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Validation of Analytical Methods: a Comprehensive Review

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ABSTRACT
Validation of analytical method development is necessary to produce reliable results for regulatory submissions. These techniques are essential for various tasks, including testing for quality control release, testing of stability samples, testing reference materials, and providing information to back up specifications. An essential step in the drug discovery process is using of an analytical method followed by a technique for creating evidence that offers a high level of assurance. Despite the drug's good potency, the lack of a recognised analytical method prevents the medicine from being sold. This preserves the drug's quality and safety. This review offers suggestions for several approaches to assure during analytical processing and different validation criteria that adopt to various regulatory agencies.

Keywords: Validation, Precision, Reproducibility, Analytical Methods

INTRODUCTION

Every year, more drugs are being released onto the market. These drugs could either be entirely new or structurally modified versions of already existing ones. Any analytical measurement goal is to get reliable, accurate data that is consistent (Wen et al., 2015). Validated analytical techniques are crucial in reaching this objective. Any excellent analytical practise should include evaluating the quality, consistency, and reliability of analytical data using the findings from method validation (Berkowitz et al., 2012; Krishnankutty et al., 2012; Verch et al., 2022).

The majority of laws and standards for quality that impact on laboratories also call for the validation of analytical methods. Frequently, there is a delay between a new drug's introduction to the market and its inclusion in pharmacopeias. This is brought on by potential risks associated with the long-term and widespread use of these drugs, reports of novel toxicities (leading to their removal from the market), the emergence of patient resistance, and the launch of superior drugs by rival companies. Standards and analytical methods for certain medications may not be included in the pharmacopoeias under these circumstances. Therefore, there is room to create newer analytical techniques for these medications.

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The discovery, development, and production of pharmaceuticals depend heavily on the development and validation of analytical procedures. Pharmaceutical products formulated with more than one drug, commonly known as combination products, are intended to meet the needs of patients who have yet to be served (Chung Chow Chan , Y. C. Lee , Herman Lam, 2004). These products require the development and validation of analytical methods to combine the therapeutic effects of two or more drugs in a single product. The analytical chemist in charge of developing and validating analytical techniques may face formidable obstacles due to these combination products (Mennickent and de Diego, 2019). To assure the identification, purity, potency, and effectiveness of drug properties, quality control laboratories use the official test procedures that originate from these processes.

To ensure quality and safety in the development of pharmaceutical processes, contaminants must be identified and quantified (Apostol et al., 2012). The impurities in pharmaceuticals, which are undesired molecules that remain with the active pharmaceutical ingredients (APIs), develop during stability testing, or develop during formulation, occur after both the API and the created APIs to medicines have aged, are related components. The efficacy and safety of pharmaceutical products may be impacted these undesirable substances, even in trace concentrations. Pharmaceutical-related components are identified using a variety of analytical methods. Creating new analytical techniques is crucial for assessing the quality of novel, emerging medications (Pratama et al., 2020).

BASIC REQUIREMENTS FOR DEVELOPING NEW DRUG ANALYSIS TECHNIQUES

Patent laws may prevent the publication of accurate drug analytical techniques in literature, formulations may be hindered by formulation excipients, and the drug or drug combination may not be listed as official in any pharmacopoeias.(Blessy et al., 2014). It may be impossible to get analytical methods for a medicine when it is combined with other medications, or the substance may not be quantifiable in biological fluids. It is possible that the existing analytical procedures require expensive solvents and reagents. In addition, intricate, and sometimes unreliable extraction and separation methods might be employed (Tavana and Chen, 2022).

METHOD VALIDATION TECHNIQUES

Analysis in the pharmaceutical sector deals with the need to validate an analytical method on a nearly daily basis because properly validated methods are required for regulatory filings to be accepted (Pandey et al., 2010). But as there is no approved industry standard for assay validation, what be suitable as a validated procedure is open to analyst opinion. The literature, commercial agencies, and regulatory bodies have all given method validation a lot of attention. An agreement text on the validation of analytical processes has been developed by the International Conference on Harmonization (ICH) on technical requirements for the registration of drugs for human use. Definitions of several validation parameters are included in the paper (Taylor, 2015; Tiwari and Tiwari, 2010). The United States Environmental Protection Agency (USP), Resource Conservation and Recovery Act (RCRA), American Association of Official Analytical Chemists (AOAC), and other academic institutions offer methodologies that have been verified through multi-laboratory research (Peris-Vicente et al., 2015). For the purpose of validating procedures, the US Food and Drug

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Administration (US FDA) has established criteria for submitting sample and analytical data. Specific criteria for validation techniques and chemical evaluation have been issued by the United States Pharmacopoeia (USP).

The goal of validating analytical techniques is to confirm that they are appropriate for the intended use. The four most prevalent forms are the focus of the discussion of the validation of analytical techniques (Rao, 2018).

- Tests for identification
- Impurities-content quantitative testing
- Limit tests for contaminants control
- Quantitative analyses of the active component in samples of drug substance, drug product, or other chosen drug product components (Liu et al., 2021)

In order to check the suitability of the developed method for its intended use it must be validated and revalidation is to be performed before they were implemented to regular usage. Whenever the condition for which the method has been validated changes, such as when an instrument has different features (Behera, 2012).

VALIDATION PARAMETERS

The developed method will be validated as per the ICH guidelines. The validation parameters are as follows**.**

Specificity

Specificity is ability of a method to measure one analyte in the presence of other pertinent substances that are anticipated to be present in a sample is known as specificity. For the purpose of validating specificity, analytical methods that can measure the analyte response while any conceivable sample components are present should be used (Whitmire et al., 2010).

It is not always possible to demonstrate that one analytical technique is unique for a given analyte. In this situation, it is advised to combine two or more analytical techniques to reach the required level of discrimination. High-performance liquid chromatography (HPLC) and to a lesser extent, gas chromatography (GC), are routinely employed methods in pharmaceutical industries. In actual reality, a test mixture is prepared that contains the analyte and all possible sample components(Wu et al., 2011). The result is contrasted with the analyte's response.

Components in pharmaceutical test mixtures might derive from excipients, degradation products, and synthesis intermediates (Nikolin et al., 2004). By subjecting the sample to stress conditions, such as high temperature, humidity, or light, the production of degradation products can be accelerated (Chan, 2016; Jain and Khan, 2022). By selecting the best columns and adjusting the chromatographic parameters, including the mobile phase composition, column temperature, and detector wavelength, specificity in liquid chromatography can be achieved (Reddy et al., 2013). The sample preparation stage can also be tuned for optimum selectivity in addition to chromatographic separation. Determining whether the peaks in a sample chromatogram are pure or contain many compounds is a challenging task in chromatography. The number of chemicals in the sample should be known by the analyser. However this is only sometimes attainable. Consequently, the purity of the target chemical peak should be assessed (Atapattu and Rosenfeld, 2018; Falaki, 2019).

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Accuracy and Recovery

The degree of agreement between the value acknowledged as either a conventional actual value or a recognised reference value and the value discovered is expressed as the analytical procedure's accuracy. Therefore, accuracy is a gauge of how precise an analytical procedure is. The degree to which test findings produced by the method and the actual value concur can also be used to define accuracy. There are numerous approaches to determine the accurate assessment's genuine value. A different approach is to contrast the method's findings with those of a recognised reference approach. This strategy presupposes that the reference method's level of uncertainty is known (Ismail and Afify, 2022).

The second way to evaluate accuracy is to analyse a sample with known concentrations (such a control sample or certified reference material) and contrast the measured value with the genuine value that was provided with the material. A blank sample matrix of interest can be spiked with a known concentration by weight or volume if certified reference materials or control samples are not available (Abdel and El-Masry, 2021). By contrasting the response of the extract with those of the reference material dissolved in a pure solvent after the analyte has been extracted from the matrix and injected into the analytical instrument, its recovery can be calculated. It is essential to precisely match the actual sample preparation because this accuracy assessment evaluates how well the sample was prepared (Theodorsson, 2012).

The recovery factor identified for various concentrations, if checked correctly, can be utilised to adjust the results (Marcelletti et al., 2015). One concentration in the middle of the range, one at the upper end of the calibration curve, and concentrations near the quantitation limit should all be included in the concentration (Moosavi and Ghassabian, 2018). It should also cover the range of concern. Another strategy is to focus on the crucial decision value, which must be the point of accuracy with the most significant degree, as the concentration point. According to the ICH publication on validation methods, accuracy should be evaluated using at least nine determinations over at least three concentration levels covering the recommended range (for example, three concentrations with three replicates each)(European Medicines Agency ICH, 2005; Gupta, 2015).

Reporting accuracy as a percentage of recovery from the assay of a known additional amount of analyte in the sample or as the difference between the mean and the recognised actual value, together with confidence intervals, is appropriate (Sahoo et al., 2018).

Precision

When several measurements are taken from the same homogeneous material under specified conditions, the precision of an analytical technique is the degree of scatter, or closeness of agreement, between those measurements. Three criteria may be used to categorize accuracy: reproducibility, intermediate precision, and repeatability. Authentic, homogenous samples should be used for research on precision. If a homogenous sample cannot be obtained, sample solutions or artificially generated samples may be used for the investigation.The variance, standard deviation, or coefficient of variation of a set of measurements is typically used to represent the accuracy of an analytical process. (Broadhurst et al., 2018).

Repeatability

Repeatability describes the accuracy over a brief period of time while using the same operating conditions. Precision within an assay is another name for repeatability (Lister, 2005).

Intermediate Precision

Variation within laboratories is expressed by intermediate precision; examples include different days, equipment, etc. By contrasting the outcomes of a process executed over a number of days in a single laboratory, intermediate precision is ascertained (Chesher, 2008). Discrepancies in findings from different operators, inconsistent working practises, different equipment, standards and reagents from various suppliers, columns from multiple batches, or a combination of these factors may be reflected in a method's intermediate precision (Betz et al., 2011). The goal of intermediate precision validation is to confirm that after the development phase is complete, the method will provide the same findings in the same laboratory (Chau et al., 2008).

Reproducibility

Reproducibility demonstrates consistency across laboratories (collaborative studies usually applied to standardisation of methodology) (Peng and Hicks, 2021). Reproducibility's goal is to confirm that a procedure will provide the same outcomes in several labs. An analytical method's repeatability is assessed by examining aliquots from homogeneous lots in various labs with various analysts (Plesser, 2018). On top of that, typical changes in operational and environmental circumstances that may deviate but remain within the method's predetermined parameters are used. If the procedure is to be utilised in many laboratories, the repeatability of the results must be validated. Differences in ambient temperature and humidity, equipment with variable properties like an HPLC system's delay volume, columns from various manufacturers or batches, and operators with various levels of experience and thoroughness are all factors that can affect repeatability (Minarik et al., 2018).

Limit of Detection

The lowest amount of analyte in the sample that can be detected but not precisely measured is the detection limit of a specific analytical process. The point at which a measured value exceeds the level of related uncertainty is known as the limit of detection (LOD) (Lavín et al., 2018). It is the lowest analyte concentration that can be identified but not always quantified in a sample. The sensitivity of the approach and the limit of detection are frequently misunderstood terms (Al-Hakkani, 2019).

An analytical method's sensitivity refers to its capacity to distinguish between minute variations in the mass or concentration of the test analyte. Sensitivity is, in actuality, the slope of the calibration curve that is determined by graphing the response against the mass or concentration of the analyte. The injection volume in chromatography that produces a peak with a height at least two or three times higher than the background noise level is known as the detection limit. In addition to the signal-to-noise approach (Armbruster and Pry, 2008).

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Quantitation Limit

The lowest amount of analyte in the sample that can be accurately and quantitatively measured is the quantitation limit of a specific analytical method (Vashist and Luong, 2018). A parameter known as "quantitation limit" is used to assess low concentrations of chemicals in sample matrices quantitatively and is particularly useful for identifying contaminants and/or degradation products (Belouafa et al., 2017). In quantitative assays for low concentrations of chemicals in sample matrices, the quantitation limit is a parameter that is particularly useful for identifying contaminants or degradation products (Bliesner, 2006).

The quantitation limit is often established by determining the least concentration the analyte can be measured with acceptable accuracy and precision. Six injections of five or six samples containing progressively lower concentrations of the analyte are made if the required precision of the procedure at the limit of quantitation has been specified. The amounts range from 20 times the LOD to the known LOD as established above (Bernal, 2014).

Linearity

The capacity to get test results that are directly proportionate to an analyte's concentration in the sample is known as the linearity of an analytical technique (Misra et al., 2017). By diluting a standard stock solution or individually weighing synthetic mixtures of the test product's parts, linearity may be proven on the test substance. A series of five to six injections of five or more standards with concentrations spanning 80 to 120 percent of the anticipated concentration range is used to determine linearity. The response must be directly proportional to the analyte concentrations or proportionate via a precise mathematical calculation. The intercept of a linear regression equation applied to the data should not deviate significantly from zero.

It should be shown that a significant nonzero intercept has no bearing on the method's accuracy if one is achieved. In addition to or instead of a quantitative examination, the linearity is frequently assessed graphically (Hibbert, 2004). By visually examining a plot of signal height or peak area as a function of analyte concentration, the assessment is made. Two extra graphical approaches can be utilised because linearity deviations might occasionally be hard to find. The first step is to plot the concentration vs the departures from the regression line (Brier and Lia dwi Jayanti, 2007) .

The test findings should be assessed using the appropriate statistical techniques if there is a linear relationship, such as Y-intercept; slope of the regression line; residual sum of squares; correlation coefficient (r^2) (Januszyk and Gurtner, 2011). Regular acceptance requirements for a linear calibration curve include: $r^2 \geq 0.999$; a y-intercept between 0 and 5% of the target concentration; and an RSD between 1.5 and 2%.

Range

The interval between the higher and lower concentration of an analyte in the sample for which it has been shown that the analytical technique has adequate precision, accuracy, and linearity is known as the range of an analytical procedure. The range is typically given in the same units (for instance, %, parts per million) as the test findings produced using the analytical method (Renger et al., 1995).

- 80 to 120% of the test concentration for assay.
- Content uniformity: 70 to 130% of test concentration
- Dissolution: Q-20% to 120%
- Impurities reporting level: 120% of impurity specification limit
- Assay and contaminations: reporting position to 120% of assay specific.
  Linearity is limited to 150 of the shelf-life specification of contaminations. Test attention can be used to determine contaminations. To determine medicine substance (assay), the test attention must be adulterated. The range is 0 –150 contamination specification (Rao, 2018).

Robustness

The robustness of a logical procedure is a measure of its capacity to remain acquitted by slight but deliberate variations in system parameters. It suggests its capability during the normal range (Vander Heyden et al., 1998). Robustness tests examine the effect that functional parameters have on the analysis results. For the determination of a system's robustness, a number of system parameters, similar as pH, inflow rate, column temperature, injection volume, discovery wavelength or mobile phase composition, are varied within a realistic range, and the quantitative influence of the variables is determined. However, the parameter is said to be within the system's robustness range, if the effect of the parameter is within a preliminarily specified forbearance. Carrying data on these goods helps to assess whether a system needs to be revalidated when one or further parameters are changed, for illustration, to compensate for column performance over time. In the ICH document it's recommended to consider the evaluation of a system's robustness during the development phase, and any results that are critical for the system should be proved.

Ruggedness

Ruggedness is the degree of reproducibility of results attained under various conditions, similar to different laboratories, judges, instruments, environmental conditions, drivers and accoutrements. Ruggedness measures the reproducibility of test results under normal, anticipated functional conditions from laboratory to laboratory and from critic to critic. Ruggedness is determined by analyzing aliquots from homogeneous lots in different laboratories (Silva et al., 2008; Vander Heyden et al., 2001).

STABILITY STUDY OF DRUG

Chemical composites can decompose previous to chromatographic examinations, for illustration, during the medication of the sample results, natural, remittal, phase transfer or storehouse of set vials (in refrigerators or in an automatic sample). Under these circumstances, system development should probe the stability of the analytes. It's a measure of the bias in assay results generated during a preselected time interval, for illustration, every hour up to 46 hours, using a single result. Stability testing (Williams et al., 2019) is important for estimating the allowed period between sample collection and sample analysis. It's also important to estimate a logical system's capability to measure medicine products in the presence of its declination products. Trials should be conducted under real sample storehouse conditions because the stability of medicine substances is a function of the storehouse conditions, the chemical parcels of the medicine, the matrix, and the vessel system

stability (González-González et al., 2022). The studies should estimate the stability of the analytes during sample collection and running after typical storehouse scripts similar to the long-term storehouse (when firmed at intended storehouse temperatures), short-term storehouse (during a series of sample analyses at room temperature), and after snap and thaw cycles. Conditions used in stability trials should reflect situations likely encountered during factual sample running, storehouse and analysis.

All stability determinations should use a set of samples prepared from a recently made stock result of the analyte in the applicable analyte-free, hindrance-free matrix. Stock results of the analyte for stability evaluation are prepared in an applicable detergent at known attention. The stability of the stock results of the medicine and the internal standard should be estimated at room temperature for at least six hours. After completion of the asked storehouse time, the stability is tested by comparing the instrument response with that of lately prepared results. System stability is determined by replicate analysis of the sample result and computation of the RSD of the responses. System stability is considered applicable when the RSD doesn't exceed more than 20 percent of the matching value of the short-term system precision. However, the maximum duration of the sample result usability can be calculated (Ahuja, 2005), If the value is advanced on conniving the assay results as a function of time. To force declination, ICH4 also recommends conducting stress studies, in conditions similar to elevated temperature, moisture or light to demonstrate the particularity of the assay in the presence of declination products. The thing is to induce typical declination products that may be anticipated. As a rule of thumb, stress conditions should be named so that 5- 20 percent of the medicine substances are degraded. In addition, it's recommended to measure the stability under different snap and thaw cycles, both short and long-term. Below are illustration conditions suggested for bioanalytical studies. Exact conditions depend on operation-specific storehouse conditions.

Studies Acidic and basic hydrolysis

The hydrolytic degradation of a new drug under acidic and basic conditions can be studied by refluxing the drug in a mixture of 0.1 N HCl/0.1 N NaOH. If moderate destruction is observed, testing can be stopped at this point. However, if degradation is not observed under these conditions, the drug must be refluxed in a stronger acid/base for a longer time. Alternatively, if complete degradation is observed after bringing the drugs to their original state, the acid/base strength can be reduced by lowering the reaction temperature (Roberto de Alvarenga Junior and Lajarim Carneiro, 2019). For oxidation it is recommended to use hydrogen peroxide with a concentration of 3-30%. Some drugs degrade extensively when exposed to 3% hydrogen peroxide for a very short time at room temperature. In other cases, exposure to high concentrations of hydrogen peroxide does not cause significant degradation even under extreme conditions (Kim et al., 2013). The behaviour is expected because some drugs are oxidizable while others are not. The latter is expected to show no change even in the presence of a high dose of oxidant. Photolytic studies should include exposure of the drug solution to sunlight. The drug solution must be exposed to sunlight for days.

UV light

To study the photolytic stability of the drug, the drug solution must be exposed to UV radiation in a UV chamber for days (Mohanan et al., 2021). The storage time for long-term stability evaluation should exceed the time between the first day of sampling and the last sample analysis. Long-term stability must be determined by storing at least three aliquots of each low and high concentration under the same conditions as the test samples (van de Merbel et al., 2014). The concentrations of all stability samples must be compared with the average of the post-calculated values of the standards at the appropriate concentrations from the first day of the long-term stability test.

Stability of Processed Samples

The stability of processed samples, including autosampler residence time, must be determined (Theodorsson, 2012). The stability of the drug and the internal standard should be evaluated in validation samples during the expected run of the expected lot size by determining the concentrations based on the initial calibration standards.

DOCUMENTATION

The validation of the analytical method is confirmed and verified by laboratory studies, and the successful completion of these studies must be documented in the analytical validation report. General and specific SOPs and good record-keeping are integrated into a validated analytical method (Pum, 2019). Data produced for bioanalytical method generation and quality control must be documented and available for data review and revision. Documentation submitted to the agency must include: summary information, method development and implementation, bioanalytical reports on method application in routine sample analysis, and other information on method development and establishment and/or routine sample analysis.

The documents on the development and implementation of the method are:

- Functional description of the analytical method (Kaza et al., 2019).
- Evidence of purity and identity of drug standards, metabolite standards and internal standards used in validation experiments.
- Description of stability studies and additional data (Pauli et al., 2014).
- Description of experiments performed to determine accuracy, precision, recovery, selectivity, limit of quantification, calibration curve (equations used and possible weighting functions) and relevant data obtained from these studies.
- Documentation of intra-assay and inter-assay accuracy and precision (Cha et al., 2011).

APPLICATION OF ANALYTICAL METHOD DEVELOPMENT

All analyte samples in a biological matrix should be determined within the period for which stability data are available. Generally, biological samples are analyzed in a single assay without a duplicate or parallel assay if there is acceptable variability in the analytical method based on validation data (Hoffman et al., 2009). The following recommendations should be considered when using a bioanalytical method for routine drug analysis. Response function: typically, the same curve fit, weight and goodness of fit determined in the repeat study validation should be used for the study

standard curve (Londhe and Rajadhyaksha, 2019).

CONCLUSION

The analytical methodology provides an analyst with the necessary data for a given analytical problem, as well as sensitivity, accuracy, range of analysis, and precision, i.e. the minimum requirements, which are essentially the specifications of the method for the intended purpose of being able to analyse the desired analyte in different matrices with certainty and surety. Analytical methods must be validated before they are used routinely; whenever the conditions for which the method was validated change (e.g., an instrument with different characteristics or samples with a different matrix), and whenever the method is changed, the difference is outside the original scope of the method. Although stability indication tests have been developed for a wide range of drugs, the vast majority of them fail to meet current regulatory standards for the separation and characterization of particular degradation products. As a result, the discussion presented would be broad and applicable. Knowing the contaminants in APIs is now an essential criterion in several pharmacopeias. Impurity isolation and characterisation are necessary for gathering and assessing data that confirms biological safety, revealing the need for and extent of drug impurity profiling in pharmaceutical research. The purpose of this article is to show how to employ methodologies with a solid scientific foundation to improve the quality of bio-analytical method development and validation. This article also considers the applications of bio analytical methods in ordinary drug analysis. A method is developed in a succession of simple steps. All conditions are optimised for the separation, and the process is validated using ICH recommendations. After that, the validated method and data can be documented.

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CONFLICT OF INTEREST

We declare that we have no conflict of interest.

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