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Review Article

Brief Concept of Validation & Calibration

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ABSTRACT

Validation is an important part of Analytical as well as Bio-Analytical Method. The procedures involved in checking data or programs for correctness, compliance with standards and conformance with the requirement specifications. It is establishing documented evidence, which provides high degree assurance that a specific process will consistently produce a product meeting its predetermined specification and quality characteristics. Calibration is totally differ from Validation But it is an integral part of validation.

Keywords: FDA Gudelines, EU Guidelines, Validation, Calibration

INTRODUCTION[1-10]:

Analytical methods described in Collaborative International Pesticide Analytical Council (CIPAC) handbooks and Association of Official Analytical Chemists (AOAC International) Manual for agricultural active constituents and agricultural chemical products, and in British Pharmacopoeia (BP), British Pharmacopoeia (Veterinary) [BP (Vet)], European Pharmacopoeia (Ph Eur) and United States Pharmacopoeia (USP) for veterinary active constituents and veterinary chemical products are legally recognised as the regulatory methods, and these procedures (if one is available) are used by the APVMA for determining compliance with the Agricultural and Veterinary Chemicals Code Act.

Note: Analytical methods described in CIPAC handbooks and AOAC International Manual, and in recognized pharmacopoeias [BP, BP (Vet), Ph Eur and USP] for a particular active constituent or formulation are regarded as validated and do not require revalidation. However, the suitability of these methods must be verified under actual conditions of use i.e., the selectivity and accuracy of the method should be demonstrated for the published method when applied to the relevant sample matrix and laboratory conditions.

FDA-guidelines:

"Validation is establishing documented evidence which provides a high degree of assurance that a specific process will consistently produce a product meeting its pre-determined specifications and quality attributes."

EU-guidelines

"Action of proving, in accordance with GMP-principles that any procedure, process, equipment, material, activity or system actually leads to the expected results."

But validation itself does not improve process but assures that the process has been properly developed and is under control.

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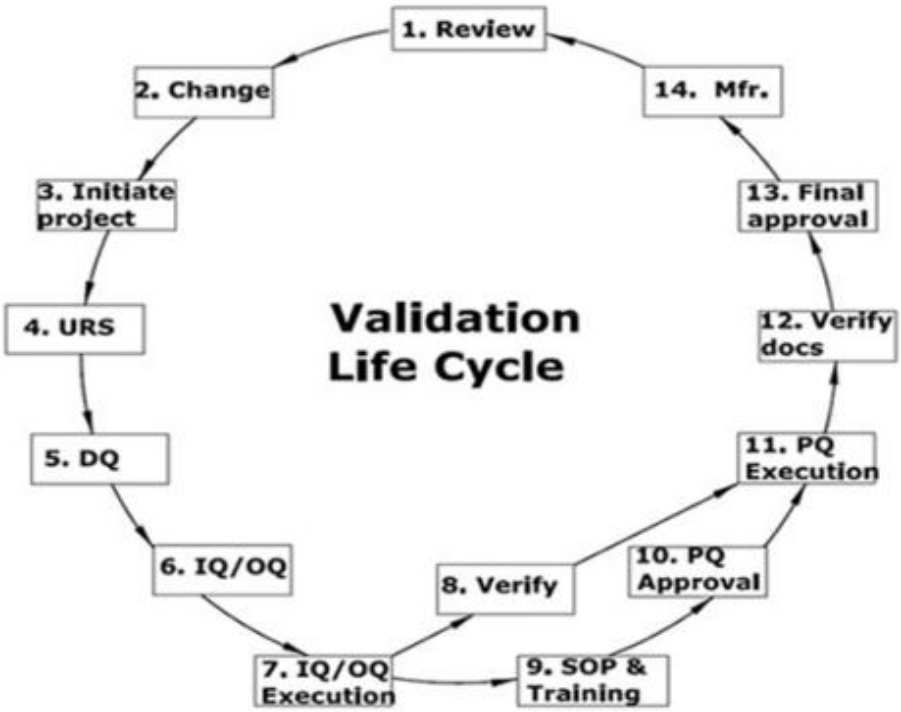

FUNDAMENTAL DESCRIPTION [1-20]:

· Need for pre-determined operational & performance user requirements (URS) of process or system

· Provide evidence of meeting pre-defined operational & performance requirements

· Provide evidence on consistency of meeting these requirements.

More specific [6-8]:

· "Methods validation is the process of

· demonstrating that analytical procedures are

· suitable for their intended use" (ICH Topic Q2B, March 1995)

Why validation [7-12]?

1. GMP-legislation
2. Good economics
3. Good science practices

VALIDATION GUIDELINES

1. ICH Q2A

Text on validation of analytical procedures: Definitions and terminology (March 1995)

2. ICH Q2B

Validation of analytical procedures: Methodology (June 1997)

3. FDA

(Draft) Guidance for Industry: Analytical procedures and methods validation

4. Pharmacopoeias

USP and European Pharmacopoeia.

WHAT METHODS TO BE VALIDATED?

Defined for:

· Identification

· Quantitative tests for content of impurities

· limit tests for control of impurities

· Quantitative tests for active moiety in drug substances and drug products

Referred to:

· Dissolution testing

· Particle size determination (drug substance).

When should methods be validated [12-28]?

Development and tox:

No validation required

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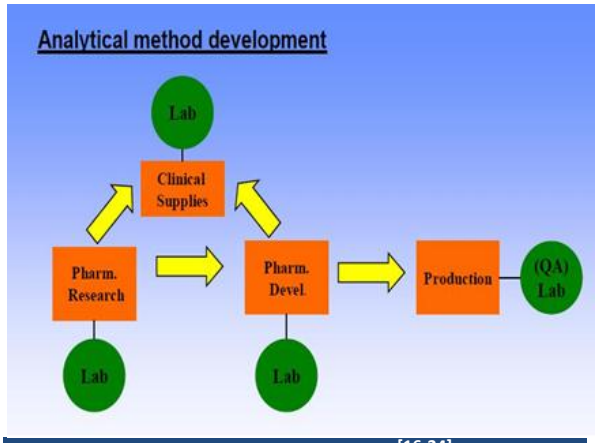
Phase 1
No validation data required.

Phase 2
For both drug substance and drug product supporting validation data on analytical methods should be available on request.

Phase 3 (Pivotal studies):
Appropriate validation information should be provided. Assay validation should cover accuracy, precision, specificity (including stress testing), quantitation & detection limits, linearity and range (where appropriate) Degradation should be identified, qualified and quantified.

Figure :-NDA submission
Full validation reports of relevant methods must be included



DIFFERENT VALIDATION TERMS [16-24]

1. Prospective validation: Validation conducted prior to the distribution of either a new product or product made under a revised manufacturing process. **Or** evidence that system does what it purports to do based upon plan **(e.g process validation plan of first three commercial batches.)**

2. Retrospective validation: Validation of a process for a product already in distribution based upon accumulated production, testing and control data. **or** evidence that system does what it purports to do based upon review and analysis of existing information **(e.g stability studies)**

3. Concurrent validation: In process monitoring of critical processing steps and end product testing of current production is involved in concurrent validation .**or** evidence that system does what it purports to do based upon information generated during implementation of the system **(e.g equipment validation)**

4. Process validation:- It is establishing documented evidence, which provides high degree assurance that a specific process (such as manufacturing of pharmaceutical dosage forms) will consistently produce a product meeting its predetermined specification and quality characteristics(at optimum cost).

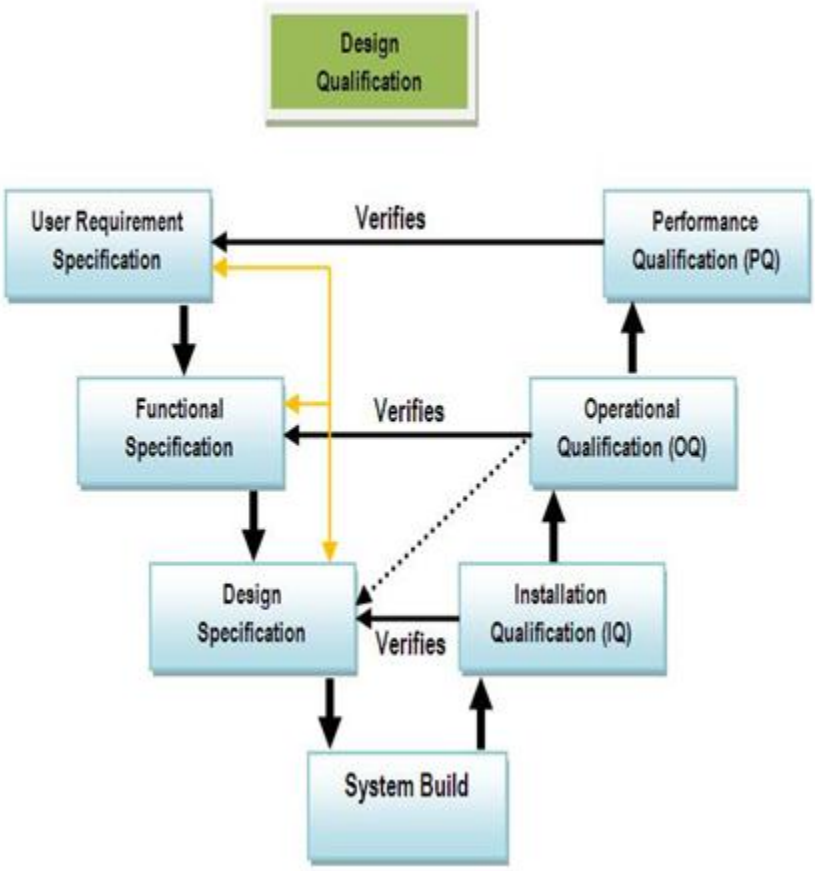
5.Design Qualification(DQ) :- Documented verification that all key aspects of the equipment and ancillary system are designed to perform as per requirements.

6.Installation Qualification(IQ):- Documented verification that all key aspects of the equipment and ancillary system installation adhere to approved design intentions & that recommended of the manufacturer are suitably considered.

7.Operational Qualification(OQ): Documented verification that all key aspects of the equipment and ancillary system perform as intended operating ranges.
An operational qualification documents specific dynamics attributes of a facility or equipment to provide that it operates as expected throughout its operation range.

8.Performance Qualification(PQ): Documented evidence that the process performs effectively & reproductively to produce a product meeting it's predetermined specifications and quality attributes.

Figure


Design Qualification
User Requirement Specification
Verifies
Performance Qualification (PQ)
Functional Specification
Verifies
Operational Qualification (OQ)
Design Specification
Verifies
Installation Qualification (IQ)
System Build

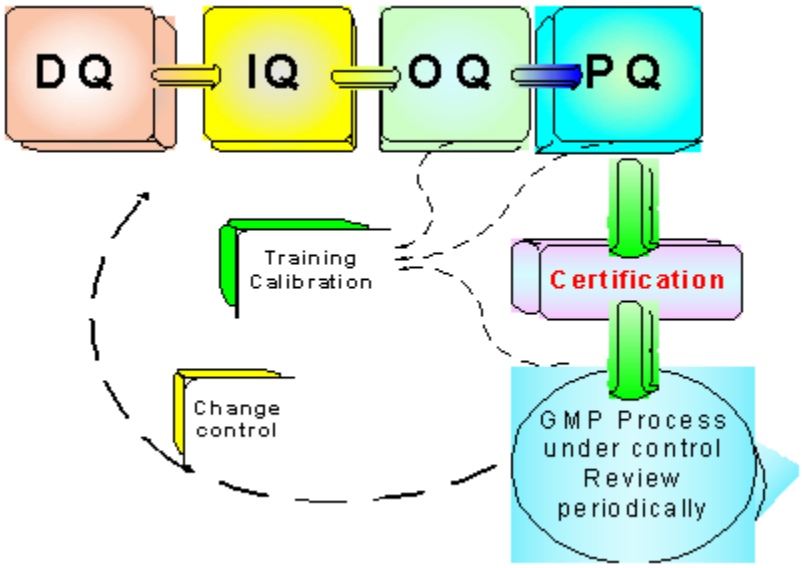

DQ
IQ
OQ
PQ
Training Calibration
Certification
Change control
GMP Process under control Review periodically

Table:-Difference between calibration and validation [32-39]

Calibration	Validation
It is **measurement of critical value** of equipments function falling with in the optimum range of its working	Validation is establishing **documented evidence** which provides a **high degree of assurance** that a specific process will consistently produce a product meeting its **pre-determined specifications and quality attributes**
It is applicable mainly for measuring and test equipment	It is applicable mainly for procedure, process or method.
Principal is comparison of it's critical value with known national/international standard having fixed value.	Principal is comparison of it's derived value with established range.
Example of equipment requiring calibration are Q.C instruments, pressure, temp./vacuum gauges, weighing balance etc.	Example of process/procedure /method requiring validation are batch manufacturing process. Aseptic fill procedure, cleaning procedure, Analytical method.

TYPES OF VALIDATION

· Equipment validation
· Method validation
· Process validation

Equipment validation:

Why?

- To established documented evidence, which provides high degree assurance that a specific process will consistently produce a product meeting its predetermined specification and quality attributes.
- It is regulatory requirement:
- For the cost reduction of the product.

When?

- Installation of the new equipment.
- Change of the location of the equipment.
- Modification of the instrument.

Design Qualification:-

To verify and document that,

- The instrument and its spares to be delivered should be as per the customer's requirements in the purchase order.
- This should be done by the manufacturer/supplier at his end before dispatching the instrument.

Installation Qualification:

To verify and document that,

- The instrument and its spares to be delivered should be as per the customer's requirements in the purchase order.
- The facilities (Physical, Electrical and Environmental) provided for the installation of the instrument should meet its specification.

Operational Qualification:

To verify and document that,

- The newly installed instrument operates as per the manufacture's as well as customers required specification.
- All the functions available with the instrument should be checked during operational qualification.

e.g operational qualification for HPLC like pump performance, injector performance, detector performance etc…

Method validation:

Why?

· Method validation provides a high level of assurance that such method should consistently yield results that are accurate, reproducible, and they are within previously established specifications.

· Mandatory requirements for product registration and approval for marketing by the drug regulatory authorities of various countries.

· To minimize product quality complaints and product recall and quick release of the product batch.

· Validation provides a high degree of confidence that same level of quality is built into each unit of finished product from batch to batch.

When?

· New method development.

· Established method revised to incorporate improvements.

· Established method used in a different laboratory, analysis or instrumentation.

· To demonstrate the equivalence between new and established method.

Objectives:

The objectives of this exercise is to consider appropriate validation characteristics to provide a sound overall knowledge of the capabilities of the analytical method.

Scope:

The scope covers analytical performance parameters like

Enlist Validation parameter as per ICH guidelines [32-39]

- Accuracy
- Precision
  - Repeatability
  - Intermediate
  - Reproducibility
- LOD (Limit Of detection)
- LOQ (limit Of Quantitation)
- Linearity
- Range
- Robustness
- Specificity
- SST (System Suitability test)
- Ruggedness
- Transferability
- Sensitivity

Table:

Glossary	Descriptions
Accuracy Known as "Truness"	* "The closeness of agreement between real value and measured value" * Accuracy should be checked across the range of spiking 5 different concentration of the active ingredient in placebo(dummy medication) preparation. * Drug recovery should be calculated. * %RSD value should not be more than 2.0 % and % recovery of individual should be between 98-102 % for the active drug.
Precision Known as "Degree of Scatter" Or "series of measurement"	* "the closness of agreement between a series of measurements." * Means measurement of reproducibility of whole analytical method. * System precision will be checked by 6 replicate injections of the same test concentration. * Method precision will be checked by preparing 5 assay samples separately from the homogenuous sample % RSD should not be more than 2.0 %
Precision repeatability Known as Intra-assay	* Method: 9 determinations covering the specified range or 6 determinations at 100 % of the

precision	test concentration.
Intermediate precision	* "express within laboratory variation" * Method: Depends on circumstances of usage of the methods. Should include variations in days ,analyst, columns.
Reproducibility	* "precision between laboratories." * Method: Dependent on usage of method Should include inter laboratory study.
LOD (Limit Of Detection)	* "lowest amount of analyte that can be detected ". Determination of LODs (limits of detect ion) LOD's may also be calculated based on the standard deviation of the response (SD) and the slope of the calibration curve (S) at levels approximating the LOD according to the formula: LOD = 3.3(SD/S). The standard deviation of the response can be determined based on the standard deviation of y-intercepts of regression lines.
LOQ (Limit Of Quantization)	* "lowest amount of analyte that can be detected but Quantity is necessary." * The value derived shall be validated by injecting same concentration of solution and determining the signal to noise (S/N) ration & that should not be less than 3 in case of LOD, But in case of LOQ S/N ratio should not be less than 10. * The calculation method is again based on the standard deviation of the response (SD) and the slope of the calibration curve (S) according to the formula: LOQ = 10(SD/S). Again, the standard deviation of the response can be determ ined based on the standard deviation of y-intercepts of regression lines.
SNR(signal to Noise Ratio)	* SNR = Mean (μ)/standard deviation (σ) Means .reciprocal of the coefficient of variation. i.e the ratio of meant to standard deviation of a signal or measurement. * It is a power ratio between a signal (meaningful information) & the background noise (unwanted signal) * SNR= P_{signal}/P_{noise}
Linearity	* "proportionality of measured value of concentration." * A linear relationship should be established by dilution of stock solution. * A minimum of 5 concentration should be tested & correlation coefficient should be checked & that should not be less than 0.99
Range	* "Concentration interval where method is precise , accurate and linear' * Interval between the upper and lower conc. Of analyte in the sample.
Robustness	* "reproducibility under normal but variable laboratory conditions.' * % RSD of assay results by small but deliberate variations should not be more than 2.0 %
Specificity	* "Ability to measure desired analyte in a complex mixture." * "it 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." * Placebo interference will checked by injection of assay preparation of placebo, [means dummy medications, No active ingredient but therapeutic effect,].
Ruggedness	* "ruggedness should be established by 2 different system, columns and analyst. * Repeatability will be checked by minimum of 5 different concentration prepared separately from homogenous sample.

	* % RSD of assay results of analyst-1 and analyst -2 should not be more than 2%
SST Known as system suitability test (SST).	* Check the theoretical plates, tailing factor , resolution and % RSD etc... * This results should be within specification limits.
Transferability	* It is the ability of the method to be used correctly by others without seeking additional information
Sensitivity	* "smallest quantity that can be detected-accurately measured"

REVALIDATION [20-39]

Analytical methods require validation whenever the conditions for which the methods have been developed change. Revalidation of the analytical method is required in the following circumstances:

• An existing method is modified to meet special requirements;

• Changes in the route of synthesis of the active constituent which may lead to different impurity profile; and

• Changes to the formulation composition of an agricultural and veterinary chemical product.

Revalidation should be performed to ensure that the analytical method maintains its characteristics. The degree of revalidation depends on the nature of the change i.e. a new dosage strength in a product may require validation of the method in terms of recovery and linearity at the new dosage strength; a new formulation would require revalidation in terms of selectivity, recovery, etc.

CONCEPT OF CALIBRATION [20-39]:

Calibration:

What is calibration?

In the simplest term calibration means to known how accurate testing and measuring instruments employed in the quality measurement system are.

This is achieved by comparing these instruments against more precise and accurate instrument called master instruments or reference standard.

Why calibration?

Calibration brings out the nature and magnitude of an error (if any) of testing measuring instruments.

This error is the deviation from the reference standard and it is the hidden deficiency of the quality measuring system of an organization.

Advantages of calibration:

The knowledge of the nature and extent of errors of the testing and measuring the instruments employed in quality measuring system, will help an organization in the following ways:

· One can take the error of an instrument into account while using it and hence correct measurements are recorded and reported .this will help an organization to set its process and quality control system correctly.

· Wherever possible, one can adjust or repair the instrument to minimize the error to the best extent.

· Any dispute arising with a customer due to instrument error can be resolved.

Where to get the instruments calibrated?

One should get all the testing and measuring instruments calibrated at a reputed institute or organization like RRSL, NC QC, atira etc. which has a set of precise reference standard, instruments and facilities backed by well – qualified and experienced personnel.

One can provided good most accurate and reliable calibration services with due traceability. Some of them are built to provide following facilities.

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- Identification of instruments for calibration
- At sit calibration
- Single window calibration service
- Calibration of special instruments
- After calibration service

If you wants to calibrate your any instruments at out side party PI. providing the following details.

- Name and type of the instruments
- Make, model and the year of manufacturing.
- Operational range with least count and accuracy.
- Relevant standards or calibration procedure.(in case of specialized critical instruments)
- General information about your organization.

CONCLUSION

Validation is an important part of Analytical as well as Bio-Analytical Method. Procedures involved in checking data or programs for correctness, compliance with standards and conformance with the requirement specifications, During the process the knowledge of process increases, Assures the repeatability of the process, Assures the fluency of production, Assures that the product is continuously according to the marketing authorization, Decreases the risk of the manufacturing problems, Decreases the expenses caused by the failures in production, Decreases the risks of failing in GMP, Decreases the expenses of the everyday production even though the validation itself will create expenses

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