUCTION

**These guidelines do not constitute additional requirements in the area of Good manufacturing practices (GMP)**

This text explains and promotes the concept of validation and assists in establishing priorities and selecting approaches when a validation programme is being developed. Since the WHO Guide on GMP is applicable essentially to the manufacture of pharmaceutical dosage forms, this annex is also addressed to the production of finished forms. However, general principles of process validation outlined here are largely relevant to the manufacture of active ingredients. While the emphasis is on the production processes, many recommendations are valid for supporting operations, such as cleaning. Analytical validation is not discussed here.\*

\* Analytical validation seeks to demonstrate that the analytical methods provide results which permit an objective evaluation of the quality of the pharmaceutical product as specified. The person responsible for the quality control laboratory should ensure that test methods are validated. The analytical devices used for these tests should be qualified and the measuring instruments used for the qualification should be calibrated. Each new test procedure should be validated.

For further advice see document "The validation of analytical procedures used in examination of pharmaceutical materials". WHO Expert Committee on Specifications for Pharmaceutical Preparations, Thirty-second report, World Health Organization, Geneva, 1992 (TRS 823).

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The guidelines on "Good manufacturing practices for pharmaceutical products" (Section 5)<sup>\*</sup> require that critical processes as well as changes in the manufacturing process which may affect product quality are validated. Experience shows that few manufacturing processes do not contain steps which are "critical", that is, may not cause variations in the final product quality. Therefore a prudent manufacturer would normally validate all production processes and supporting activities including cleaning operations. The term "critical process" in this context indicates a process, operation or a step that requires particularly close attention, for example sterilization, where the impact on the product quality is crucial. It may be noted that certain GMP guides, e.g. that of the European Community, do not distinguish between critical or non-critical processes regarding validation.

## GLOSSARY

### Manufacturing process\*\*

The transformation of starting materials into finished products (drug substance or pharmaceutical dosage forms) through a single operation or a sequence of operations involving installations, personnel, documentation and environment.

### Qualification of equipment

The act of planning, carrying out and recording tests on equipment to demonstrate that such will perform as intended. Measuring instruments and systems must be calibrated (see validation elements).

### Revalidation

Repeated validation of an approved process (or a part thereof) to ensure continued compliance with established requirements.

### Validation\*\*\*

The collection and evaluation of data, beginning at the process development stage and continuing through the production phase which ensures that the manufacturing processes – including equipment, buildings, personnel and materials – are capable of achieving the intended results on a consistent and continuous basis. It is the establishment of documented evidence that a system does what it purports to do.

### Validation elements

#### – Installation qualification

The performance of tests to ensure that installations (such as machines, measuring devices, utilities, manufacturing areas) used in a manufacturing process, are appropriately selected, correctly installed and work in accordance with established specifications.

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\* WHO Expert Committee on Specifications for Pharmaceutical Preparations, Thirty-second Report, World Health Organization, Geneva, 1992 (TRS 823).

\*\* For the purpose of this document "manufacturing process" is used as a synonym of "production process".

\*\*\* For the sake of consistency the definition is also quoted from the general GMP text as published in the WHO TRS 823 (p. 22): "The documented act of proving that any procedure, process, equipment, material, activity, or system actually leads to the expected results". Other definitions have been offered.

– Calibration

The performance of tests and retests to ensure that equipment for measurement (e.g. for temperature, weight, pH, etc.) used in a manufacturing process or analytical procedure (in production or quality control) leads to correct measurement results within established limits.

– Operational qualification

Documented verification that the system or subsystem performs as intended throughout all anticipated operating ranges.

– Challenge tests/worst case

A condition or set of conditions encompassing upper and lower processing limits and circumstances, within standard operating procedures, that pose the greatest chance of process or product failure when compared to ideal conditions.

– Certification

Final review and formal approval of a validation or revalidation, followed by approval of a process for routine use.

**Validation protocol (or plan)**

A document describing activities to be performed in a validation, including acceptance criteria for the approval of a manufacturing process – or a part thereof – for routine use.

**Validation report**

A document assembling the records, results and evaluation of a completed validation programme. It may also contain proposals for improvement of processes and/or equipment.

**General**

Validation is an integral part of quality assurance. The term "validation" in manufacturing often mystifies people as a subject difficult to understand. Validation may be explained as a systematic study which helps to prove that the systems, facilities and processes perform their intended job adequately and consistently as specified. A validated operation is one which has been proven, and consequently was formally approved, to have a high degree of assurance for the manufacture of uniform batches meeting the required specifications.

Unlike many other provisions of GMP, validation in itself does not improve processes. It can only confirm (or disprove, as the case may be) that the process was well developed and is under control. Ideally any developmental activity in the later stages should be crowned by a validation phase.\* This includes especially the manufacture of investigational products and the scaling-up of processes from pilot plant to the production unit. In this event, GMP as *manufacturing* practice may only be concerned with revalidation: either when processes are transferred from development to production, after modifications are introduced (starting materials, equipment, etc.) or when periodic revalidation is performed.

However, it cannot be assumed that all processes in the pharmaceutical industry worldwide have been properly validated at the developmental stage. Consequently, validation is here discussed in a broader context

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\* It may be noted that in some countries data on process validation is required at the pre-registration stage (in submissions or applications for marketing authorizations).

as an activity which originates in development and is extended to full scale production. In fact it is in the course of development that critical processes, steps or unit operations are identified.

Good validation practice requires close collaboration of company's departments such as Development, Production, Engineering, Quality Assurance and Control. This is most essential in transferring processes from pharmaceutical development via pilot-plant operations to routine full-scale production. With a view to facilitating subsequent validation and its assessment in the course of quality audits or regulatory inspections, it is recommended that all documentation reflecting such transfers be kept together in a separate file ("technology transfer document").

An adequate validation may be beneficial for the manufacturer in many ways:

- it deepens the understanding of processes; it decreases risks for process troubles and thus assured smooth running of the process;
- it decreases risks of defect costs;
- it decreases risks of regulatory non-compliance ;
- a fully validated process may require less in-process control and end-product testing;

#### Types of process validation

Depending on the time when it is performed relative to production, validation can be prospective, concurrent, retrospective or revalidation (repeated validation).

*Prospective validation* is carried out during the developmental stage and is the result of a risk analysis on the production process. The production process is conceptually broken down into individual steps which are then evaluated on the basis of past experience to determine whether they might lead to critical situations. Where possible critical situations are identified, the risk is evaluated, the potential causes are investigated and assessed for probability and extent, the trial plans are drafted and the priorities set. The trials are then performed and evaluated and an overall assessment is made. If at the end, the results are acceptable, the process is satisfactory. Unsatisfactory processes have to be amended and improved until a validation exercise proves the process to be satisfactory. This form of validation is essential for restricting the risk of errors occurring on a production scale as the validation is done in advance, e.g. the preparation of injectable products require this form of validation.

*Concurrent validation* is the form of validation carried out during the normal production. For this method to be effective, it must be presumed that the fundamentals have been understood at the development stage. *The first three production scale batches must be monitored as comprehensively as possible.* The evaluation of the results is used in stipulating the nature and specifications of subsequent in-process control tests and final tests.

Concurrent validation combined with a trend analysis including stability should be carried out to an appropriate extent throughout the life of the product.

*Retrospective validation* is the form of validation which involves looking back into past experiences obtained during production. On the precondition that composition, procedures, and equipment remain unchanged, facility experience and the results from in-process and final control tests are evaluated. Recorded difficulties and failures in production are analyzed and reveal the boundaries of process parameters. A trend analysis may be compiled to determine the extent to which the process is within the permissible range of the process parameters.

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\* This close monitoring of the first three production batches is sometimes listed under "Prospective validation."

Obviously retrospective validation is not a quality assurance measure in itself, and in no case should be applied to new processes or products. It may be considered in special circumstances only, e.g. when validation requirements are first introduced in a company. Then retrospective validation may be useful in establishing priorities in the validation programme. Positive results of a retrospective validation indicate that the process is not in need of immediate attention and may be validated in accordance with the schedule. In the case of tablets which have been compressed under individual pressure-sensitive cells, and with qualified equipment, retrospective validation is the most comprehensive test of the overall manufacturing process of this dosage form. On the other hand, retrospective validation should not be applied in the manufacture of sterile products.

*Revalidation* is needed to assure that changes in process and/or in the process environment, whether introduced intentionally or unintentionally, do not adversely affect process characteristics and product quality.

Revalidation may be classified into two broad categories;

- Revalidation in case of changes – after any change having a bearing on the product quality
- Periodic revalidation – at scheduled intervals.

#### **Revalidation in case of changes**

Revalidation must be performed on introduction of any change affecting a manufacturing and/or standard procedure having a bearing on the established product performance characteristics. Such changes may include starting material, packaging material, manufacturing processes, equipment, in-process controls, manufacturing areas, or support systems (water, steam etc.).

It is recommended that every requested change be reviewed by a qualified Validation group. This group will judge if a change is significant enough to justify revalidation and decide upon its extent.

Revalidation in case of changes may be based on the performance of the same tests and activities that were used during the original validation, including subprocesses and equipment affected. Some typical changes which require revalidation are listed below.

#### **– Change of starting material(s)**

Change of physical properties, such as density, viscosity, particle size distribution, crystal type and modification etc., in active ingredients or excipients may affect the mechanical properties of the material and as a consequence unfavourably affect the process or the product.

#### **– Changes of packaging material**

Exchange of packaging material, such as substituting glass for plastics, may require changes in packaging procedure and may affect the product stability.

#### **– Changes in the process**

Changes of mixing time, drying temperature, cooling regime etc., may affect subsequent process steps and product quality.

#### **– Change of equipment**

Exchange of equipment, including measuring instruments, could affect the process and the product; important repair and maintenance work, such as exchange of major parts of equipment may affect the process.

– Production area and support system changes

Rearrangement of manufacturing areas and/or support systems may result in changes in the process. Repair and maintenance of support systems, such as ventilation, may change the environmental conditions and, as a consequence, revalidation/requalification may be necessary, mainly in the field of sterile manufacturing.

– Unexpected changes and deviations

Such changes may be observed during a self-inspection, or an audit, or during the continuous process data trend analysis.

### **Periodic revalidation**

It is a well-known fact that changes in process may occur gradually even if experienced operators work correctly according to established methods. Similarly, equipment wearing may cause gradual changes. Consequently, it is advisable to perform revalidation on a scheduled basis even if no intentional changes have been introduced.

The decision for periodic revalidation should primarily be made through review of historical data (data generated during in-process testing and finished product testing after the latest validation) in order to verify that the process is under control. During review of historical data, any trend in the data collected should be evaluated.

Some processes, such as sterilization, need additional process testing as a complement to the historical data. The degree of testing required is apparent from the original validation.

Additionally, the following points should be checked at the time of a scheduled revalidation:

- The occurrence of any changes in master formula and methods, batch size etc. If changes have occurred, have they been assessed for impact on the product?
- Have calibrations been made according to established programme and time schedule?
- Has preventive maintenance been performed according to programme and time schedule?
- Are the Standard Operating Procedures (SOP's) properly updated?
- Are the SOP's followed?
- Have cleaning and hygiene programmes been followed?
- Have any changes been made in the analytical control methods?

### **Prerequisites for process validation**

Before process validation can start, manufacturing equipment and control instruments, as well as the formulation, have to be qualified. The formulation of a pharmaceutical product should be studied in detail and qualified at the development stage, i.e. before the application for the marketing authorization is submitted. This involves preformulation studies, compatibility studies between active ingredients and excipients, between final drug product and packaging material, stability studies etc.

Other aspects of manufacture have to be validated, including critical services (water, air, nitrogen, power supply etc.), supporting operations, such as equipment cleaning, sanitation of premises. Proper training and motivation of personnel is a prerequisite to successful validation.

## Approaches

Two basic approaches exist, when it comes to the process itself (apart from the qualification of equipment used in production, calibration of control and measurement instruments, evaluation of environmental factors etc.): the experimental approach, and the approach based on the analysis of historical data.

### - Experimental approach

The experimental approach, which is applicable to prospective and concurrent validation, may involve:

- extensive product testing
- simulation process trials
- challenge/worst case trials
- controls of process parameters (mostly physical).

One of the most practical forms of process validation, mainly for non-sterile products is the final testing of the product, which goes beyond routine quality control (Q.C.). It could involve extensive sampling: much larger than in routine Q.C. and testing to normal Q.C.-specifications, often for certain parameters only. Thus for instance, several hundred tablets per batch may be weighed to determine unit dose uniformity. The results are statistically treated to verify the "normality" of the distribution; standard deviation from the average weight. Confidence limits for individual results and between batch homogeneity are also estimated. Strong assurance is given for samples taken at random that they will meet regulatory requirements if the confidence limits are well within compendial specifications.

Similarly, extensive sampling and testing may be performed with regard to any quality requirements. Intermediate stages may be validated in the same way. For instance, dozens of samples may be assayed individually to validate mixing or granulation stages in low dose tablet production for content uniformity.

Occasionally, products (intermediate or final) may be tested for non-routine characteristics. Thus, sub-visual particulate matter in parenteral preparations may be determined by electronic devices or tablets/capsules may be tested for dissolution profile if this is not performed on every batch.

Simulation process trials are mostly used to validate aseptic filling of parenterals that cannot be terminally sterilized. This involves filling culture media under normal conditions with subsequent incubation and control of the microbial growth. A level of less than 0.3 % contamination was considered to be acceptable, however, the present level aimed at should be no more than 0.1 %.

Challenge experiments are performed to determine the robustness of the process, i.e. its capacity to run smoothly when parameters approach acceptable limits. The use of ranges for parameters of quality for starting materials for experimental batches may permit to estimate to what extent the process is still capable of keeping the end-product within specifications.

Physical parameters of the process are monitored in normal production runs to obtain additional information on the process and its reliability. Extra temperature-sensitive devices installed in an autoclave or dry-heat sterilizer (in addition to probes used routinely), will permit an in-depth study of the heat distribution for several loads. Heat penetration measurements are recommended for injectables of higher viscosity or of volumes larger than 5 ml. A tableting press equipped with pressure-sensitive cells will be helpful in collecting statistical data on the uniformity of die-fill and therefore mass uniformity.

### - Approach based on the analysis of historical data

No experiments are performed in retrospective validation, but instead, all available historical data concerning a number of batches are combined and jointly analyzed. If production is running smoothly

during the period preceding validation, the data from in-process inspection and final testing of the product are combined and treated statistically. Results, such as the outcome of process capability studies, trend analysis etc. would indicate whether the process is under control or not.

The technique of quality control charts may be used for retrospective validation. Ten to 25 batches or more are used for this purpose, preferably processed over a time period of no longer than 12 months, and reviewed together. (Batches rejected during routine quality control are not included in this review since they belong to a different "population", but failure investigations are performed separately). A critical quality parameter of the end-product is selected, for example, assay value or potency, unit dose uniformity, disintegration time, extent of dissolution. Analytical results for this parameter for batches under review are extracted from the past batch release documentation and pooled together while results from each batch are treated as sub-groups. The grand average ("process average") and control limits are calculated and plotted on the graphs or charts in accordance with instructions given in many publications on control charts (see selected bibliography, items 29-31).

A careful review of the charts permits estimation of the reliability of the process. The process may be considered reliable, if the plotted data are within the control limits and the variability of individual results is stable or tends to decrease. Otherwise, an investigation and possibly an improvement is needed.\*

In addition, information on product related problems is also analyzed. Reliability of the process is increased if for a considerable time period the product manufactured and marketed shows no rejections, complaints, returns, unaccountable adverse reactions etc. The process may be certified as retrospectively validated, if the results of statistical analysis are positive and the absence of serious problems is documented. However, it should be emphasized, that this approach is not applicable to the manufacture of sterile products.

### Organization

Several possibilities are available for the organization of validation efforts. One successful means of organization can be through the establishment of a Validation group.

The management appoints a person responsible for validation (validation officer), who forms a Validation group (team, committee), headed by a group leader, that represents major departments: Development, Production, Engineering, Quality Assurance and Control. It is recommended that the composition of the group is changed from time to time to give opportunities to other people to generate new ideas and to gain experience.

The Validation group prepares a programme, which determines the scope of the work, its priorities, time-schedule and resources needed etc. The programme is sent for review and approval to departments and functions concerned. The final review and approval is made by the validation officer.

As an example, the following suggested priorities may be applied for defining the scope of a process validation programme:

1. New manufacturing processes

Every new process must be validated before approval for routine production.

2. Existing manufacturing processes

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\* It may be noted that once control charts for past batches are constructed, they become a powerful tool for the prospective Quality management. Data for new batches are plotted on the same charts and for every result outside control limits a reason, that is a new factor affecting the process, is looked for and when found - eliminated. By consistently applying this approach over a period of time the process may be considerably improved.

## 2.1 Processes designed to render a product sterile

All processes affecting sterility and manufacturing environment must be validated. The top priority is the sterilization stage.

## 2.2 Non-sterile production

- low dose tablets and capsules containing highly active substances, priority: mixing and granulation in relation to content uniformity;
- other tablets and capsules, priority: tablet compressing and capsule filling in relation to uniformity of mass.

For new processes it is recommended that the first few full scale production batches (e.g. three batches) are not released from quarantine after it is approved by Quality Control, until the validation has been completed, the results are presented and reviewed and the process is approved (certified).

## VALIDATION PROTOCOL AND REPORT

The following scheme may be suggested for the validation protocol and subsequent report concerning a particular process.

### Contents

Part 1	Purpose (for the whole validation) and prerequisites
Part 2	Presentation of the whole process and sub-processes. Flow diagram. Critical steps/risks
Part 3	Validation protocol, approval
Part 4	Installation qualification. Drawings.
Part 5	Qualification protocol/report
5.1	Subprocess 1
5.1.1	Purpose
5.1.2	Methods/Procedures. List of manufacturing methods, SOP's, and written procedures, as applicable
5.1.3	Sampling and testing procedures, acceptance criteria (detailed description or reference to established procedures, such as described in pharmacopoeias)
5.1.4	Reporting
5.1.4.1	Calibration of test equipment used in the production process
5.1.4.2	Test data (raw data)
5.1.4.3	Results (summary)
5.1.5	Approval and requalification procedure
5.2	Subprocess 2 – Contents, see subprocess 1.
5.n	Subprocess n.
Part 6	Product characteristics. Test data from validation batches.
Part 7	Evaluation against the acceptance criteria and recommendations (including frequency for revalidation/requalification).
Part 8	Certification (Approval).
Part 9	If applicable, an abbreviated version of the validation report for external use such as regulatory authority.

The validation protocol and report may also include copies of the product stability report or its summary, validation documentation on cleaning and analytical methods

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