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CALIBRATION AND VALIDATION AS PER ICH AND USFDA GUIDELINES

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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.
KEY WORDS: *ICH Guidelines, FDA Guidelines, validation, calibration.*

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INTRODUCTION:

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.

CALIBRATION:

"Calibration of an instrument is the process of determining its accuracy. The process involves obtaining a reading from the instrument and measuring its variation from the reading obtained from a standard instrument."

Calibration of an instrument also involves adjusting its precision and accuracy so that its readings come in accordance with the established standard.

This is important for justifying the processes of Qualification and Validation.

• The instrument or equipment with the known accuracy is known as standards. All the other instruments are measured against this standard.

It is important to know that the standards vary from one country to the other depending upon the type of industry.

• Calibration Achieves 2 Main Objectives :

a) It checks the accuracy of an instrument.

b) It determines the traceability of the measurement.

Calibration is basically of three types:

1. Electro-technical Calibration: It consist calibration of electronic devices like resister, capacitor etc.
2. Non Electrical Calibration: It consist calibration of mass, pressure etc.
3. On Site Calibration: It consist calibration of any other type of quantity which contain both quantities.

Scope/Purpose of Calibration

Calibration is primarily done to achieve 5 main purposes which are:

✓To make sure that the readings of equipment or instruments are consistent with other measurements and display the correct readings every single time

✓To determine the accuracy, precision, reliability and deviation of the measurements produced by all the instruments

✓To establish the reliability of the instrument being used and whether it can be trusted to deliver repeatable results each time

To map the 'drift' as documented. Instruments have a tendency to produce inaccurate measurements over a period of time, following repeated use.

✓Ensuring that the industry standards, quality assurance benchmarks such as current good manufacturing practice (cGMP) and government regulations are adhered to.

What Is Instrument Calibration?

Instrument calibration can be defined as the process of comparing the measurements made by the instrument to be calibrated against a known measurement of either standards or an instrument known to be making measurements that exceed the acceptable limits of accuracy and precision. Usually, calibration labs prefer a standard with 10 times the accuracy; however, most regulating organizations and authorities also accept a 3:1 accuracy ratio.

Frequency Of Instrument Calibration

How often you conduct instrument calibration mainly depends upon its tendency to drift from the true measurement and how it impacts the quality of the end product. Examine each instrument being used and study its behaviour. Based on this information, you can design a calibration schedule for each instrument. The interval between calibrations can vary as:

- Weekly
- Monthly or bi-monthly
- Quarterly, semi-annually or annually

After every heavy usage of the instrument When Should The Measuring Instruments Be Calibrated?

The frequency of calibrating the measuring instruments depends on a number of different factors. The following is a guide outlining when instruments need to be calibrated as a part of GMP:

As soon as you bring in a new instrument, you should calibrate it before you test it out.

Before and after you take critical measurements

After any instance of electrical or mechanical shock or a similar event that includes a fall, bump, etc.

VALIDATION:

Validation is an integral part of quality assurance; 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 process 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.

Validation in itself does not improve processes but confirms that the processes have been properly developed and are under control.

"Establish documented evidence which provides a high degree of assurance that a specific process will consistently produce a product meeting its predetermined specifications and quality attributes."

Scope of validation: Validation requires an appropriate and sufficient infrastructure including: -- organization, documentation, personnel and finances Involvement of management and quality assurance personnel with appropriate qualifications and experience.

- Extensive preparation and planning before validation is performed Validation should be performed: for new premises, equipment, utilities and systems, and processes and procedures; at periodic intervals; and when major changes have been made.Validation in accordance with written protocols.
- Validation over a period of time, e.g. at least three consecutive batches (full production scale) to demonstrate consistency. (Worst case situations should be considered.)

  Significant changes (facilities, equipment, processes) - should be validated
- Risk assessment approach used to determine the scope and extent of validation needed.

Importance of Validation

1. Assurance of quality
2. Time bound
3. Process optimization
4. Reduction of quality cost.
5. Minimal batch failures, improved efficiently and productivity.
6. Reduction in rejections.
7. Increased output.
8. Fewer complaints about process related failures.
9. Reduced testing in process and in finished goods.
10. More rapid and reliable start-up of new equipment.
11. Easier maintenance of equipment.
12. Improved employee awareness of processes.
13. More rapid automation.
14. Government regulation (Compliance with validation requirements is necessary for obtaining approval to manufacture and to introduce new products.

TYPES OF VALIDATION:

Prospective validation

- It is defined as the established documented evidence that a system does what it purports to do based on a pre-planned protocol.
- This validation usually carried out prior to distribution either of a new product or a product made under a revised manufacturing process Performed on at least three successive production-size (Consecutive batches).
- The objective of the prospective validation is to prove or demonstrate that the process will work in accordance with validation protocol prepared for the pilot production trials. Prospective validation should normally be completed prior to the distribution and sale of the medicinal product.
- In Prospective Validation, the validation protocol is executed before the process is put into commercial use.

Concurrent validation

- It is a process where current production batches are used to monitor processing parameters. • Concurrent Validation means establishing documented evidence a process does what it is supposed to based on data generated during actual implementation of the process.
- It is important in these cases when the systems and equipment to be used have been fully validated previously.
- It is similar to prospective, except the operating firm will sell the product during the qualification runs, to the public at its market price, and also similar to retrospective validation. This validation involves in-process monitoring of critical processing steps and product testing. This helps to generate and documented evidence to show that the production process is in a state of control.

Retrospective validation

- It is defined as the established documented evidence that a system does what it purports to do on the review and analysis of historical information. This type of validation of a process is for a product already in distribution.
- Retrospective validation is only acceptable for well-established processes and will be

inappropriate where there have been recent changes in the composition of the product, operating procedures or equipment.

- ❖ Validation of such processes should be based on historical data.
- ❖ For retrospective validation, generally data from ten to thirty consecutive batches should be examined to access process consistency, but fewer batches may be examined if justified.

Revalidation

- ❖ Re-validation provides the evidence that changes in a process and /or the process environment that are introduced do not adversely affect process characteristics and product quality. Documentation requirements will be the same as for the initial validation of the process.
- ❖ Re-validation becomes necessary in certain situations. Some of the changes that require validation are as follows:
- ❖ Changes in raw materials (physical properties such as density, viscosity, particle size distribution etc., that may affect the process or product).
- ❖ Changes in the source of active raw material manufacturer.
- ❖ Changes in packaging material (primary container/closure system)
- ❖ Changes in the process (e.g., mixing time, drying temperatures and batch size)

ORGANIZATION FOR VALIDATION

Validation organization can be divided into three basic areas;

1. Establishing the organization.
2. Operating it from a quality and cost effectiveness basis.
3. Maintaining a functioning organization.

Establishing the organization:

Formulating a department mission is necessary so that, not only process validation staff members understand the breadth of their job, but also the other corporate groups with whom there is interaction, can also understand.

Departments responsible:

Site validation committee: - Develop site master validation plan.

Manufacturing department: - Prepares the batches as though their routine production batches.

Quality assurance: - Ensure compliance and that documentation, procedures are in place. Approves protocols and reports.

Quality controls: - Perform testing contracts validation testing and reviews protocol and report as needed.

Research and development: - Deals with product design.

Engineering department: - Installation, quality and certify plant, facilities, equipment and support systems.

• Validation team

A multidisciplinary team is primarily responsible for conducting and supervising validation studies. Personnel qualified by training and experience in a relevant discipline may conduct such studies.

Responsibilities of validation team:

- Creates updates and reviews/approves individual project validation plans and validation deliverables.
- Ensures validation compliance with the company validation master plan and project validation plan.
- Coordinates, implements, verify elements of VMP.
- Consults on, evaluates and approves changes.
- Reviews and approves IQ/OQ/PQ procedures and plans.
- Reviews test results and makes recommendations regarding release.
- Assess risks and develops contingency plan.

ORGANIZATION FOR VALIDATION

Quality Assurance Committee (Head of quality control/quality assurance, Production, Engineering and GMP section).

Validation Steering Committee (Members represent the above departments).

Validation Team(Those responsible from Quality control, production and engineering).

Department interaction:

Once the validation team has been constituted and mission have been formalized, the team will interact with different departments which are:

- Research and development department
- Engineering department,
- Production department,
- Maintenance department,
- Quality control department,
- Quality assurance department.

VALIDATION MASTER PLAN

The validation master plan should provide an overview of the entire validation operation, its organizational structure, its content and planning.
The main elements of it being them list/inventory of the items to be validated and the planning schedule.
All validation activities relating to critical technical operations, relevant to product and process controls within a firm should be included in the validation master plan.s

CALIBRATION v/s VALIDATION
CALIBRATION
Calibration ensures that instrument or measuring devices producing accurate results.
Shall be performed periodically, to identify the 'drift' of the measuring device or equipment and make them accurate.
Shall be performed as per calibration SOP.

VALIDATION
Validation provides documented evidence that a process, equipment, method or system produces consistent results (in other words, it ensures that uniforms batches are produced).
• No such requirements. Shall be performed when changes or modifications happen to the existing system or once revalidation period is reached.
• Shall be performed as per validation protocol.

INTRODUCTION TO INTERNATIONAL COUNCIL FOR HORMONISATION (ICH):
The International Council for Harmonization.
Requirements for Pharmaceuticals for Human Use of Technical (ICH) is unique in bringing together the regulatory authorities and pharmaceutical industry to discuss scientific and technical aspects of pharmaceuticals and develop ICH guidelines.

Since its inception in 1990, ICH has gradually evolved, to respond to increasingly global developments in the pharmaceutical sector and these ICH guidelines are applied by a growing number of regulatory authorities.

ICH's mission is to achieve greater harmonization worldwide to ensure that safe, effective and high quality medicines are developed, and registered and maintained in the most resource efficient manner whilst meeting high standards.
ICH Secretariat office is at Geneva, Switzerland(13).

The ICH topics are divided into the four categories- QSEM The ICH topics are divided into the four categories- QSEM

Quality guidelines: Quality Guidelines in the Quality area including stability studies, impurities testing and a more flexible approach to pharmaceutical quality based on GMP risk management.

Efficacy Guidelines : The Efficacy heading is concerned with the design, conduct, safety and reporting of clinical trials.
It also covers novel types of medicines derived from biotechnological processes and the use of pharmacogenetics/genomics techniques to produce better targeted medicines.

Safety Guidelines : Safety Guidelines to uncover potential risks like carcinogenicity, genotoxicity and reprotoxicity non clinical testing strategy for assessing the QT interval prolongation liability.
Guidelines Multidisciplinary: Cross-cutting topics which do not fit uniquely into one of the Quality, Safety and Efficacy categories. It includes the ICH medical terminology (MedDRA). The Common Technical Document (CTD) and the development of Electronic Standards for the Transfer of Regulatory Information (ESTRI).(17)

ICH GUIDELINES FOR CALIBRATION OF EQUIPMENT

- Local identification by a unique identification number and involvement in the master GMP instrument list.
- Procedure for instrument history file.
- Approval by quality unit.
- Generation of procedure for verification and standardization of accuracy and reliability.
- For approval of procedure, it must contains steps and forms required for calibration.
- Involvement of calibration stickers and auxiliary stickers program.
- Procedure for tracking of scheduled calibration activities.
- Procedure for notifying users of calibration due dates, overdue calibrations and out of tolerance findings. Review of all systems, calibration records and procedure by quality unit.
- Involvement of procedure for reporting any GMP critical instrument.
- Involvement of calibration forms which are developed to record the calibration results.(16)

ICH GUIDELINES FOR VALIDATION OF EQUIPMENTS

- 1 meter distance from walls and other obstacles.

- ❖ Easy to operate, clean and maintainable.
- ❖ Working should be at proper commissioned position.
- ❖ Certification of equipment.
- ❖ Checking of overhead heights.
- ❖ Proper source of light..
- ❖ Drop down utility system.
- ❖ Design of equipment.
- ❖ Layout of equipment.
- ❖ Marking of pipelines as per their flow of direction.
- ❖ Sop the equipment.
- ❖ Tracing of equipment.
- ❖ Identification marking for equipment.
- ❖ Cleaning of equipment.
- ❖ Distinguishing of the equipment.
- ❖ Record of each processing.(18)

Validation Requirements & Parameters as per ICH guideline

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

ICH takes system suitability as a part of the method validation, whereas the USP deals it in a separate chapter. Robustness for the ICH is part of precision.

Specificity/Selectivity:
Ability of an analytical method to measure the analyte free from interference due to other components.
Specificity:
‣ Ability to assess unequivocally the analyte in the presence of components which May be expected to be present (impurities, degradants, matrix).

Selectivity:
Describes the ability of an analytical method to differentiate various Substances in a Sample Original term used in USP Also Preferred by IUPAC and AOAC Also used to characterize Chromatographic columns Degree of Bias (Used in USP)
The difference in assay results between the two groups -the sample containing added impurities, degradation products, related chemical compounds, placebo ingredients
-the sample without added substances

LINEARITY
Linearity is a mathematical relationship between two variables quantities (they may be same unit), which are directly proportional to each other.
Graphically it represent a straight line when plotted against each other.

RANGE :
›Acceptable range having linearity, accuracy, precision.
►For Drug Substance & Drug product Assay 80 to 120% of test Concentration
For Content Uniformity Assay 70 to 130% of test Concentration
‣ For Dissolution Test Method +/- 20% over entire Specification Range
For Impurity Assays
From Reporting Level to 120% of Impurity Specification for Impurity Assays
From Reporting Level to 120% of Assay Specification for Impurity/Assay Methods

Accuracy :
Closeness of the test results obtained by the method to the true value

Precision :
• The Closeness Of Agreement (degree of Scatter) Between A Series Of Measurements Obtained from multiple samplings of the same homogeneous sample
The Closeness Of Agreement (degree of Scatter) multiple samplings of the same homogeneous sample. Should be investigated using homogeneous, authentic samples. Considered at 3 Levels
Repeatability
Intermediate Precision
Reproducibility

- **Limit of detection :**
Lowest amount of analyte in a sample that can be detected but not necessarily
quantitated. Estimated by Signal to Noise Ratio of 3:1.

- **Limit of Quantitation:**
Lowest amount of analyte in a sample that can be quantified with suitable accuracy and precision. Estimated by Signal to Noise Ratio of 10:1.(13)

INTRODUCTION FOR USFDA GUIDELINES
The Food and Drug Administration (FDA or USFDA) is an agency of the United States Department of Health

and Human Services, one of the United States federal executive departments.

The FDA is responsible for protecting and promoting public health through the regulation and supervision of food safety, tobacco products, dietary supplements, prescription and over-the-counter pharmaceutical drugs (medications), vaccines, bio- pharmaceuticals, blood transfusions, medical devices, electromagnetic radiation emitting devices (ERED), veterinary products, and cosmetics.
The FDA also enforces other laws, notably Section 361 of the Public Health Service Act and associated regulations.

CALIBRATION AS PER USFDA GUIDELINES
"Equipment shall be calibrated, inspected, or according to a written designed to assure routinely checked program proper performance. Written records of those calibration checks and inspections shall be maintained."

Regular calibration can help to identify issues with an instrument early on, allowing for prompt repairs adjustments to be made. Or So the calibration is a critical component of pharmaceutical quality control. It helps to ensure the accuracy and consistency of pharmaceutical instruments, which is essential for maintaining the safety and efficacy of pharmaceutical products.(18)

VALIDATION AS PER USFDA GUIDELINES
Method Validation.
Analytical Procedures and Methods Validation.
FDA - Industry Guidance Bio analytical method Validation.
Methods Validation for Abbreviated New Drug Applications.
Guideline for Submitting Samples and Analytical Data for Methods Validation.
Validation of Chromatographic Methods.(13)

USFDA GUIDELINES FOR BIOANALYTICAL METHOD VALIDATION
A specific, detailed, written description of the bio-analytical method should be established a priori.
This can be in the form of a protocol, study plan, report, and/or SOP. Each step in the method should be investigated to determine the extent to which environmental, matrix, or procedural variables could affect the estimation of analyte in the matrix from the time of collection of the samples to the time of analysis.
Appropriate steps should be taken to ensure the lack of matrix effects throughout the application of the method.(12)

USFDA GUIDELINES FOR PROCESS VALIDATION:
The collection and evaluation of data, from the process design stage, through commercial production, which establishes scientific evidence that a process is capable of consistently delivering quality product. (12)

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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