Pharmaceutical analysis

ICH GUIDELINES FOR VALIDATION

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PART I:

TEXT ON VALIDATION OF ANALYTICAL PROCEDURES

ICH Harmonised Tripartite Guideline

1. INTRODUCTION

This document presents a discussion of the characteristics for consideration during the validation of the analytical procedures included as part of registration applications submitted within the EC, Japan and USA.

The objective of validation of an analytical procedure is to demonstrate that it is suitable for its intended purpose. A tabular summation of the characteristics applicable to identification, control of impurities and assay procedures is included. Other analytical procedures may be considered in future additions to this document.

2. TYPES OF ANALYTICAL PROCEDURES TO BE VALIDATED

The discussion of the validation of analytical procedures is directed to the four most common types of analytical procedures:

- Identification tests;
- Quantitative tests for impurities' content;
- Limit tests for the control of impurities;
- Quantitative tests of the active moiety in samples of drug substance or drug product or other selected component(s) in the drug product

The objective of the analytical procedure should be clearly understood since this will govern the validation characteristics which need to be evaluated. Typical validation characteristics which should be considered are listed below:

- Accuracy
- Precision
- Repeatability
- Intermediate -Precision
- Specificity Detection
- Limit Quantitation
- Limit Linearity
- Range

Furthermore revalidation may be necessary in the following circumstances

- changes in the synthesis of the drug substance;
- changes in the composition of the finished product;
- changes in the analytical procedure.

GLOSSARY

1. ANALYTICAL PROCEDURE

The analytical procedure refers to the way of performing the analysis. It should describe in detail the steps necessary to perform each analytical test. This may include but is not limited to: the sample, the reference standard and the reagents preparations, use of the apparatus, generation of the calibration curve, use of the formulae for the calculation, etc.

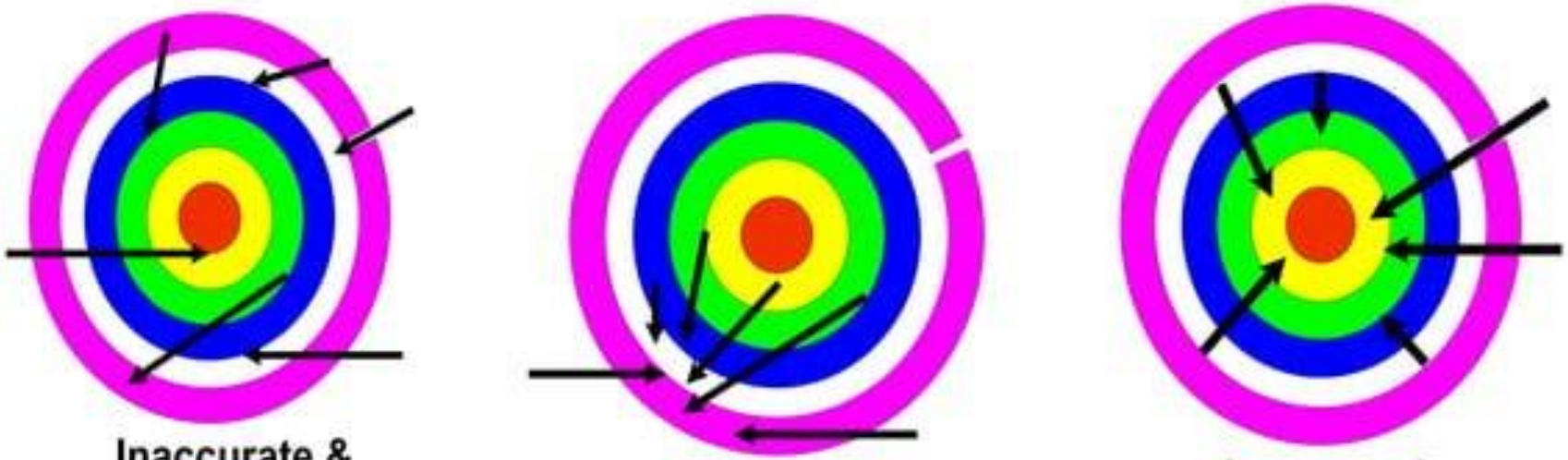
2.SPECIFICITY

Specificity is the ability to assess unequivocally the analyte in the presence of components which may be expected to be present. Typically these might include impurities, degradants, matrix, etc.

3. ACCURACY

The accuracy of an analytical procedure expresses the closeness of agreement between the value which is accepted either as a conventional true value or an accepted reference value and the value found.

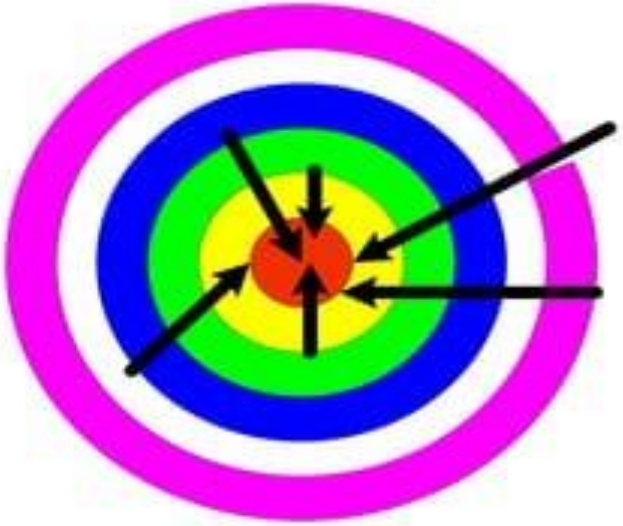
This is sometimes termed trueness.



Inaccurate & imprecise

Inaccurate but precise

Accurate but imprecise



Accurate and
precise

4. PRECISION

The precision of an analytical procedure expresses the closeness of agreement (degree of scatter) between a series of measurements obtained from multiple sampling of the same homogeneous sample under the prescribed conditions. Precision may be considered at three levels: repeatability, intermediate precision and reproducibility.

i. Repeatability

Repeatability expresses the precision under the same operating conditions over a short interval of time. Repeatability is also termed intra-assay precision .

ii. Intermediate precision

Intermediate precision expresses within-laboratories variations: different days, different analysts, different equipment, etc.

iii. Reproducibility

Reproducibility expresses the precision between laboratories (collaborative studies, usually applied to standardization of methodology).

5.DETECTION LIMIT

The detection limit of an individual analytical procedure is the lowest amount of analyte in a sample which can be detected but not necessarily quantitated as an exact value.

6.QUANTITATION LIMIT

The quantitation limit of an individual analytical procedure is the lowest amount of analyte in a sample which can be quantitatively determined with suitable precision and accuracy. The quantitation limit is a parameter of quantitative assays for low levels of compounds in sample matrices, and is used particularly for the determination of impurities and/or degradation products.

7.LINEARITY

The linearity of an analytical procedure is its ability (within a given range) to obtain test results which are directly proportional the concentration (amount) of analyte in the sample.

8.RANGE

The range of an analytical procedure is the interval between the upper and lower concentration (amounts) of analyte in the sample (including these concentrations) for which it has been demonstrated that the analytical procedure has a suitable level of precision, accuracy and linearity.

PART II:

VALIDATION OF ANALYTICAL PROCEDURES: METHODOLOGY

ICH Harmonised Tripartite Guideline

INTRODUCTION

This document is complementary to the parent document which presents a discussion of the characteristics that should be considered during the validation of analytical procedures. Its purpose is to provide some guidance and recommendations on how to consider the various validation characteristics for each analytical procedure.

1. SPECIFICITY

An investigation of specificity should be conducted during the validation of identification tests, the determination of impurities and the assay. The procedures used to demonstrate specificity will depend on the intended objective of the analytical procedure.

It is not always possible to demonstrate that an analytical procedure is specific for a particular analyte (complete discrimination).

❑ Identification

Suitable identification tests should be able to discriminate between compounds of closely related structures which are likely to be present. The discrimination of a procedure may be confirmed by obtaining positive results (perhaps by comparison with a known reference material) from samples containing the analyte, coupled with negative results from samples which do not contain the analyte.

❑ Assay and Impurity Test(s)

For chromatographic procedures, representative chromatograms should be used to demonstrate specificity and individual components should be appropriately labelled. Similar considerations should be given to other separation techniques.

2. LINEARITY

A linear relationship should be evaluated across the range (see section 3) of the analytical procedure. It may be demonstrated directly on the drug substance (by dilution of a standard stock solution) and/or separate weighings of synthetic mixtures of the drug product components, using the proposed procedure

3. RANGE

The specified range is normally derived from linearity studies and depends on the intended application of the procedure

4. ACCURACY

Accuracy should be established across the specified range of the analytical procedure.

Assay

- ***Drug Substance***

Several methods of determining accuracy are available:

a)application of an analytical procedure to an analyte of known purity (e.g. reference material);

b)comparison of the results of the proposed analytical procedure with those of a second well-characterized procedure, the accuracy of which is stated and/or defined.

c) accuracy may be inferred once precision, linearity and specificity have been established.

- ***Drug Product***

Several methods for determining accuracy are available:

a)application of the analytical procedure to synthetic mixtures of the drug product components to which known quantities of the drug substance to be analysed have been added;

b)in cases where it is impossible to obtain samples of all drug product components , it may be acceptable either to add known quantities of the analyte to the drug product or to compare the results obtained from a second, well characterized procedure, the accuracy of which is stated

c)accuracy may be inferred once precision, linearity and specificity have been established.

- **Impurities (Quantitation)**

Accuracy should be assessed on samples (drug substance/drug product) spiked with known amounts of impurities.

In cases where it is impossible to obtain samples of certain impurities and/or degradation products, it is considered acceptable to compare results obtained by an independent procedure (see 1.2.). The response factor of the drug substance can be used.

- **Recommended Data**

Accuracy should be assessed using a minimum of 9 determinations over a minimum of 3 concentration levels covering the specified range (e.g., 3 concentrations/3 replicates each of the total analytical procedure).

4. PRECISION

Validation of tests for assay and for quantitative determination of impurities includes an investigation of precision.

5. DETECTION LIMIT

Several approaches for determining the detection limit are possible, depending on whether the procedure is a non-instrumental or instrumental. Approaches other than those listed below may be acceptable.

6. QUANTITATION LIMIT

Several approaches for determining the quantitation limit are possible, depending on whether the procedure is a non-instrumental or instrumental. Approaches other than those listed below may be acceptable.

7. ROBUSTNESS

- Measure of the capacity to remain unaffected by small (deliberate) variations in method parameters
- Indication of reliability during normal use

The evaluation of robustness should be considered during the development phase and depends on the type of procedure under study. It should show the reliability of an analysis with respect to deliberate variations in method parameters.

8. SYSTEM SUITABILITY TESTING

System suitability testing is an integral part of many analytical procedures. The tests are based on the concept that the equipment, electronics, analytical operations and samples to be analyzed constitute an integral system that can be evaluated as such.

W H O GUIDELINES ON VALIDATION

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INTRODUCTION

Validation is an essential part of good practices including good manufacturing practices (GMP) *(4)* and good clinical practices (GCP). It is therefore an element of the pharmaceutical quality system.

SCOPE

These guidelines focus mainly on the overall concept of validation and are not intended to be prescriptive in specific validation requirements. This document serves as general guidance only and the principles may be considered useful in its application in the manufacture and control of starting materials and finished pharmaceutical products (FPPs), as well as other areas. Validation of specific processes and systems, for example, in sterile product manufacture, requires much more consideration and a detailed approach that is beyond the scope of this document.

3. GLOSSARY

The definitions given below apply to the terms used in these guidelines.

They may have different meanings in other contexts.

CALIBRATION

The set of operations that establish, under specified conditions, the relationship between values indicated by an instrument or system for measuring (for example, weight, temperature and pH),recording, and controlling, or the values represented by a material measure, and the corresponding known values of a reference standard.Limits for acceptance of the results of measuring should be established.

CHANGE CONTROL (INCLUDING CHANGE MANAGEMENT)

Aformal system by which qualified representatives of appropriate disciplines review proposed or actual changes that might affect a validated status. The intent is to determine the need for action that would ensure that the system is maintained in a validated state.

CLEANING VALIDATION.

Documented evidence to establish that cleaning procedures are removing residues to predetermined levels of acceptability, taking into consideration factors such as batch size, dosing, toxicology and equipment size.

COMMISSIONING.

The setting up, adjustment and testing of equipment or a system to ensure that it meets all the requirements, as specified in the user requirement specification, and capacities as specified by the designer or developer. Commissioning is carried out before qualification and validation.

COMPUTER VALIDATION

(INCLUDING COMPUTERIZED SYSTEM VALIDATION).

Confirmation by examination and provision of objective documented evidence that computerized system specifications conform to use needs and intended uses, and that all requirements can be consistently Fulfilled.

CONCURRENT VALIDATION.

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

DESIGN QUALIFICATION.

Documented verification that the proposed design of facilities, systems and equipment is suitable for theintended purpose.

GOOD ENGINEERING PRACTICES.

Established engineering methods and standards that are applied throughout the project life-cycle to deliverappropriate, cost-effective solutions.

INSTALLATION QUALIFICATION.

Documented verification that the installations (such as machines, computer system components, measuring devices, utilities and manufacturing areas) used in a processor system are appropriately selected andcorrectly installed in accordance with established specifications.

OPERATIONAL QUALIFICATION.

Documented verification that the system or subsystem operates as intended over all anticipated operating ranges.

PERFORMANCE QUALIFICATION.

Documented verification that the equipment or system performs consistently and reproducibly withindefined specifications and parameters in its normal operating environment (i.e. in the production environment).(In the context of systems, the term "process validation" may also be used.)

PROCESS VALIDATION.

The collection and evaluation of data, throughout the product life cycle, which provides documented scientificevidence that a process is capable of consistently delivering quality products.

PROSPECTIVE VALIDATION.

Validation carried out during the development stage on the basis of a risk analysis of the production process, which is broken down into individual steps; these are then evaluated on the basis ofpast experience to determine whether they maylead to critical situations.

QUALIFICATION.

Documented evidence that premises, systems or equipment are able to achieve the predetermined specifications properly installed, and/or work correctly and lead to the expected Results.

REVALIDATION.

Repeated validation of a previously validated system (or a part thereof) to ensure continued compliance with established requirements.

STANDARD OPERATING PROCEDURE.

An authorized written procedure giving instructions for performing operations not necessarily specific to agiven product or material but of a more general nature (e.g. equipment operation, maintenance and cleaning; validation; cleaning of premises andenvironmental control; sampling and inspection).Certain standard operating procedures may be used to supplement product-specific master batch production documentation.

VALIDATION.

Action of proving and documenting that any process, procedure or method actually and consistently leads to the expectedresults.

VALIDATION MASTER PLAN.

The validation master plan is a high-level document that establishes an umbrella validation plan for the entireproject and summarizes the manufacturer's overall philosophy and approach, to be used for establishing performance adequacy. It provides information on the manufacturer's validation work programme and defines details of and timescales for the validation work to be performed, including a statement of the responsibilities of those implementing the plan.

VALIDATION PROTOCOL.

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

VALIDATION REPORT.

A document in which the records, results andevaluation of validation are assembled and summarized.It may also contain proposals for the improvement of processes and/or systems and/or equipment.

VERIFICATION.

The application of methods, procedures, tests and other evaluations, in addition to monitoring, to determine compliance with established requirements and specifications.

RELATIONSHIP BETWEEN VALIDATION AND QUALIFICATION

Qualification and validation are essentially the same. The term qualification is normally used for equipment and utilities, and validation for systems and processes. In this sense, qualification can be seen as part of validation. Where the term "validation" is used in the document, the same principles may be applicable for"qualification)

VALIDATION

Approaches to validation

- Manufacturers should organize and plan validation in a manner that will ensure product quality, safety
and efficacy throughout its life cycle.

- The scope and extent of qualification and validation should bebased on risk management principles.

- Statistical calculations should be applied, where appropriate, and provide scientific evidence that the process, system or other related aspect is appropriately validated.

- Qualification and validation should be done in accordance withpredetermined protocols, and the results appropriately documented, e.g. in reports.

- There should be an appropriate and effective quality system ensuring the organization and management of validation.

- Senior management should ensure that there are sufficient resources to perform validation in a timely manner. Management and persons responsible for quality assurance should be actively involved in

DOCUMENTATION

- Qualification and validation should be done according to written procedures.

- Documents associated with qualification and validation include:

– validation master plan (VMP);
– standard operating procedures (SOPs);
– specifications;
– protocols and reports;
- risk assessment outcomes;
- process flow charts;
- operator manuals;
- training records;
- calibration procedures and records;
- sampling plans;
- testing plans and methods;
- statistical methods and results;
- history of qualification or validation;
- plan for ensuring review of validation status;
- plan for ensuring maintaining a validated state.

VALIDATION MASTER PLAN

A manufacturer should have a VMP which reflects the key elements of validation. It should be conciseand clear and contain at least the following:

- TITLE PAGE AND AUTHORIZATION (APPROVAL SIGNATURES AND DATES);
- TABLE OF CONTENTS;
- ABBREVIATIONS AND GLOSSARY;
- VALIDATION POLICY;
- PHILOSOPHY, INTENTION AND APPROACH TO VALIDATION;
- ROLES AND RESPONSIBILITIES OF RELEVANT PERSONNEL;
- RESOURCES TO ENSURE VALIDATION IS DONE;
- OUTSOURCED SERVICES (SELECTION, QUALIFICATION, MANAGEMENT THROUGH LIFE CYCLE);
- DEVIATION MANAGEMENT IN VALIDATION;
- CHANGE CONTROL IN VALIDATION;
- RISK MANAGEMENT PRINCIPLES IN VALIDATION;
- TRAINING;
- SCOPE OF VALIDATION;
- DOCUMENTATION REQUIRED IN QUALIFICATION AND VALIDATION SUCH AS
- PROCEDURES, CERTIFICATES, PROTOCOLS AND REPORTS;
- PREMISES QUALIFICATION;
- UTILITIES QUALIFICATION;
- EQUIPMENT QUALIFICATION;
- PROCESS VALIDATION;
- CLEANING VALIDATION;
- PERSONNEL QUALIFICATION SUCH AS ANALYST QUALIFICATION;

QUALIFICATION AND VALIDATION PROTOCOLS

There should be qualification and validation protocols describing the qualification and validation to be performed.
As a minimum the protocols should include the following significant background information.

- The objectives
- The site
- The responsible personnel
- Description of the standard operating procedures (SOPs) to be followed
- Equipment or instruments to be used
- Standards and criteria as appropriate
- The Stage of validation or qualification
- The processes and/or parameters
- Sampling ,testing and monitoring requirements
- Stress testing where appropriate
- Calibration requirement
- Predetermined acceptance criteria for drawing conclusions
- Review and interpretation of results
- Change control, deviations
- Archiving and retention

There should be a description of the way in which the results will be analysed, including statistical analysis where appropriate.

QUALIFICATION AND VALIDATION REPORTS

- There should be written reports on the qualification and validation performed.

- Reports should reflect the protocols and procedures followed and include at least the title and objective of the study; make reference to the protocol; reference to the appropriate risk assessment; details of materials, equipment, programmes and cycles used; procedures and test methods with appropriate traceability.

- Results should be recorded and be in compliance with good data and record management practices.

- Results should be reviewed, analysed and compared against the justified predetermined acceptance criteria, interpreted and statistically analysed where appropriate.

- Results should meet the acceptance criteria. Deviations, out-of-specification and out-of-limitresults should be documented and
investigated according to appropriate procedures. If these deviations are accepted, this should be justified. Where necessary, further studies should be performed.

10. QUALIFICATION

- There are different approaches in qualification and validation.
- The manufacturer should select an appropriate approach for the conduct thereof

- The V-model as an example of an approach to qualification and validation.

- All relevant SOPs for operation, maintenance and calibration should be prepared during qualification.

- Training should be provided to operators and training records should be maintained.

- Normally, qualification should be completed before process validation is performed.

- The process of qualification should be a logical, systematic process and should follow a logical flow from the premises, followed by utilities,equipment, to procedures and processes.
- Stages of qualification should normally start with the preparation

CHANGE MANAGEMENT

- Changes should be controlled in accordance with an SOP as changes may have an impact on a qualified utility or piece of equipment, and a validated process, system and/or procedure.

- When a change is initiated, consideration should be given to previous changes and whether requalification and/or revalidation is needed as a result of the cumulative effect of the changes.

- The procedure should describe the actions to be taken, including the need for and extent of qualification or validation to be done.

11. DEVIATION MANAGEMENT

Deviations during validation and qualification should be documented and investigated, through the deviation management procedure

12. CALIBRATION AND VERIFICATION

• Calibration and verification of equipment, instruments and other devices, as applicable, should be initiated during installation qualification to ensure that the system operates according to the described specifications and because the calibration status could have been affected during transport and installation.

• Thereafter, it should be performed at regular intervals in accordance with a calibration programme and SOPs.

• Personnel who carry out calibration and preventive maintenance should have an appropriate qualification and training.

• A calibration programme should be available and should provide information such as calibration standards and limits, responsible persons ,calibration intervals, records and actions to be taken when problems are identified.

• There should be traceability to standards (e.g. national, regional or international standards) used in the calibration.

REFERENCES

- Supplementary guidelines on good manufacturing practices: Validation. *WHO Technical Report Series, No. 937,* 2006, Annex 4.
- Good manufacturing practices: Quality assurance of pharmaceuticals. WHO guidelines , good practices,related regulatory guidance and GXP training materials. CD-ROM, update 2016.

THANK YOU