Review On:Analytical Method Validation and Development

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ABSTRACT

Validation is one of the key factors to meet current Good Manufacturing Practice (CGMP) and Good Laboratory Practice (GLP) requirements. In any pharmaceutical industry, testing of raw materials, in-process materials, final containers and excipients must be done efficiently. Validation of analytical methods is considered an essential requirement for the testing of such pharmaceutical materials. An analytical procedure should be developed to test the API, excipient and final product. Such a well-designed procedure must essentially ensure that it consistently produces the intended and precise result with high accuracy. To obtain such a specific result, the analytical method must be validated(1).These methods are necessary for many purposes, including quality control release, stability sample testing, comparative test materials and provide information to determine the grant(2).

Key words: *Validation , (CGMP), (GLP)*

INRODUCTION

Analysis is crucial and also important for any product or service medicine because it contains life . Analytical chemistry is analysis isolation, quantification and identification of chemical impurities vegetable and synthetic materials consisting of one or more compounds or factors. Analytical chemistry is divided into two parts dominant classes, quality assessment i.e. identification of chemical additives sample while quantity estimation estimates the quantity a positive detail or composition in a substance, i.e. sample . The number of drugs on the market is increasing every year These drugs can also be either new entities or a partial structural change from the current one. Medicines should be available in such a form that quality and bioavailability, sufficient plasma concentration, desired period, onset of effect, correct dosage, safety, efficacy and preservation of the product during storage, is guaranteed during the storage of the products . The drug development is a long process, including drugs invention, laboratory tests, preclinical trials, clinical trials and mandatory registration. In addition to improving fitness and drug protection after approval, many management organizations such as the United States Food and Drug Administration (USFDA) also requires that the drug its recognition, power, properties, quality, stability and purity before it can be cleared for use. Therefore pharmaceutical validation and process control are crucial ignoring the problems that may arise . often there is a delay from the date of introduction of the drug on the market until the day it is considered in the pharmacopoeias. This arise from persistent potential vulnerabilities and the more widespread use of these drugs, reports ofpersistent toxicity (removal from the market), development affected the resistance of man and the healing of higher medicine the purpose of the competition. In these situations, requirements and analytical methods for those drugs that may not be available in pharmacopoeias. It becomes necessary, then development of newanalytical strategies for such drugs . Refinement and validation of the analytical approach is important works to find, improve and produce them medicines The main purpose of analytical metrics is to achieve consistency,realistic and correct information. Validated analyticalstrategies play a important role in achieving this goal. Results of the methodology

validation can be used for standard selection, reliability and the consistency of the analysis results, which is an important part related of any acceptable analytical practice. Confirmation Most rules and quality also require analytical strategies standards affecting laboratories.(3)

Analytical chemistry :

The branch of chemistry that studies and provides information about the separation of chemicals Identified compounds are then referred to as analytical process

Quantification and qualification are considered when analyzing chemicals. Different mixtures of chemicals compounds or samples are first isolated. These are then identified in what is called a quality process. The amount of certain chemical components is determined by an analytical process called quantification process. The choice of analysis method depends on several aspects, e.g. incarnation; sample matrix, concentration of analytes, its physical and chemical properties, cost and speed of analysis, amount of sample, and quantitative or qualitative measurements of the sample. If the data deals with chemical identification and characterization, it is called a qualitative method of analysis. Similarly, if a method processes numerical data and determines the amount of an ingredient in a sample, it known as the method of quantitative analysis. There are different processes based on the developed method methods development and then method validation.

General method the development and validation of the analysis method is completed by the following process :

1)Development of an appropriate development method.
2) Work-related information must be collected.
3) Qualitative and quantitative analytical methods that can be carried out in the laboratory should be developed.procedure must be established to test the sample. A well-developed method should be easily validated, which is a key criterion in the analytical process. Since the beginning of drug discovery, analytical methods have been developed and validated very necessary And he is also responsible for the manufacture and development of the drug. These processes provide a formal testing methods. Testing laboratories choose a process that monitors drug activity .identification, purification and potential(4).

Objectives of analytical methods of validation

1) If the composition or concentration is changed, validation is still performed

is not required if and only if the analytical method is validated.

2) It reduces the risk of non-compliance.

3) The critical parameters of the process can be fully understood thanks to the analytical method.

4) Minimize interference with accuracy and precision

5) It is used to grant product and sales authorizations for new products not included in the pharmacopoeia.

Method validation :

The need for explanatory technological acceptance is felt practically every day in the review of the pharmaceutical industry, considering that sufficiently approved strategies require reasonable administrative notices. What constitutes an accepted technique depends on the interpretation of the researcher, as there are no universally accepted practices for accepting procedures. Acceptance of technology has received impressive attention in writings as well as from contemporary councils and leading organizations. The International Conference on Harmonization (ICH), which deals with the special needs of the introduction of medicines for human use, has produced an agreement text on the acceptance of scientific systems. The archive contains the meanings of various reception limits.

The United States Environmental Protection Agency (USP) and other logical associations provide strategies validated by studies from several research institutions . The US Food and Drug Administration (US FDA) has proposed rules for submitting test and diagnostic data for the approval of technologies. . The United States Pharmacopoeia (USP) has shared clear guidelines for strategy approval and compound evaluation. The purpose of accepting scientific methods is to show that it is suitable for the intended reason. The debate on the acceptance of explanatory techniques has been divided into four main categories Identification tests.

• Quantitative tests for the amount of impurities.

• Holding tests to prevent contamination.

• Quantitative testing of the dynamic part in drug substance or drug product trials or other selected segments of the drug.

Method needs to be validation and revalidation(5).

Validation:

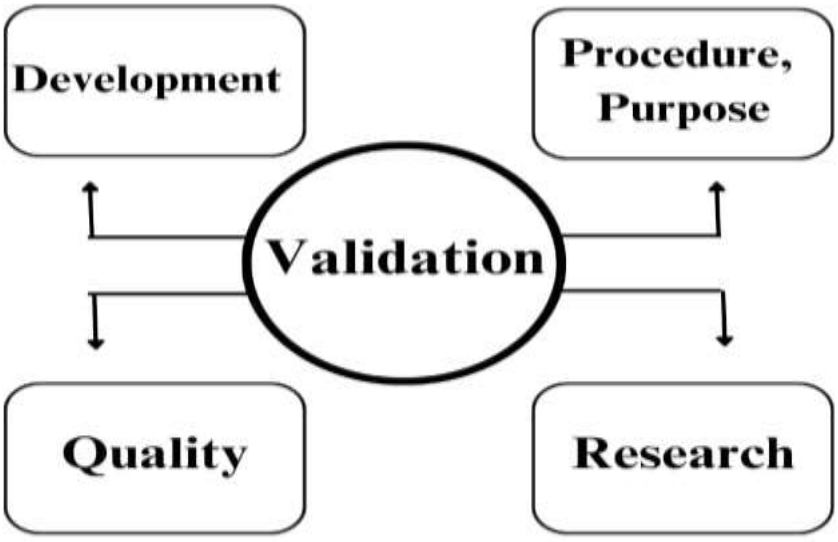
Validation is an integral part of quality assurance involves systematic study of systems, facilities and processes aimed to determining whether they perform their intended functions adequately

According to USFDA :

"To establish documented evidence which provides a high degree of assurance will consist produce that o specific process product meeting its pre-determined specifications and quality attributes."

According to ISO:

"Validation is confirmation examination and the provision objective evidence that the particular requirements for a specific intended use are fulfilled."



Needs of validation:-

1) Validation is needed before introduction of a new method into routine use.

2) Whenever the conditions change for which a method has been validated e.g. instrument with different characteristics.

3) When ever the method is changed and the change is outside the original scope of the method.

Importance of Validation :-

1) During validation knowledge of process increases.

2) Assures the repeatability of the process.

3) Assures the fluency of production.

4) Assures that the product is continuously produce as per specifications.

5)Decreases the risk of the manufacturing problem.

6)Decreases the expenses caused by failures in production.

7)Decreases the risk of failure in GMP

8) Decreases the expenses of every day production.

Scope of Validation :-

1]Validation requires an appropriate and sufficient infrastructure including organization, documentation, personnel and finances.

2]Validation requires the involvement of management and quality assurance.

3]Drug manufacturers must ensure that the validation program covers all important areas of the pharmaceutical industry.

Example:

- Analytical validation

-Cleaning validation

-Instrument calibration

-Process validation

Types of Validation

1] Process validation

2]Cleaning validation

3]computer system validation

4]Analytical method validation

1]Process validation :

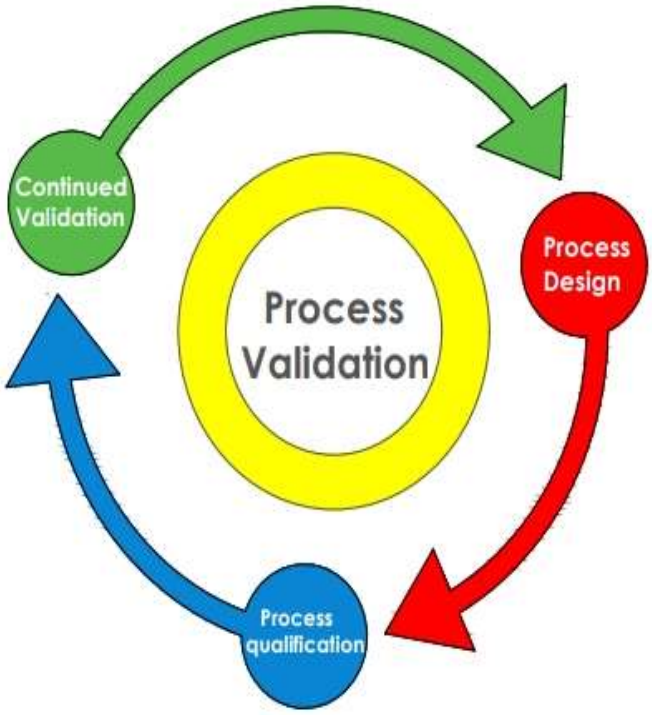


Fig:Process validation

"Process validation is the documented evidence which gives a high degree of certainty that certain the process constantly produces a product that fulfills it given specifications and quality indicators." This greatly benefits the manufacturer:

●It deepens the understanding of processes, reduces risk, prevents problems and thus ensures smooth process flow.

●This reduces the risk of error.

●This reduces the risk of non-compliance.

● A fully validated process may require less in-process inspection and product testing

Basic concept of Validation:

● Process calibration, verification and maintenance equipment

●retraining or extending the validity period.

● Defining definitions and performance characteristics

●choice of methods, processes and equipment to ensure this the product meets the requirements.

● Process and equipment qualification or validation.

●Testing of the final product using validated analytical methods method to meet specifications.

● Reporting, auditing, monitoring or sampling recognized critical steps in the process.

Goals of process validation:

1]In addition, the production process individual devices must be validated.

2]The goal is to create a robust production process which constantly produces the drug the minimum difference that meets the quality criteria purity, identity and power.

Advantages of process validation:

1] Manufacturing validation plan engineers must prepare and execute in order according to the instructions. A valid plan in general contains only the PQ part.

2]Same as device validation, important changes later the first confirmation leads to the need for the following ones extension of validity period.

3] Finally, process validation ensures operational reliability a product that is highly repeatable over time. Advantages of process validation

4]Improved real-time monitoring and regulation process

5] Better ability to evaluate the process statistically performance and product variables. e.g. individuals; middle; area; control limits

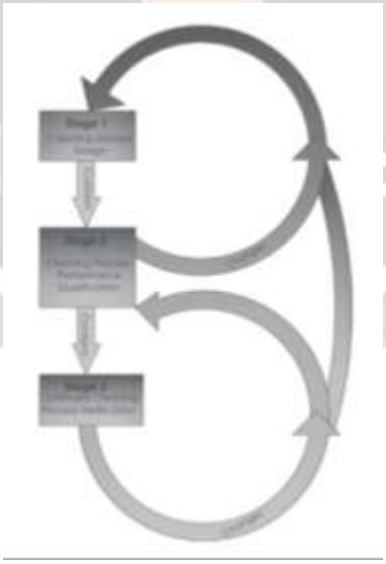
6] Improved data and assessment capabilities and increased confidence in process repeatability and product quality.

7] Better ability to configure and manage target parameters limitations of routine production, correlations valid results.

8]Improved reporting capabilities(6).

Type of process validation:

2]Cleaning validation:



Confirmation of cleaning is documented evidence great confidence that you can constantly clean the system or device given and acceptable limits. Cleaning validation is mainly about cleaning process manufacturing equipment in the pharmaceutical industry area Effective cleaning is essential programs used due to regulation standard But the more fundamental reason is this produce products that are equally clean and free pollution as much as possible and possible.

Why cleaning Validation is important?

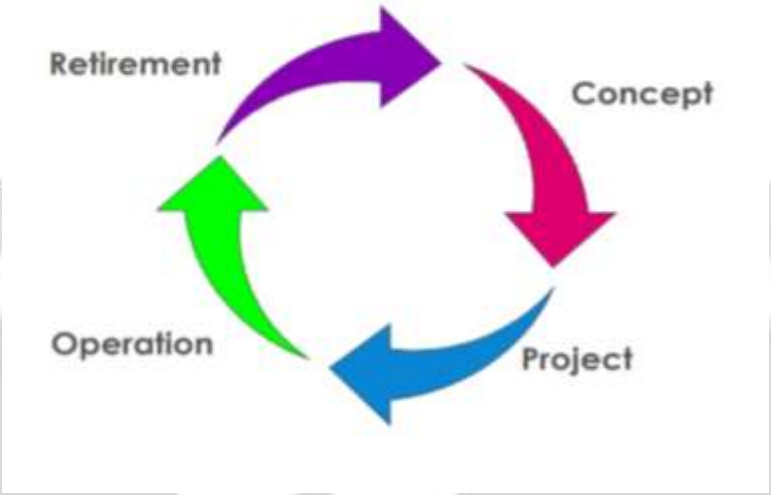
To verify effectiveness of cleaning procedures and ensures there is no risk of cross-contamination active ingredient or detergent/disinfectant.

Advantages of cleaning validation:

1] safety

2]better customer quality(7)

Computer system validation:



Computer System Validation (CSV) is a procedure for protecting (and documenting) computer-based information systems produce information or data that meet specified synchronization requirements. If the system is suitable These claims can be accepted to be presented permanently as intended. The quality is essential for customers when considering a product or service. It is also important because it has to do with saving lives products such as medicines. In that sense, the Food and Drug Administration has come up with a good one manufacturing practices (GMP) to maintain and improve the quality of pharmaceutical products. GMP guarantee that the products are produced and continuously monitored according to the applicable quality standards for use and according to the sales license. One of the most important GMP requirements is this critical manufacturing equipment, utilities and pharmaceutical plants must be properly located certified and finally approved for production. Currently, this practice occupies a key position in the regulations Compliance is strictly enforced by pharmaceutical companies around the world. Confirmation decision is required pharmaceutical industry to ensure compliance with cGMP guidelines for drugs and help companies maintain them consistent quality. The same principles apply to the validation of a computer system or a computer system of a computer system information technology system. Due to non-compliance, it is important to maintain quality standards in the pharmaceutical industry can have far-reaching consequences. Computer system validation checks for efficiency and effectiveness by which the system fulfills the purpose for which it was created. The purpose of this study is to find out the needs validation of instrument/equipment computer systems from a pharmaceutical industry perspective.

Advantages of computer system validation :

1 Compliance with FDA Laws

2 Reduces risks associated with the pharmaceutical industry

3 Solve the problem before implementing the system architecture

. 4 Continuous improvement in the pharmaceutical industry

5 Reduces both operating and labor costs.

6 Maintains the consistency of the final product.

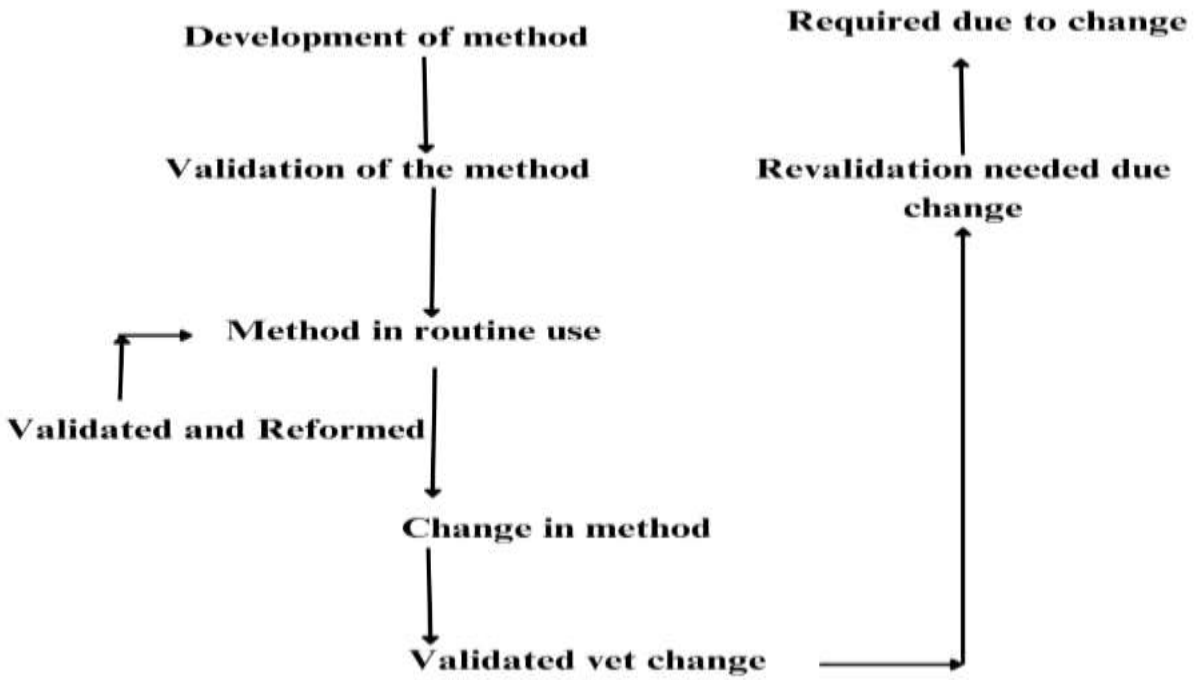
Analytical method validation:

Analytical method validation is a key requirement for chemical evaluation. Method validation is a method of playing different estimates to verify that the method is correct the analysis shows relevant expected explanation and equipped with dignified, acceptable measurement according to regulations. According to the rules and guidelines, the method should give value information that ensures product quality. Multiple testing of the sample is used to determine this result A well-validated method must meet all criteria. Validation of the analytical method should be includes excipient testing and should focus on typical test conditions. All these conditions proves that the validation of the analytical method is valid for the product(4)

Advantages of analytical method:

1. The main advantage of analytical method validation is that it builds trust, not only that for the developer and also for the user
2. although validation can seem expensive and time consuming to spend, it is expensive, to remove frustrating repetitions and leads to better time management
3. .Finally Small changes in conditions, such as reagent suppliers or quality, analytical arrangement is inevitable due to obvious areas but in method validation absorb the shock of such conditions and liver more than investing in the process (7)

Analytical method development:



If there are no established techniques, new methods are developed evaluation of new products. Research whether or not the pharmacopoeia New technologies are being developed for pharmacopeial products to reduce not only the value of time greater accuracy and strength. These methods are optimized and temporary runs To change the current order, alternative ways are planned and implemented in practice comparative laboratory data with all available advantages and disadvantages(8)

Need of Analytical method:

It is important to use well-characterized and fully validated analytical methods in laboratories analyzing registration lots and accelerated stability test samples to obtain reliable results. It is also important to emphasize that each analytical method has its own characteristics that differ from analyte to analyte. In such cases, it may be necessary to develop specific validation criteria for each analyte. In addition, the ultimate goal of the research may affect the appropriateness of the technology. If the sample analysis for a particular study is performed at more than one site and in a commercial batch intended for human consumption, it is necessary to validate the analytical method(s) according to ICH guidelines and provide relevant validation data for different sites and parameters.

Type of analyticalprocedure to be validated :

Types of analytical procedures to be validated Validation of analytical procedures is addressed for the four most common analytical procedures:

1. Identification test

2. Quantitative tests for impurity concentration

3. Impurity control limit tests

4. Quantitative tests of active substance in samples of drug or drug or other selected drug components/components. The purpose of identification tests is to verify the identity of the analyte in the sample. This is usually achieved by comparing sample characteristics (e.g, spectrum, chromatographic behavior, chemical reactivity, etc.) with those of a reference standard. Impurity testing can be either a quantitative test or a limit test for the impurities present in the sample. Both tests are designed to accurately reflect the purity characteristics of the sample. A quantitative test requires different validation functions than a limit test. The purpose of analytical methods is to measure the analyte present in a given sample.From the perspective of this document, analysis represents a quantitative measurement of the main component(s) of a drug substance. Similar drug validation metrics apply to the determination of an active or other eligible component. The same validation functions can be applied to determinations related to other analytical methods.

Steps in method validation:

1.Develop a valid protocol or operating procedure for validation

2. Define the application, purpose and scope of the method

3. Define performance parameters and acceptance criteria

4. Define validation tests

5. Check the relevant performance characteristics of the equipment

6. Accept materials such as standards and reagents

7. Perform pre-validation tests

8. Adjust method parameters and/or acceptance criteria as needed

9. Perform full internal (and external) validation tests

10. Develop SOPs (Standard Operating Procedures) to routinely implement this method

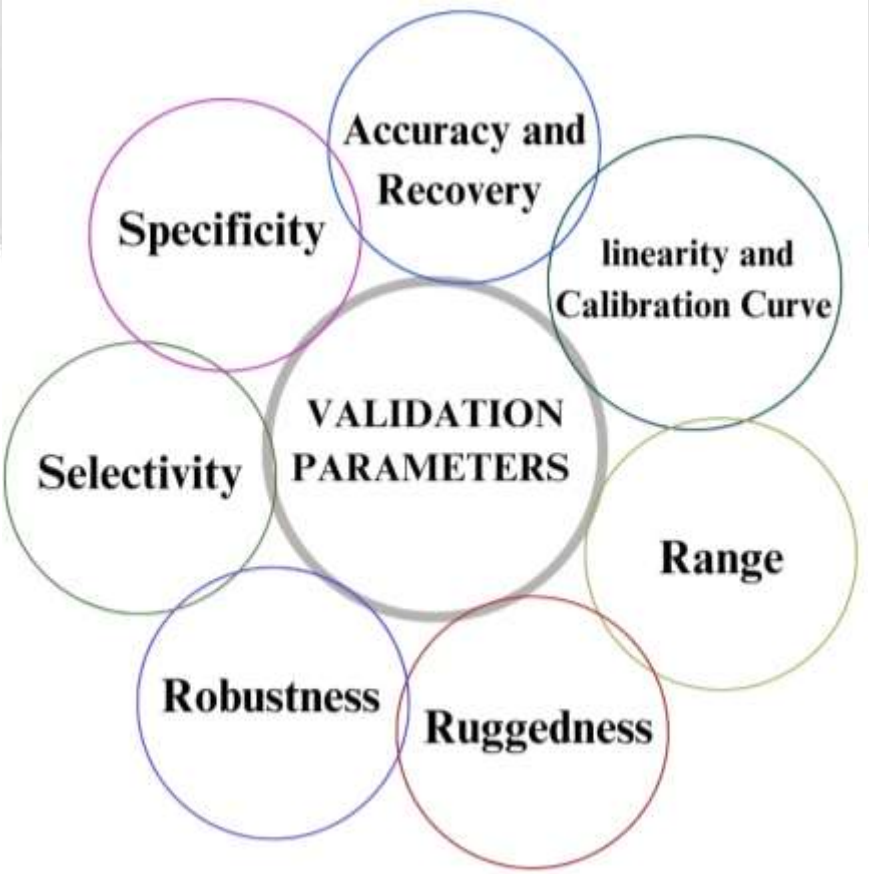
11. Define the criteria for revalidation

12. Determine the type and frequency of routine system suitability tests and/or analytical quality control (AQC)

13. Document validation tests and validation results. First, the scope of the method and its validation criteria should be defined.

These include: compositions, matrices, type of data, qualitative or quantitative, detection and quantitative limits, linear range, accuracy and precision, type and location of equipment. The scope of the method should include different types of equipment and locations where the method is run. The method and performance parameters must be based on the intended use of the method. If the method is used, for example, for qualitative trace level analysis, the method and its linearity do not need to be tested and validated across the entire dynamic range of the device (9).

Analytical method validation parameters :



According to ICH guideline has set a certain criteria for the validation of analytical method

Followings are the parameters of analytical method:

1.Specificity

2.Accuracy

3.Precision

-Repeatability

-Intermediate precision

-Reproducibility

4.Limit of Detection

5.Limit of Quantification

6.Linearity, 7.Range, 8.Robustness.

1]Specificity :

Impurities, chemical deterioration, and other issues are often present in raw materials.

Specificity is the assessment of these substances that are highly potent in the raw material. consists of

Identification :Guarantees that the substances are identified.

Tests for purity: Total elimination

almost impossible to contain contaminants. As a result, impurity limitations are established. Excess solvent content, heavy metals, associated compounds, and other elements could be considered impurities. Purity tests can be used to determine the presence of certain compounds.

The quantitative assessment of an API is known as an assay (content or potency). Drug strength is indicated by the API. (ICH harmonized triangular recommendation, 2005)

2]Linearity:-Linearity can be expressed by the calibration curve, which indicates that a test substance has been measured or data is of direct correlation with the amount of testing chemicals in the sample.

Linearity can be expressed by a calibration curve, which indicates that the test substance has been measured or the data is directly correlated with the amount of test chemicals in the sample. Such a strength is linearity. It must be done within this. Linearity must be assessed for the R2 value. It must be in the area, which means close to one of them. Samples should be prepared by diluting the standard stock solution or by weighing a different sample according to the protocol.

3]Range: Range is one of the valid parameters. The range is the range within which the concentration of the API must be. This gives an overview of the upper and lower limits of API concentration. Between this period, the API can show good performance. The range should be set to a range that can show linearity. accuracy and precision at an acceptable level. A linear result of a suitable range is usually extracted, which must be favorable to the method. The range must be set so that it does not affect the result of linearity, accuracy and precision. Even at the extreme level it should fit. Areas to follow include: 1) Typically, the assay range for the final drug product is 80 to 120 percent of the label claim. 2) When achieving uniformity of content, it should be 70-130 percent of the claim on the label. Appropriate justification must be provided for establishing a wide range, such as metered dose inhalers. 3) Plus or minus 20 percent is recommended for the dissolution test. (ICH Harmonized Tripartite Guideline, 2005)

4]Accuracy: If the data agreements are close enough, this is agreed upon as either a consensus truth value or an accepted reference value. Then it is called the validation accuracy of the analysis procedure. Truth is another term for accuracy. At least 9 conclusions from at least three concentration levels are known exactly, which should cover a given range. For example, three replicates of three concentrations may be performed for an analytical procedure. As a result of precision, either the percentage return or the difference between the mean and the accepted true value and confidence intervals should be recorded. (ICH Harmonized Tripartite Guideline, 2005)

5]Precision: For a homogeneous sample, multiple sampling is required. Measurement errors are obtained. Accuracy is done in a defined mode. The result, or the spread of the result, must be very close. Three types of precision can be considered, which are repeatability, average precision and repeatability. 1) Repeatability: a type of precision which is done in the corresponding work environment and parameter. It must be completed within a short period of time. Internal accuracy is another term for this. The assessment of this test is based on nine findings. When preparing a sample, it must cover a certain area. For example, at least three replicates can be made for each of the three concentrations. Another option for analysis is to examine at least six 100% samples.) Average accuracy: 2 of this type accuracy can be achieved with different laboratory conditions.The test can be done alternately, by another person, with another machine, etc**.**

Repeatability: This type of precision is done between laboratories. It can be collaborative research between different laboratories. Methods must be standardized to ensure **reproducibility**. (ICH Harmonized Tripartite Guideline, 2005) Detection limit The detection limit of a given analytical procedure is the smallest amount of a chemical in a sample that can be detected but not actually estimated because the exact measurement or quantification cannot be precise. Based on an instrumental or non-instrumental process, a number of methods are possible to determine the detection limit. Some approaches to specification are explained below.

6]Limit of detection :

1) Visual evaluation criterion: The non-instrumental method uses visual evaluation more than the instrumental method. The level of ingredient detection depends on the configuration. Samples of known concentration check the limit of detection.

2) Signal-to-noise basis: The noise basis of the exposure is essential for this type of analysis. The sample gives signals. This signal is compared to the analyte with the lowest sample concentration. A blank sample is also analyzed. The determination of the minimum detectable concentration can be explained. A generally satisfactory signal-to-noise ratio is 3 or 2:1.

3) Standard deviation slope bases:

4)Standard deviation of the blank: The magnitude of the analytical background response is estimated. An appropriate number of blanks are prepared and analyzed. The standard deviation is estimated from the responses.

5) Base of the calibration curve: A linearity calibration curve should be plotted. There are two options for standard deviation. This can be either from the y-intercepts of the regression or from the residual standard deviation of the regression line. (ICH Tripartite Guideline, 2005)

7]Quantification limit

In certain analytical methods, limits of quantification are the smallest amount of sample chemicals from which quantification of a component can be calculated. The result must be within an acceptable range. Few quantitative limit determination methods can be based on a non-instrumental or instrumental procedure. Some approaches to specification are explained below.

1)**Visual Assessment Criterion**: The non-instrumental method makes more use of visual assessment than the instrumental method. The level of ingredient detection depends on the configuration. Samples of known concentration check the limit of detection.

2)**Signal-to-noise basis:** The noise basis of the exposure is necessary for this type of analysis. The sample gives signals. This signal is compared to the analyte with the lowest sample concentration. A blank sample is also analyzed. The determination of the minimum detectable concentration can be explained

8]Robustness:strength If little considered changes are applied, but the result of the analysis method still does not make a difference, it is a coin in terms of durability. In normal use, it signals its reliability. If sensitive results are observed during a change in the analytical process, an appropriate or preliminary explanation should be given. Running multiple system compatibility tests is tedious. However, this process ensures suitability when tested at any time during use. Listed below are the changes that can be made for validation. Stability test in analytical solution; . Time of deletion. Similarly, changes in **chromatography may include:**

1)Change in mobile phase pH

2) Changes in mobile phase composition

3)Changes in columns (different lots or suppliers)

4). Change of temperature the flow rate changes

5) Variations in gas chromatography may include: Changes in columns (different lots or suppliers) Change of temperature changes in flow rate (ICH Harmonized Tripartite Guideline, 2005) (11).

System suitability:

Applicability of the system It is considered an essential part of most analytical steps. This test is a specific method. The configuration of the system suitability method depends on the type of procedure being validated. The tests are based on the idea that the devices, electronics, analytical functions and samples analyzed form an essential framework that can be regarded as such. Listed below are the parameters that should be considered for system suitability: . Theory Plates (NLT 2000) . Tail factor (NMT 2.0) Accuracy as needed (NLT 2.0) Reproducibility (% RSD of retention time, peak range) (NMT 2.0). (DDA Guidelines, 2016) BASIC)(10).

CONCLUSION:

This article aims to provide easy-to-use approaches which have the right scientific background for improvement quality of analysis method development and validation process. This article provides an overview of the topic sample preparation quantity, procedure and acceptance criteria for all analytical methods valid parameters in a wider range. Applications the method of analysis and the transfer of the method are also considered discussed in this article. Their different types key development and validation functions is discussed in terms of analytical methodology with the aim of improving the standard and acceptance in this field of research.This article aims to provide easy-to-use approaches which have the right scientific background for improvement quality of analysis method development and validation process. This article provides an overview of the topic sample preparation quantity, procedure and acceptance criteria for all analytical methods valid parameters in a wider range. Applications the method of analysis and the transfer of the method are also considered discussed in this article. Their different types key development and validation functions is discussed in terms of analytical methodology with the aim of improving the standard and acceptance in this field of research.

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