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A Review: On Analytical Method Validation

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Abstract:

Development and validation of analytical method play an essential role in the discovery, development and manufacturing of pharmaceutical Validation is one of the key elements to fulfil the requirement of current good manufacturing specifications (CGMP) and good laboratory specifications (GLP). An effective analytical method development and its validation can provide significant improvements in precision and a reduction in bias errors. It can further help to avoid costly and time consuming exercises.

Keyword: validation, cGMP, GLP, analytical method.

Introduction:

Quantification and qualification are examined in the analysis of chemical. The different mixtures of chemical compound or samples are firstly separated. These are then identified which is called qualitative process. (1)

There are two types of analysis, one is qualitative analysis and another one is quantitative analysis. In qualitative analysis, there is identification of components or analyte of mixture or sample is carried out. In quantitative analysis, there is determination of amount of components or analyte of mixture or sample is carried out. (2)

The method development provides the following requirements to the analyst so as to enable him to estimate the drug.

- The required data for a given analytical problem.
- The required sensitivity.
- The required accuracy.
- The required range of analysis.
- The required precision. (3)

Analytical method development:

Method validation, required by regulatory agencies at certain stages of the drug approval process, is defined as the "process of demonstrating that analytical procedures are suitable for their intended use." Method transfer is the formal process of assessing the suitability of methods in another laboratory. Each of these processes contributes to continual improvement of the methods and results in more efficient drug development. Analytic methods are intended to establish the identity, purity, physical characteristics and potency of the drugs that we use.

According to the International Conference on Harmonization (ICH), the most common types of analytic procedures are:

(i) Identification tests.

(ii) Quantitative tests of the active moiety in samples of API or drug product or other selected component(s) in the drug product.

(iii) Quantitative tests for impurities' content.

(iv) Limits tests for the control of impurities. [4]

A well-developed method helps in drug testing against specification during manufacturing and quality release operations; similarly, it promotes the studies regarding characters of chemical, safety examination and analysis of activities of the medicine. The development of analytical process is utilized for assisting the procedure of synthesis of drug. The formulation studies assist to screen the drug with potential activities. The finished pharmaceutical drug should be stable from the phase of raw material to final formulation. So stability studies should be regularly monitored. The identification, purification, physical specification and potential activities of the medicine are set up by these methods. [1]

Table 1. [4]

Table 1

Parameter	Definition
Accuracy	an assessment of the difference between the measured value and the real value
Precision	a measure of the agreement for multiple measurements on the same sample
Specificity	the ability to assess the analyte when in the presence of other components
Limits of detection and quantitation	the lowest amounts of analyte that can be detected / determined accurately, respectively
Linearity and range	the proportionality of the measurement to the concentration of the analyte within a specified range
Robustness	a check of the effect of deliberate small changes to the method on the results

Guidelines:

ICH, FDA, AOAC, USP, ISO 9000, and ISO 17025 It includes following:

Q1A (R2): Stability Testing of New Drug Substances and Products (Second Revision).

Q1B: Photo stability testing of New Drug Substances and Products.

Q1C: Stability Testing for New Dosage Forms.

Q1D: Bracketing and Matrixing Designs for Stability Testing of Drug Substances and Drug Products.

Q1E: Evaluation of Stability Data.

Q1F: Stability Data Package for Registration Applications in Climatic Zones III and IV.

Q2A: Text on Validation of Analytical Procedures.

Q2B: Validation of Analytical Procedures —Methodology.

Q3A(R): Impurities in New Drug Substances (Revised Guideline).

Q3B(R): Impurities in New Drug Products (Revised Guideline).

Q3C: Impurities —Guideline for Residual Solvents.

Q9: Quality Risk Management. [5]

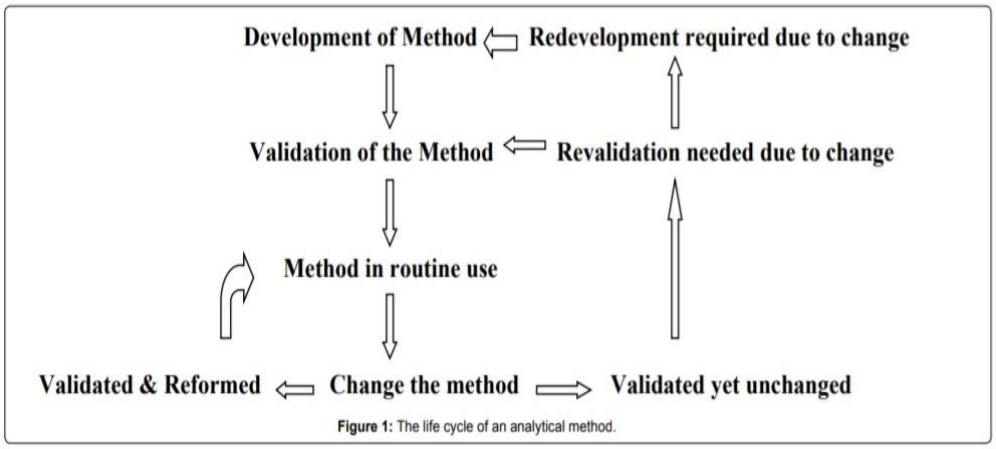

Figure.1 1[6]

Types of Analytical Procedures to be Validated

There are 3 types of analytical procedure:

· Regulatory analytical procedures.

· Alternative analytical procedures.

· Stability indicating assay.

Regulatory analysis procedures are those procedures which are official in compendia of standards recognized by legislation of country. Alternative analytical procedures are alternative procedures for regulatory analytical procedures. Generally, pharmacopoeia state alternative method can be used provided their performance is equivalent or more then pharmacopoeia analytical procedure Stability indicating assay is a validated quantitative method that can detect changes with time in particular properties of drug substance and drug product. It accurately measure the active ingredient without interference from degradation products, process impurities excipients or other potential impurities. [7]

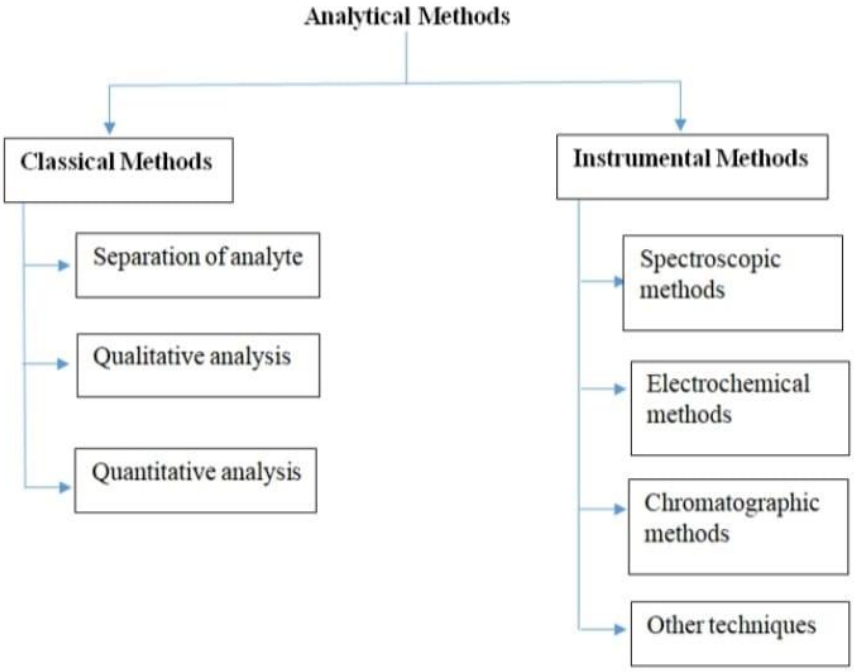

Figure 2. [2]

Steps in Method Validation:

1. Develop a validation protocol or operating procedure for the Validation.
2. Define the application, purpose and scope of the Method.
3. Define the performance parameters and acceptance criteria.
4. Define validation experiments.
5. Verify relevant performance characteristics of Equipment.
6. Qualify materials, e.g. standards and reagents.
7. Perform pre-validation experiments.
8. Adjust method parameters or/and acceptance criteria if necessary.
9. Perform full internal (and external) validation Experiments.
10. Develop SOPs for executing the method in the Routine.
11. Define criteria for revalidation.
12. Define type and frequency of system suitability tests and/or analytical quality control (AQC) checks for the routine. [8]

Importance of validation:

• Assured high quality.

• Time boundation.

• Optimization of the method the validation Minimum batch product failure, enhanced efficiency, manufacturing, and productivity.

• Quality cost decreased.

• Rejection decreased.

• Yield increases.

• Fewer complaints about process related issues.

• Fast and realistic start-up of new equipment's.

• Increased worker consciousness of the process. [9]

Application of analytical method development:

• Assays of all samples of an analyte in a biological matrix should be completed within the time period for which stability data are available. In general, biological samples are analyzed with a single determination without duplicate or replicate analysis if the assay method has acceptable variability as defined by validation data. The following recommendations should be noted in applying a bio-analytical method to routine drug analysis.

• Response Function: Typically, the same curve fitting, weighing, and goodness, of fit determined during restudy validation should be used for the standard curve within the study. Response function is determined by appropriate statistical tests based on actual standard points during each run in the validation. Changes in the response function relationship between pre-study validation and routine run validation indicate potential problems.

• The QC samples should be used to accept or reject the run. These QC samples are matrix spiked with analyte.

• System Suitability.

• Based on the analyte and technique, a specific SOP (or sample) should be identified to ensure optimum operation of the system used. [10]

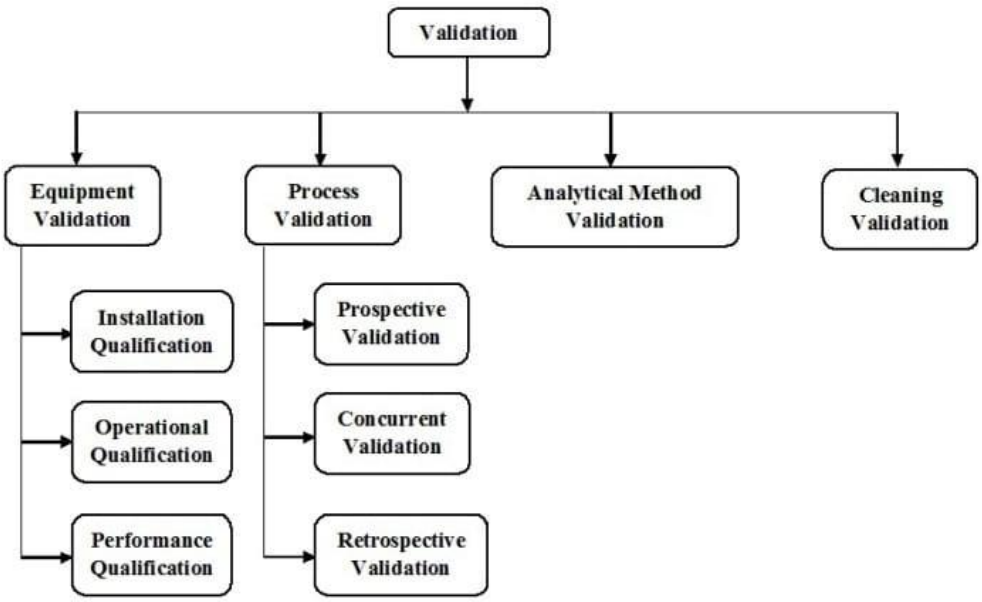

Figure 3. [9]

Types of 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.

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.

ANALYTICAL METHOD VALIDATION: Validation of an analytical approach is established through laboratory research, that the execution attributes of the procedure meet the requirements for the proposed scientific application. Validation is required for any new or altered procedure to verify that it is fit for giving predictable and dependable outcomes, once used by various administrators by usage of comparable instrumentation inside the similar or absolutely distinct laboratories. [9]

Conclusion:

The main purpose of development of analytical methods are for identification, purification and finally to quantification any required drug etc., The main activities involved in the analytical development of a method are separation and characterization of impurities as well as degraded products, analytical investigations, studies for identification and finally setting up of parameters optimization to specific requirements. Therefore, the salient points enumerated in the above review article are immense use to an analyst while estimating the pharmaceutical formulations as well as bulk drugs.

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