General Guideline for Manufacturing Validation

1. Type of process validation
2. Prerequisites for process validation
3. Approaches
4. Organization
5. Scope of a process validation programme
6. Validation protocol and report

INTRODUCTION

These guidelines do not constitute additional requirements in the area of good manufacturing practices (GMP). The purpose of this Annex is to explain and promote the concept of validation, and to assist in establishing priorities and selecting approaches when a validation programme is being developed. Since the WHO guide on GMP (1) is applicable essentially to the manufacture of pharmaceutical dosage forms, this text is also concerned with the production of such finished forms. However, the general principles of process validation outlined here are relevant mainly to the manufacture of active ingredients. While the emphasis is on the production processes, many recommendations are also valid for supporting operations, such as cleaning. Analytical validation is not discussed here. Further advice is given “Validation of analytical procedures used in the examination of pharmaceutical materials” (2).

The guide on GMP for pharmaceutical products (section 5) (1, page 27) requires the validation of critical processes as well as of changes in the manufacturing process which may affect product quality. Experience shows that few manufacturing processes do not contain steps which are "critical" that may cause variations in final product quality. A prudent manufacturer would therefore normally validate all production processes and supporting activities, including cleaning operations. The term “critical process” in this context indicates a process, operation or step that requires particularly close attention, e.g., sterilization, where the effect on product quality is crucial. It may be noted that certain GMP guides, e.g., that of the European Community (3), do not distinguish between critical and non-critical processes from the point of view of validation.

GLOSSARY

The definitions given below apply to the terms used in these guidelines. They may have different meanings in other contexts.

Calibration

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

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

**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 change of process or product failure when compared with ideal conditions.

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

**Manufacturing process**
(For the purpose of these guidelines, “manufacturing process” is used as a synonym of “production process”.)
The transformation of starting materials into finished products (drug substances or pharmaceutical dosage forms) through a single operation or a sequence of operations involving installations, personnel, documentation and environment.

**Operational qualification**
Documented verification that the system or subsystem performs as intended over all anticipated operating ranges.

**Qualification of equipment**
The act of planning, carrying out and recording the results on equipment to demonstrate that it will perform as intended. Measuring instruments and systems must be calibrated.

**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 ensure that the manufacturing processes— including equipment, building, personnel and materials— are capable of achieving the intended results on a consistent and continuous basis. Validation is the establishment of documented evidence that a system does what it is supposed to do. Other definitions also exist, e.g. that given in the guidelines on GMP for pharmaceutical products.

**Validation protocol (or plan)**
A document describing the activities to be performed in a validation, including the acceptance criteria for the approval of a manufacturing process or a part thereof for routine use.

**Validation report**

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

**General**

Validation is an integral part of quality assurance, but the use of this term in connection with manufacturing often gives rise to difficulties. As defined above, it involves the systematic study of systems, facilities and processes aimed at determining whether they perform their intended functions adequately and consistently as specified. A validated operation is one, which has been demonstrated to provide a high degree of assurance that uniform batches will be produced that meet the required specifications, and has therefore been formally approved.

Unlike many other requirements of GMP, validation in itself does not improve processes. It can only confirm (or not, as the case may be) that the process has been properly developed and is under control. Ideally, any development activity in the later stages should be finalized by a validation phase. This includes, in particular, the manufacture of investigational products and the scaling up of processes from pilot plant to production unit. In this event, GMP as manufacturing practice may only be concerned with revalidation, e.g. when processes are transferred from development to production, after modifications are introduced (in starting materials, equipment, etc.) or when periodic revalidation are required at the preregistration stage (in the submission of, or application for, marketing authorizations).

However, it cannot be assumed that all processes in the pharmaceutical industry worldwide have been properly validated at the development stage. Consequently, validation is discussed here in a broader context as an activity, which is initiated in development and is continued until the stage of full-scale production is reached. In fact, it is in the course of development that critical processes, steps or unit operations are identified.

Good validation practice requires the close collaboration of departments such as those concerned with development, production, engineering, quality assurance and control. This is most important when processes go into routine full-scale production following pharmaceutical development and pilot-plant operations. 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").

Adequate validation may be beneficial for the manufacturer in many ways:

1. It deepens the understanding of processes, decreases the risks of processing problems, and assures the smooth running of the process.
2. It decreases the risks of defect costs.
3. It decreases the risks of regulatory non-compliance.
4. A fully validated process may require less in-process control and end-product testing.

1. TYPES OF PROCESS VALIDATION

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

Prospective validation is carried out during the development stage by means of a risk analysis of the production process, which is broken down into individual steps; these 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 drawn up, 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 must be modified and improved until a validation exercise proves them to be satisfactory. This form of validation is essential in order to limit the risk of errors occurring on the production scale, e.g. in the preparation of injectable products.

Concurrent validation is carried out during normal production. This method is effective only if the development stage has resulted in a proper understanding of the fundamentals of the process. The first three production-scale batches must be monitored as comprehensively as possible. (This careful monitoring of the first three production batches is sometimes regarded as prospective validation.) The nature and specifications of subsequent in-process and final tests are based on the evaluation of the results of such monitoring.

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

Retrospective validation involves the examination of past experience of production on the assumption that composition, procedures, and equipment remain unchanged; such experience and the results of in-process and final control tests are then evaluated. Recorded difficulties and failure in production are analysed to determine the limits of process parameters. A trend analysis may be conducted to determine the extent to which process parameters are within the permissible range.

Retrospective validation is obviously not a quality assurance measure in itself, and should never 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. Retrospective validation may then be useful in establishing the priorities for the validation programme. If the results of a retrospective validation are positive, this indicates that the process is not in need of immediate attention and may be individual accordance with the normal schedule. For 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, it should not be applied in the manufacture of sterile products.

Revalidation is needed to ensure that changes in the process and/or in the process environment, whether international or unintentional, do not adversely affect process environment, whether international or unintentional, do not adversely affect process characteristics and product quality.

Revalidation is needed to ensure that changes in the process characteristics and product quality.

Revalidation may be divided into two board categories:

1. Revalidation after any change having a bearing on product quality.
2. Periodic revalidation carried out at scheduled intervals.

Revalidation after 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 those in material, packaging material, manufacturing processes, equipment, in-process controls, manufacturing areas, or support systems (water, system, etc.). Every such change requested should be reviewed by a qualified validation group, which will decide whether it is significant enough to justify revalidation and, if so, its extent.

Revalidation after changes may be bases on the performance of the same tests and activities as those used during the original validation, including tests on subprocesses and on the equipment concerned. Some typical changes which require revalidation include the following:

1. Changes in the starting material(s). Changes in the physical properties, such as density, viscosity, particle size distribution, and crystal type and modification, of the active ingredients or excipients may affect the mechanical properties of the materials; as a consequence, they may adversely affect the process or the product.
2. Changes in the packaging procedure material, e.g. replacing plastics by glass, may require changes in the packaging procedure and therefore affect product stability.
3. Changes in the process, e.g. changes in mixing time, drying temperature and cooling regime, may affect subsequent process steps and product quality.
4. Changes in equipment, including measuring instruments, may affect both the process and the product; repair and maintenance work, such as the replacement of major equipment components, may affect the process.
5. Changes in the production area and support system, e.g. the rearrangement of manufacturing areas and/or support systems, may result in changes in the process. The 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 manufacture of sterile products.
6. Unexpected changes and deviations may be observed during self-inspection or audit, or during the continuous trend analysis of process data.

Periodic revalidation. It is well known that process changes may occur gradually even if experienced operators work correctly according to established methods. Similarly, equipment wear may also cause gradual changes. Consequently, revalidation at scheduled times is advisable even if no changes have been deliberately made.

The decision to introduce periodic revalidation should be based essentially on a review of historical data, i.e. data generated during in-process and finished product testing after the latest validation, aimed at verifying that the process is under control. During the review of such historical data, any trend in the data collected should be evaluated.

In some processes, such as sterilization, additional process testing is required to complement the historical data. The degree of testing required will be apparent from the original validation.

Additionally, the following points should be checked at the time of a scheduled revalidation:
1. Have any changes in master formula and methods, batch size etc., occurred? If so, has their impact on the product been assessed?
2. Have calibrations been made in accordance with the established programme and time schedule?
3. Has preventive maintenance been performed in accordance with the programme and time schedule?
4. Have the standard operating procedures (SOPs) been properly updated?
5. Have the SOPs been implemented?
6. Have the cleaning and hygiene programmes been carried out?
7. Have any changes been made in the analytical control methods?

2. PREREQUISITES FOR PROCESS VALIDATION

Before process validation can be started, manufacturing equipment and control instruments, as well as formulation, must 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, studies on the compatibility of active ingredients and excipients, and of final drug product and packaging material, stability studies, etc.

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

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

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

1. Extensive product testing.
2. Simulation process trials.
3. Challenge/worst case trials.
4. 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 to an extent greater than that required in routine quality control. It may involve extensive sampling, for beyond that called for in routine quality control and testing to normal quality control specifications, and often for certain parameters only. Thus, for instance, several hundred tablets per batch may be weighed to determine unit dose uniformity. The results are then statistically to verify the “normality” of the distribution, and to determine the standard deviation from the average weight. Confidence limits for individual results and for batch homogeneity are also estimated. Strong assurance is provided that samples taken at random 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. In addition, intermediate stages may be validated in the same way, e.g. dozens of samples may be assayed individually to validate mixing or granulation stages of low-dose tablet production by using the content uniformity test. Products (intermediate or final) may occasionally be tested for non-routine characteristics. Thus, subvisual particulate matter in parenteral preparations may be determined by means of electronic devices, or tablets/capsules tested for dissolution profile if such tests are not performed on every batch.

Simulation process trials are used mainly to validate the aseptic filling of parenteral products that cannot be terminally sterilized. This involves filling ampoules with culture media under normal conditions, followed by incubation and control of microbial growth. In the past, a level of contamination of less then 0.3% was considered to be acceptable; however, the current target level should not exceed 0.1%.

Challenge experiments are performed to determine the robustness of the process, i.e. its capacity to operate smoothly when parameters approach acceptable limits. The use of ranges of parameters for the quality of the starting materials in experimental batches may make it possible to estimate to extent to which the process is still capable of producing an end-product that meets the specifications.

The 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 injectable products of higher viscosity or with volumes larger than 5ml.

In the 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 analysed. If production is proceeding smoothly during the period preceding validation, the data from in-process inspection and final testing of the product are combined and treated statistically. The results, including the outcome of process capability studies, trend analysis, etc. will indicate whether the process is under control or not.

Quality control charts may be used for retrospective validation. A total of 10-25 batches or more are used for this purpose, preferably processed over a 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, e.g. the assay value or potency, unit dose uniformity, disintegration time, or extent of dissolution. The analytical results for this parameter for the batches under review are extracted from treated as subgroups. The grand average (“process average”) and control limits are calculated and plotted on graphs or charts in accordance with the instructions given in numerous publications on control charts (see Bibliography, page 63).

A careful review of the charts will enable the reliability of the process to be estimated. A process may be considered reliable if the plotted data are within the control limits and the variability of individual results is stable or tends decrease. Otherwise, an investigation and possibly an improvement are needed. (It may be noted that, once control charts for past batches have been prepared, they become a powerful tool for 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 sought and, when found, eliminated. By consistently applying this approach over a period of time the process may be considerably improved.)

In addition, information on product-related problems is also analysed. The reliability of the process is demonstrated if, for a considerable time, there are 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 approach is not applicable to the manufacture of sterile products.

4. ORGANIZATION

Several possible methods of organizing validation are available, once of which is the establishment of a validation group. For this purpose, the management appoints a person responsible for validation (validation officer), who then forms the group (team, committee). This is headed by a group leader, and represents all major departments; development, production, engineering, quality
assurance and control. The composition of the group should be changed from time to give opportunities to other people to generate new ideas and to gain experience. The validation group then prepares a programme, which determines the scope of its work, its priorities, the time-schedule, the resources needed, etc. The final review and approval are the responsibility of the validation officer.

Table 1. Example of priorities for a process validation programme

<table>
<thead>
<tr>
<th>Type of process</th>
<th>Validation requirements</th>
</tr>
</thead>
<tbody>
<tr>
<td>New</td>
<td>Every new process must be validated before approval for routine production</td>
</tr>
<tr>
<td>Existing: Processes designed to render a product sterile</td>
<td>All processes affecting sterility and manufacturing environment must be validated; the most important is the sterilization stage.</td>
</tr>
<tr>
<td>Non-sterile production</td>
<td>Low-dose tablets and capsules containing highly active substances:</td>
</tr>
<tr>
<td>Other tablets and capsules:</td>
<td>Validation of mixing and granulation in relation to content uniformity</td>
</tr>
</tbody>
</table>

5. SCOPE OF A PROCESS VALIDATION PROGRAMME

Suggested priorities for a validation programme are listed in Table 1. For new processes, it is recommended that the first few full-scale production batches (e.g. three batches) should not be released from quarantine after approval by the quality control department until the validation has been completed, the results presented and reviewed, and the process approved (certified).

6. VALIDATION PROTOCOL AND REPORT

A suggested scheme for the validation protocol and subsequent report concerning a particular process is shown below:

Part 1. Purpose (the validation) and prerequisites
Part 2. Presentation of the entire process and subprocesses, 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, SOPs and written procedures, as applicable.

5.1.3 Sampling and testing procedures, accordance criteria (detailed description of, or reference to, established procedures, 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 (same as for Subprocess 1)
5.n Subprocess n

Part 6. Product characteristics, test data from validation batches
Part 7. Evaluation, including comparison with the acceptance criteria and recommendations (including frequency of revalidation/requalification)
Part 8 Certification (approval)
Part 9 If applicable, preparation of an abbreviated version of the validation report for external use, for example by the regulatory authority

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

Authorized person- role, functions and training
1. The role and position of the authorized person in the company
2. Implementation of the quality system
3. Routine duties of an authorized person
4. Education and training
   5. Selected references