

Updated Review: Validation and Method Validation Parameters

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ABSTRACT

Validation is an act of proving that any procedure, process, equipment, material, activity or system performs as expected under given set of conditions and also give the required accuracy, precision, sensitivity, ruggedness. Validation parameter is used for establishing documented evidence which proves that performance characteristics of the method meet the requirements for the intended analytical applications. The goal of validation is to demonstrate that analytical results produced by the application of a particular method are fit for an intended purpose. In this review article we discussed about the validation and its important parameter.

Keywords: Validation, Validation Parameters, Good Manufacturing Practices

INTRODUCTION

Method validation is the process of demonstrating that an analytical method is suitable for its intended use, and involves conducting a variety of studies to evaluate method performance under defined conditions. Validation is required for herbal procedure, new process and reaction, new molecules, active ingredients, residues, impurity profiling and component of interest in different matrices. An analytical methodology consists of the techniques, method, procedure and protocol. This methodology includes the required data for a given analytical problem, required sensitivity, required accuracy, required range of analysis and required precision to the analyst.

The International Conference on Harmonization (ICH) of Technical Requirements for the Registration of Pharmaceuticals for Human Use

^[1] has developed a text on the validation of analytical procedures. The United States Food and Drug Administration (USFDA) have proposed guidelines on submitting samples and analytical data for methods validation.^[2-5] The United States Pharmacopoeia (USP) has published specific guidelines for method validation for compound evaluation.^[5]

The word validation was not mentioned in the current Good Manufacturing Practices (cGMP's) of 1971, and precision and accuracy were stated as laboratory controls. The need for validation was implied only in the cGMP guideline of March 1979. It was done in two sections: (1) Section 211.165, where the word 'validation' was used and (2) section 211.194,^[6] in which the proof of suitability, accuracy and reliability was made compulsory for regulatory submissions.

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PUBLICATIONS ON VALIDATION (1990 TO PRESENT)

A review on validation of bioanalytical methods was published by Karnes et al. in 1991 which was intended to provide guidance for bioanalytical chemists.^[7] One year later, Shah et al. published their report on the conference on "Analytical Methods Validation: Bioavailability, Bioequivalence and Pharmacokinetic Studies" held in Washington in 1990 (Conference Report). During this conference, consensus was reached on which parameters of bioanalytical methods should be evaluated, and some acceptance criteria were established.^[8] In the following years, this report was actually used as guidance by bioanalysts. And also US FDA Technical Review Guide gives Validation of Chromatographic Methods prepared by Center for Drug Evaluation and Research (CDER) in 1993.^[9] That give fully authorized guideline for validation of chromatographic methods. Despite the fact, however, that some principle questions had been answered during this conference, no specific recommendations on practical issues like experimental designs or statistical evaluation had been made. In 1994, Hartmann et al. analyzed the Conference Report performing statistical experiments on the established acceptance criteria for accuracy and precision.^[10] Based on their results they questioned the suitability of these criteria for practical application. From 1995 to 1997, application issues like experimental designs and statistical methods for bioanalytical method validation were discussed in a number of publications of Dadgar et al.^[11], Wieling et al.^[12], Bressolle et al.^[13]. And Causon.^[14] An excellent review on validation of bioanalytical chromatographic methods has been published by Hartmann et al. in 1998, in which theoretical and practical issues were discussed in detail. Finally, in an update conference of the Washington conference,^[15] experiences and progress since the first conference have been

discussed. The results were again published by Shah et al. in a report (Conference Report II).^[16] which has also been used as a template for their own guidelines by the U.S. Food and Drug Administration (FDA). Besides, it should be mentioned that some journals like Journal of Chromatography B or Clinical Chemistry have established their own criteria for validation.^[17] Two other documents that seem to be important in this context have been developed by the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) and approved by the regulatory agencies of the European Union, the United States of America and Japan. Despite the fact, that these were focused on analytical methods for pharmaceutical products rather than bioanalysis, they still contain helpful guidance on some principal questions and definitions in the field of analytical method validation. The first document, approved in 1994^[18], concentrated on the theoretical background and definitions, the second, approved in 1996, on methodology and practical issues^[19]. Both can be downloaded from the ICH homepage free of charge (www.ich.org). validation of analytical methods – strategies & importance Ravichandran v, Shalini s, Sundram k. m and harishrajak in 2010. In few time before gives validation and peer review of U.S. environmental protection agency chemical methods of analysis in 2005,^[20] After that validation a critical parameter for quality control of pharmaceuticals Tangri Pranshu, Rawat Prakash Singh, Jakhmola Vikash, Laksh Mayya in 2012,^[21] method development and validation- a review article by Sudha t, Krishanankanth v, Nukalapooran in 2012. Guidance for Industry Guideline for Analytical Procedures and Methods Validation for Drugs and Biologics by FDA and CDER in 2014.^[22]

VALIDATION POLICY

1. The company's overall policy, intentions, and approach to validation, including the validation of production processes, cleaning procedures, analytical methods, in-process control test procedures, computerized systems, and persons responsible for design, review, approval and documentation of each validation phase, should be documented.

2. The critical parameters/attributes should normally be identified during the development stage or from historical data, and the ranges necessary for the reproducible operation should be defined. This should include:

- Defining the Medicinal Product/Drug in terms of its critical product attributes;
- Identifying process parameters that could affect the critical quality attributes of the Medicinal Product/Drug;
- Determining the range for each critical process parameter expected to be used during routine manufacturing and process control

3. Validation should extend to those operations determined to be critical to the quality and purity of the Medicinal Product/Drug.

TYPES OF ANALYTICAL PROCEDURES TO BE VALIDATED

the four most common types of analytical procedures:

1. Identification tests
2. Quantitative tests for impurities content
3. Limit tests for the control of impurities
4. Quantitative tests of the active moiety in samples of drug substance or drug product or other selected component in the drug product.

ADVANTAGES OF VALIDATION

The biggest advantage of validation is that it builds a degree of confidence, not only for the developer but also to the user. Although the validation exercise may appear costly and time consuming, it results inexpensive, eliminates frustrating repetitions and leads to better time management in the end. Minor changes in the

conditions such as reagent supplier or grade, analytical setup are unavoidable due to obvious reasons but the method validation absorbs the shock of such conditions and pays for more than invested on the process.

IMPORTANCE OF VALIDATION

The most compelling reasons to optimize and validate pharmaceutical productions and supporting processes are quality assurance and cost reduction .the basic principles of quality assurance has as their goal and the production of articles that are fit for their intended use.¹⁰ These principles are Quality, safety, and effectiveness must be designed and built in to the product, quality cannot be inspected or tested in the finished products and each step of the manufacturing process must be controlled to maximize the probability that the finished product meets all quality and design specification. The relationship of quality assurance and process validation^[23] goes well beyond the responsibility of any quality assurance functions, nevertheless it is fair to say that process validation is a quality assurance tool because it is establishes a quality standard for the specific process.

TYPE OF VALIDATION

- EQUIPMENT VALIDATION
- PROCESS VALIDATION
- CLEANING VALIDATION
- MISCELLANEOUS VALIDATION
- METHOD VALIDATION

EQUIPMENT VALIDATION

Equipment validation is usually carried out by conducting the following activities, individually or combined:

- Design Qualification (DQ): documented verification that the proposed design of the facilities, equipment, or systems is suitable for the intended purpose.

- Installation Qualification (IQ): documented verification that the equipment or systems, as installed or modified, comply with the approved design, the manufacturer's recommendations and/or user requirements.
- Operational Qualification (OQ): documented verification that the equipment or systems, as installed or modified, perform as intended throughout the anticipated operating ranges.
- Performance Qualification (PQ): documented verification that the equipment and ancillary systems, as connected together, can perform effectively and reproducibly based on the approved process method and specifications.

PROCESS VALIDATION

The number of process runs for validation should depend on the complexity of the process or the magnitude of the process change being considered. For prospective and concurrent validation, three consecutive successful production batches should be used as a guide, but there may be situations where additional process runs are warranted to prove consistency of the process (e.g., complex processes). For retrospective validation, generally data from ten to thirty consecutive batches should be examined to assess process consistency, but fewer batches can be examined if justified. Critical process parameters should be controlled and monitored during process validation studies. Process parameters unrelated to quality, such as variables controlled to minimize energy consumption or equipment use, need not be included in the process validation.

CLEANING VALIDATION

Cleaning procedures should be validated. In general, cleaning validation should be directed to situations or process steps where contamination or carryover of materials poses the greatest risk to bulk product or Medicinal Product/Drug quality. Validation of cleaning

procedures should reflect actual equipment usage patterns. If various bulk products or Medicinal Products/Drugs or intermediates are manufactured in the same equipment and the equipment is cleaned by the same process, a representative intermediate or bulk product or Medicinal Product/Drug can be selected for cleaning validation. This selection should be based on the solubility and difficulty of cleaning and the calculation of residue limits based on potency, toxicity, and stability.

METHOD VALIDATION

Method validation guideline has been prepared by the Analytical Methods Technical Committee of the Chemistry Manufacturing Controls Coordinating Committee (CMC CC) of the Center for Drug Evaluation and Research at the Food and Drug Administration.^[1]

STEPS IN METHOD VALIDATION

1. Develop a validation protocol.
2. Define purpose and scope of the method
3. Define the performance parameters and acceptance criteria
4. Define validation experiments
5. Verify performance characteristics of equipment
6. Qualify materials, e.g. standards and reagents
7. Perform pre-validation experiments
8. Adjust method parameters
9. Perform full internal (and external) validation experiments
10. Develop SOPs (standard operating procedures) for executing the method in the routine
11. Define criteria for revalidation
12. Define type and frequency of analytical quality control (AQC) checks for the routine
13. Document validation experiments and results in the validation.

PARAMETERS FOR METHOD VALIDATION

The parameters as defined by the ICH^[24] and by other organizations and authors are Specificity, selectivity, precision, intermediate precision, reproducibility, repeatability, accuracy, stability, recovery, trueness, bias, linearity and calibration model, range, limit of detection, limit of quantitation, robustness and ruggedness.

SELECTIVITY / SPECIFICITY

The terms selectivity and specificity are often used interchangeably. A detailed discussion of this term as defined by different organizations has been made by Vessmann. Even inconsistent with ICH, the term specific generally refers to a method that produces a response for a single analyte only, while the term selective refers to a method which provides responses for a number of chemical entities that may or may not be distinguished from each other. If the response is distinguished from all other responses, the method is said to be selective. Since there are very few methods that respond to only one analyte, the term selectivity is usually more appropriate. The USP monograph 8 defines selectivity of an analytical method as its ability to measure accurately an analyte in the presence of interference, such as synthetic precursors, excipients, enantiomers and known (or likely) degradation products that may be expected to be present in the sample matrix.^[12]

Determination of Selectivity / Specificity:-

In the case of qualitative analyses, the ability to select between compounds of closely related structure that are likely to be present should be demonstrated. This should be confirmed by obtaining positive results from samples containing the analyte, coupled with negative results from samples that do not contain the analyte and by confirming that a positive response is not obtained from materials structurally similar to or closely related to the analyte.

Selectivity in liquid chromatography^[19] is obtained by choosing optimal columns and setting chromatographic conditions such as mobile phase composition, column temperature and detector wavelength. It is a difficult task in chromatography to ascertain whether the peaks within a sample chromatogram are pure or consist of more than one compound. While in the past chromatographic parameters such as mobile phase composition or the column has been modified.

PRECISIONS

The precision of a method is the extent to which the individual test results of multiple injections of a series of standards agree. The measured standard deviation can be subdivided into three categories: repeatability, intermediate precision and reproducibility.^[17] Repeatability is obtained when one operator using one piece of equipment over a relatively short time-span carries out the analysis in one laboratory. At least 5 or 6 determinations of three different matrices at two or three different concentrations should be done and the relative standard deviation calculated.^[21]

INTERMEDIATE PRECISION

Intermediate precision is a term that has been defined by ICH-2^[26] as the long-term variability of the measurement process and is determined by comparing the results of a method run within a single laboratory over a number of weeks. A method's intermediate precision may reflect discrepancies in results obtained by different operators, from different instruments, with standards and reagents from different suppliers, with columns from different batches or a combination of these.

Objective of intermediate precision validation is to verify that in the same laboratory the method will provide the same results once the development phase is over.

REPRODUCIBILITY

Reproducibility as defined by ICH-2, 3^[24] represents the precision obtained between laboratories. Objective is to verify that the method will provide the same results in different laboratories. Reproducibility means the precision of the procedure when it is carried out under different conditions-usually in different laboratories-on separate, putatively identical samples taken from the same homogenous batch of material. Comparisons of results obtained by different analysts, by the use of different equipments, or by carrying out the analysis at different times can also provide valuable information.

REPEATABILITY

Repeatability involves analysis of replicates by the analyst using the same equipment and method^[21] and conducting the precision study over short period of time while reproducibility involves precision study at different occasions, different laboratories and different batch of reagent, different analysts and different equipments.

Determination of repeatability:

It is normally expected that at least six replicates be carried out and a table showing each individual result provided from which the mean, standard deviation and co-efficient of variation should be calculated for set of n value. The RSD values are important for showing degree of variation expected when the analytical procedure is repeated several time in a standard situation. (RSD below 1% for built drugs, RSD below 2% for assays in finished product). The ICH documents recommend that repeatability should be assessed using a minimum of nine determinations covering the specified range for the procedure (i.e. three concentrations and three replicates of each concentration or using a minimum of six

determinations at 100% of the test concentration).

ACCURACY

The accuracy of an analytical method^[27] may be defined as the closeness of the test results obtained by the method to the true value. It is the measure of the exactness of the analytical method developed. The accuracy of an analytical method may be determined by any of the following ways:

- Analysing a sample of known concentration and comparing the measured value to the 'true' value. However, a well characterized sample (e.g., reference standard) must be used.
- Spiked – placebo (product matrix) recovery method. In this method, a known amount of pure active constituent is added to formulation blank [sample that contains all other ingredients except the active(s)], the resulting mixture is assayed, and the results obtained are compared with the expected result.
- Standard addition method. In this method, a sample is assayed, a known amount of pure active constituent is added, and the sample is again assayed. The difference between the results of the two assays is compared with the expected answer.

In both methods (spiked – placebo recovery and standard addition method), recovery is defined as the ratio of the observed result to the expected result expressed as a percentage.

The accuracy of a method may vary across the range of possible assay values and therefore must be determined at several different fortification levels. The accuracy should cover at least 3 Concentrations (80, 100 and 120%) in the expected range.

STABILITY

stability of the drug substance or drug product after preparation according to the test method should be evaluated according to the test method. Most laboratories utilize auto samplers

with overnight runs and the sample will be in solution for hours in the laboratory environment before the test procedure is completed. This is of concern especially for drugs that can undergo degradation by hydrolysis, photolysis or adhesion to glassware.^[25]

RECOVERY

Recovery is expressed as the amount weight of the compound of interest analyzed as a percentage to the theoretical amount present in the medium. Full recovery^[12] should be obtained for the compound(s) of interest. During the sample preparation procedure, the compound of interest is recovered from excipients in the formulation matrix ranging from a simple aqueous solution to complex cream formulation, and from potential adhesion to container/closure components, e.g., glass vial, metered valve. In general, a simpler sample preparation procedure will result in a lower variation of recovery.

BIAS/TRUENESS

Bias refers to the overall magnitude of known systematic (determinate) errors associated with the use of an analytical method. The presence of systematic errors can only be determined by comparison of the average of many results with a reliable, accepted reference value. Method bias may be estimated by measuring materials whose composition is reasonably well known, such as reference materials, by comparing results to those from at least one alternate method or procedure, or by analyzing spiked materials.^[22]

The “trueness” of a measurement method is of interest when it is possible to conceive of a true

value for the property being measured. Although, for some measurement methods, the true value cannot be known exactly, it may be possible to have an accepted reference value for the property being measured; for example, if suitable reference materials are available, or if the accepted reference value can be established by reference to another measurement method or by preparation of a known sample. The trueness^[22] of the measurement method can be investigated by comparing the accepted reference value with the level of the results given by the measurement method. Trueness is normally expressed in terms of bias. Bias can arise, for example, in chemical analysis if the measurement method fails to extract all of an element, or if the presence of one element interferes with the determination of another.

LINEARITY AND CALIBRATION CURVE

The linearity of an analytical method is its ability to elicit test results that are (directly or by means of well-defined mathematical transformations) proportional to the concentration of analytes in samples within a given range. Linearity is determined by a series of three to six injections of five or more standards whose concentrations span 80-120 percent of the expected concentration range. The response should be (directly or by means of a well-defined mathematical calculation) proportional to the concentrations of the analytes. A linear regression equation applied to the results should have an intercept not significantly different from zero. If a significant nonzero intercept is obtained, it should be demonstrated that there is no effect on the accuracy of the method.^[28]

The linearity is affected by the various factors like stray light, concentration of sample, wavelength of sample, ultraviolet lamp frequency. [figure 1] represent linearity of sample in case of concentration vs absorbance.

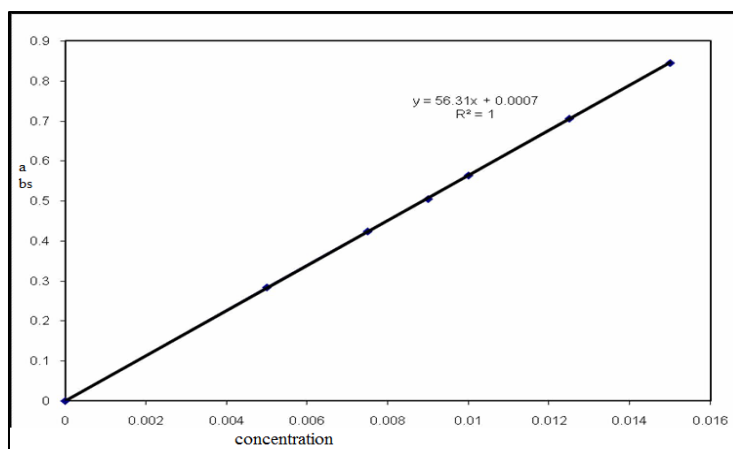


Figure 1 : Linearity of Concentration Vs Absorbance^[30]

Figure 2 represent the effect of stray light on the true absorbance of the sample depend on the percentage of stray light interfere with the absorbance of the sample.

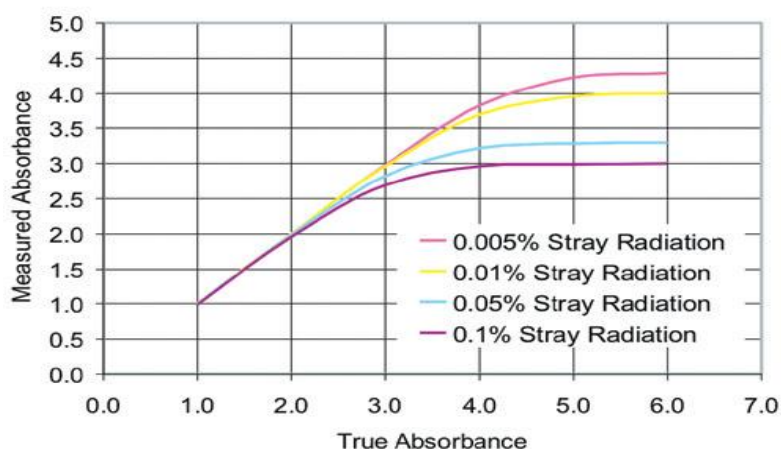


Figure 2. Effect of instrumental stray light on absorbance linearity.^[31]

RANGE

The range of an analytical method is the interval between the upper and lower levels (including these levels) that have been demonstrated to be determined with precision, accuracy and linearity using the method as written. The range is normally expressed in the same units as the test results (e.g. percentage, parts per million) obtained by the analytical method.

The range of the method is validated by verifying that the analytical method provides acceptable precision, accuracy and linearity

when applied to samples containing analyte at the extremes of the range as well as within the range.^[8]

QUANTITATION LIMITS

The term “quantitation range”^[17] is used to describe the span of analyte levels, as contained in a sample matrix, for which method performance has been tested, and data quality is deemed acceptable for its intended use. A quantitation range must include either a regulatory or other type of action level. It is the

minimum injected amount that gives precise measurements, in chromatography typically requiring peak heights 10 to 20 times higher than baseline noise.

DETECTION LIMIT

The term “detection limit” is used to describe the lowest analyte level that can be confidently identified. There are many specific definitions for this term, and it is used to describe the detection capabilities of detectors, instruments, and analytical methods. The term “detection limit” must be defined, and a description of how it was evaluated during method validation must be provided. Limits derived from mathematical definitions or statistical models must be verified by testing materials containing analyte at the claimed detection level. It is the lowest concentration of analyte in a sample that can be detected but not necessarily quantified. In chromatography the detection limit is the injected amount that results in a peak with a height at least twice or three times as high as the baseline noise level.^[29]

ROBUSTNESS

The robustness of an analytical method is a measure of its capacity to remain unaffected by small but deliberate variation in method parameters and provides an indication of its reliability during normal usage. The robustness of a method is evaluated by varying method parameters such as percent organic solvent, pH, ionic strength, temperature and determine the effect (if any) on the results of the method. The evaluation of robustness should be considered during the development phase and depends on the type of procedure under study.

If measurements are susceptible to variations in analytical conditions, the analytical conditions should be suitably controlled or a precautionary statement should be included in the procedure. One consequence of the evaluation of robustness should be that a series of system

suitability parameters (e.g., resolution test) is established to ensure that the validity of the analytical procedure is maintained whenever used. Examples of typical variations are stability of analytical solutions and extraction time^[28]

RUGGEDNESS

The ruggedness of an analytical method is the degree of reproducibility of test results obtained by the analysis of the same samples under a variety of normal test conditions such as different laboratories, different analysts, using operational and environmental conditions that may differ but are still within the specified parameters of the assay. The testing of ruggedness is normally suggested when the method is to be used in more than one laboratory. Ruggedness is normally expressed as the lack of the influence on the test results of operational and environmental variables of the analytical method.

For the determination of ruggedness^[25], the degree of reproducibility of test result is determined as function of the assay variable. This reproducibility may be compared to the precision of the assay under normal condition to obtain a measure of the ruggedness of the analytical method.

REVALIDATION

A revalidation is necessary whenever a method^[21] is changed and the new parameter is outside the operating range. Operating ranges should be clearly defined for each method based on experience with similar methods, or they should be investigated during method developments. These ranges should be verified during method validation in robustness studies and should be part of the method characteristics. Availability of such operating ranges makes it easier to decide when a method should be revalidated. If, for example, the operating range of the column temperature has been specified to be between 35 and 40°C, if, for whatever reason,

the new operating parameter has been selected as 42°C, and then the method should be revalidated. Revalidation is also required if the sample matrix changes and if the instrument type changes.

VALIDATION DOCUMENTATION

A written validation protocol should be established that specifies how validation of a particular process will be conducted. The protocol should be reviewed and approved by the quality unit(s) and other designated units. The validation protocol should specify critical process steps and acceptance criteria as well as the type of validation to be conducted (e.g. retrospective, prospective, concurrent) and the number of process runs.

A validation report that cross-references the validation protocol should be prepared, summarizing the results obtained, commenting on any deviations observed, and drawing the appropriate conclusions, including

recommending changes to correct deficiencies. Any variations from the validation protocol should be documented with appropriate justification.^[26,28]

CONCLUSION

Validation is the first requirement in pharmaceutical company. In addition timely and appropriate validation improves quality assurance, reduces cost in pharmaceuticals. Analytical methods development plays important roles in the discovery, development and manufacture of pharmaceuticals. Methods should be validated to include consideration of characteristics included within the ICH guidelines on validation of analytical methods. The degree of analytical validation performed should reflect the purpose of the analysis. So in this review that gives few principles, steps, policy of validation and method validation parameter.

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