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Role of Validation in Pharmaceutical Industry

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ABSTRACT

Validation is one of the key elements to meet the requirements of current Good Manufacturing Practices (CGMP) and Good Laboratory Practices (GLP). In every pharmaceutical industry, testing of raw materials, in-process materials, final containers and excipients should be done effectively. Analytical method validation is considered a basic requirement for testing such pharmaceutical materials. An analytical procedure should be developed to test the API, excipient and final product. Such a well-developed procedure should fundamentally ensure that it will consistently produce the intended and exact result with a high degree of accuracy. To obtain such a specific result, the analytical method should be validated.

Keywords: Validation of analytical methods, CGMP, GLP.

INTRODUCTION

The part of chemical science that studies and provides knowledge about the separation of chemical compounds that are subsequently identified is known as analytical process chemistry. Quantification and qualification are explored in chemical analysis. First, different mixtures of chemical compounds or samples are separated. These are then identified, which is called a qualitative process. The amount of a specific chemical component is determined by an analytical process known as the quantification process. Decisions about analysis methodology depend on many considerations, for example; sample matrix, analyte concentration, its physical and chemical properties, cost and speed of analysis, amount of sample and quantitative or qualitative measurement of the sample. If the data relate to chemical identification and characterization, this is referred to as a qualitative analytical method. Similarly, if a method deals with numerical data and determines the amount of a sample component, it is known as a quantitative analytical method. On the basis of the developed method is various processes for method development and then method validation. Basically, the common method for developing and validating an analytical method is supplemented by the following process [1].

1) Planning the appropriate method to be developed.
2) Job related information should be collected.
3) A qualitative and quantitative analytical method that can be performed in the laboratory should be developed.
4) A procedure should be established for testing the sample.

A well-developed method should be easily validated, which is a fuamental criterion of the analytical process. From the beginning of drug discovery, the development of an analytical method and its validation is very esndsential. And it is also responsible for the production and development of the drug. These processes provide official test methods. Testing laboratories choose the process that monitors drug activity [2]. Identification, purification and potential the effect of the drug is ensured by this process [3].

Development of analytical methods

The process of confirming that the analytical testing strategy used for a particular test is adequate for its anticipated use is referred to as method validation. The results that are obtained through the method validation process are used to assess the consistent results of the analysis. This guarantees the quality and reliability of the product. A well-developed method is considered the basic process for a reliable test procedure. This characterizes the test method requirement. The reliability for the process requirement is confirmed by the performance capacities of the considered method. The analytical testing process is designed to ensure the identification, purification and potential action of the drug. Physical properties are also studied in this process. A long-term stability study is provided by a well-developed method. It also confirms the quality of the drug during the production of the drug. Similarly, the developed process can strengthen the evaluation of the drug's effectiveness. It ensures safety parameters and the study of physical characteristics [4].

Method development is a consistent procedure that arises in parallel with the development of pharmaceutical products. When we talk about the cost, time, productivity and effectiveness of a medicinal product, the idea of developing an appropriate method is fundamental or fundamental. The goal and purpose of the method should be taken into account in the drug development phase. API characterization was focused on the initial stage of drug development. Safety evaluation for preclinical evaluation is a crucial step. Pre-formulation studies should then be carried out. This is followed by stability studies. Analytical method validation is reasonable to help these parameters. Then, by studying the nature and properties of the API, analytical testing methods

are clarified and expanded throughout the drug development process. The method must not be complicated. It must be robust. Appropriate regulatory guidelines [5] must be followed.

The purpose of the analytical method from product development to product production is to provide information on the point below :

1) Product degradation that indicates stability
2) Analysis and evaluation of API properties eg uniformity of drug, crystalline properties of chemical, release of API etc. It helps in studying bioavailability.
3) The study of impurities that in identifying the profile of the drug for safety.
4) A study of the potential activities of the finished product, which deals with the calculation of the correct dose.

VALIDATION

Validation is defined as demonstrating that any procedure, strategy, process, tool, materials, action, framework or analyzer is proceeding as planned according to a predetermined set of criteria. The validated procedure guaranteed reliability and consistency in the planned result. It also focuses on product compliance and final product analysis. In the pharmaceutical industry, this is a significant thing. Analytical method validation focuses on the consistent accuracy and reliability of test sample results. Any method can show problems, limitations, and interference from external materials when performing testing. Therefore, such problems should be addressed. It has a significant role in fulfilling these goals [8].

Types of validation

Verifications / validation are of different types which are listed below:

1) Process validation
2) Validation of the analytical method
3) cleaning validation
4) Computer validation of the system

1. Process validation

The manufacturing process should be flexible with certain constraints during the product manufacturing process. Achieving attractive properties should be ensured with prevention of basic properties. To achieve these goals, process validation is performed [10].

Objectives of process validation

1) It provides a guarantee to ensure the good quality that is required for the industry.
2) To reduce different batch variations.
3) To save time and money in repeated testing and rework.
4) For a process with the fulfillment of robustness criteria.
5) For product manufacturing consistency and process reproducibility.

2. Validation of the analytical method

Validation, which deals with the analytical method, is a basic necessity to play with chemical assessment. Method validation is a method of playing various evaluations aimed at verifying that the analysis method shows the appropriate expected explanation and that are equipped to provide a profitable, acceptable measurement according to the prescription. According to regulations and guidelines, the method should provide valuable data that ensures product quality. Multiple sample testing is used to determine such results. A well-validated method should meet all criteria. Analytical method validation should include excipient testing and focus on typical test conditions. All these conditions prove that the validation of the analytical method is specific to the product [11].

Objectives of validation of analytical method

1. Critical process parameters can be fully understood thanks to the analytical method.
2. Minimizing interference with accuracy and precision
3. It is used in product authorization and marketing license for new non-prescription products.

3. Cleaning validation

It is very important that the product is free of contamination, which can only be affected by validating the cleaning process. The cleaning technique should be guaranteed to remove unwanted substances from the operations and equipment used in cleaning. The unwanted contamination should be less than required by the regulatory requirement. Cleaning validation is basically done in the drug factory. Validation of the cleaning process can be done by various analytical procedures. The swab test is the most common test to check the cleanliness of the device. Cleaning of equipment and facilities should

be effective. Residues of previous products are removed from the device, which protects the product from degradation. This process confirms the chemical and microbial stability of the API, including excipients

The purposes of cleaning verification are listed below:

1) Recipient of the drug to be safe and pure can be obtained
2) The client's request and his satisfaction can be met.
3) Contamination caused by microbes, chemicals including API cross contamination can be minimized.

4. Computer validation of the system

Currently, the computer system is gathering excellent fame in the world. The pharmaceutical industry is not separated from this computer system. From the research and development phase to the development of the production computer system, it is an integral part of the pharmaceutical sector. A computer system can be used to operate machines and equipment. The meaning of validation speaks of the suitability of validation in all branches of the pharmaceutical industry such as documentation, production quality control and warehouse

Computer system verification refers to the process rather than the application of the computer system. Validation must cover its relationship to another system and the control of the system. It should be user friendly. Documentation of all processes, training, validation, how to operate machines, equipment and system etc. should be safe while using this system.

Validation of the analytical method

An appropriate standard method should be set up to generate reliable analytical data from the relevant laboratory. This is only possible by validating the analytical method. General information about the chemical should be studied for method setup and validation. The analytical procedure should provide reproducible data, even if performed by different analysts in different laboratory centers using different reagents, different instruments and equipment. Certain parameters such as linearity, accuracy, precision, specificity, and reproducibility of the sample result should be observed in the validation of the analytical method.

Types of analytical methods to validate

Validation of analytical methods must be performed for the following test:

1) Identification tests
2) Analysis of impurities for their quantification and its limit test
3) Analysis of the active pharmaceutical ingredient for quantification

Analytical method validation characteristics

The ICH guideline has established certain criteria for analytical method validation. The parameters are listed below:

1) Specificity
2) Accuracy
3) Precision
   - Repeatability
   - Medium accuracy
   - Reproducibility
4) Detection limit
5) Quantification limit
6) Linearity
7) Range
8) Robustness

An explanation of the analytical method validation parameters is given below:

I. Specificity

Normally, raw materials show the presence of impurities, chemical degradation, etc.

The evaluation of such things that have a very high potential of being present in the raw material is defined as specificity. It Includes:

Identification:

Ensures ingredient identification.

Purity test:

Complete removal of impurities is almost impossible. Certain limits are therefore set for impurities. Impurities may be present in the form of residual solvent content, heavy metals, related substances, etc. The test for these substances can be carried out with a purity test.

Assay (Content or Potency):

Refers to the quantitative determination of an API. The API indicates the strength of the drug.

II. Linearity

Linearity is generally indicated by a calibration curve that shows that the test substance measurement or data is directly proportional to the amount of the test chemical in the sample. Such capacitance is known as linearity. It should be done within the scope. The R2 value is studied in linearity. It must be in range, i.e. close to one. Samples are prepared either by diluting the standard stock solution or weighing different amounts of sample according to the protocol. A solution of different concentration should be prepared. At least five concentrations must be prepared for analysis.

III. Range

Range is one of the validation parameters. The range is the interval within which the concentration of the API must lie. It gives an idea of the upper and lower limit of API concentration. Between this interval, the API can demonstrate good efficacy. The range should be set in an interval that can exhibit linearity, precision and accuracy at an acceptable level. Usually, the extraction of a suitable range is done as a result of linearity, which must be favorable for the procedure. The range should be set so as not to affect the result of linearity, precision and accuracy. Even at the extreme level it should be suitable.

The range criteria to be followed are listed below:

1) Normally, the assay range of the final drug product lies between 80 and 120 percent of the label claim.
2) When implementing content uniformity, it should be within 70 to 130 percent of the label claim. If a wide range needs to be set, for example with metered dose inhalers, a proper justification should be given.
3) In the case of the dissolution test, plus or minus 20 percent is recommended.

IV. Accuracy

When the data matches are close enough, this is agreed as either a conventional true value or an accepted reference value. Then this is called precision in the validation of the analytical procedure. Verity is another term for accuracy.

At least 9 inferences could be made at a minimum of 3 concentration levels, which should cover a predetermined range known as precision. For example, three replicates, each of three concentrations, can be performed for an analytical procedure. As a precision result, either the percent recovery or the difference between the mean and the true value received should be recorded, along with confidence intervals.

V. PRECISION

For a homogeneous sample, sampling should be done several times. A number of measurements are obtained. Accuracy is performed under predetermined conditions. The result, i.e. the variance of the result, must be very close. Three types of precision can be considered, which are repeatability, mean precision and reproducibility.

- ***Repeatability:***

The type of accuracy that is performed in an equivalent work environment and parameters. It must be completed in a small time interval. Intra-assay precision is another term used for it. The evaluation of this test is made from nine conclusions. It should cover a specific range in sample preparation. For example, at least three replicates, each of three concentrations, can be performed. Another method of analysis is the examination of at least six 100% samples.

- ***Medium precision:***

This type of precision can be done by changing laboratory conditions. The the test can be performed every other day, by a different person, by a different machine, etc.

- ***Reproducibility:***

This type of precision is one that is performed between laboratories. It can be a collaborative study between different laboratories. Methodology standardization must be done for reproducibility.

VI. Detection limit

The detection limit in a particular analytical procedure is the smallest amount of a chemical in a sample that can be identified but cannot actually be evaluated because the exact measurement, i.e. quantification, cannot be precise.

Based on an instrumental or non-instrumental process, several methodologies are possible for determining the detection limit. Some approaches to determination are explained below.

1. **Basis of visual assessment:** The non-instrumental method uses visual assessment more than the instrumental method. A level is set at which the additive can be detected in dependence. Samples of known concentration control the limit of detection.
2. **Signal-to-Noise Basis:** For this type of analysis, the exhibition noise baseline is essential. The pattern gives signals. This signal is compared to the analyte containing the lowest sample concentration. A blank is also analyzed. The identification of the minimum concentration that can be identified can be found. A commonly satisfactory signal-to-noise ratio is 3 or 2:1.
3. **Response Standard Deviation and Slope Base:** The equation for the analysis is, A. σ = standard deviation of the response B. S = slope of the calibration curve. It can be calculated from the linearity calibration curve of the sample. Calculation of σ can be done by different methods
4. Standard deviation of the base 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. Basis of calibration curve: Linearity calibration curve should be drawn. There are two options for the standard deviation. This can be the gain from either the y-intercepts of the regression or the residual standard deviation of the regression line.

VII. Limit of quantification

Limits of quantification in specific analytical methods are the smallest amount of a chemical sample from which a quantitative determination of a component can be calculated. The result should be within an acceptable range. Few methodologies in deciding the limit of quantification can be done based on a non-instrumental or instrumental procedure. Some approaches to determination are explained below.

1. **Basis of visual assessment:** The non-instrumental method uses visual assessment more than the instrumental method. A level is set at which the additive can be detected in dependence. Samples of known concentration control the limit of detection.
2. **Signal-to-Noise Basis:** For this type of analysis, the exhibition noise baseline is necessary. The pattern gives signals. This signal is compared to the analyte containing the lowest sample concentration. A blank is also analyzed. The identification of the minimum concentration that can be identified can be found. The commonly satisfactory signal-to-noise ratio is 10:1.
3. **Response Standard Deviation and Slope Base**: The equation for the analysis is, σ = standard deviation of the response S = slope of calibration curve. It can be calculated from the linearity calibration curve of the sample. Calculation of σ can be done by different methods

- 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.

Basis of calibration curve: Linearity calibration curve should be drawn. There are two options for the standard deviation. This can be the gain from either the y-intercepts of the regression or the residual standard deviation of the regression line.

VIII. Robustness

When little with intentional changes are applied, but still there is no difference in the result of the analytical method, it is like robustness. In normal use, it shows its reliability. In the case of sensitive results during a change in the analysis process, an appropriate or preparatory explanation should be provided. Carrying out a large number of system suitability tests is a tedious task. However, this process ensures the suitability of the test at any time of use.

The list below contains the changes that can be made for validation. Stability test in analytical solution; Extraction time.

Similarly, changes in liquid chromatography can be as follows:

- Mobile phase pH change
- Mobile phase composition changes
- Column changes (different batches or suppliers)
- Temperature change
- flow rate changes

For gas chromatography, there may be the following variations:

- Changes in columns (different batches or suppliers)
- Temperature change,

- flow rate changes

CONCLUSION

Validation provides evidences for a analytical method in terms of its accuracy ,precision ,limit of detection ,linearity ,range and quantification limit for better quality of pharmaceutical products ,their analysis and identification of impurities as well as products efficacy and toxicity Validation plays an important role in provision of good quality medicines also a well validated method gives procedures to to quality control department to check the products thoroughly. Hence validation ensures good quality product manufacturing and processing

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