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Importance of bioanalysis in drug discovery and development: A review

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Abstract
In the present review article, various scientific and technical aspects of bioanalysis were proposed. Bioanalysis plays a vital role in the pharmacokinetics or pharmacodynamics characterization of lead components from the time of its discovery and during various stages of drug development. Here the importance of bioanalysis and bioanalytical parameters in drug discovery and development are discussed, which will help in the development of safe and more efficacious drugs with reduced development time and cost.

Keywords: bioanalysis, method development, drug discovery, drug development

Introduction

Determination of drugs in biological fluids or samples becoming important for the study of bioavailability, bioequivalence- Pharmacokinetic studies, quantitative evaluation of drugs, concentration, and their metabolites, new drug development, and pharmaceutical science. health care [1]. The reliability of analytical findings is important in forensic, clinical toxicology, and drug discovery. The method development and validation are much important for routine analytical methods [2]. The bioanalytical study of biological samples plays a major role in the Pharmacokinetic and Pharmacodynamics parameters include the measurement of drug concentration in the plasma, blood, or another biological matrix for selected time periods. Pharmacokinetic data provides information for future studies [3].

High-pressure liquid chromatography (HPLC) and Liquid Chromatography-Mass Spectroscopy (LC-MS/MS) is widely applied analytical techniques for the bioanalysis of biological samples because of its highly selective and high reliability. It is specially used in pharmaceutical, environmental, forensic, and clinical analysis. High-performance Liquid Chromatography is the primary technique for the analysis of non-volatile active pharmaceutical ingredients and impurities. LC-MS/MS method is widely used for bioanalysis because of its highest accuracy and sensitivity [4]. Validation parameters like sensitivity/Specificity, accuracy, precision, etc. are covered in bioanalytical method validation [5].

The application for new drugs can be divided into two stages: discovery and development. Drug discovery is included generating a hypothesis of the target receptor for a particular disease. It also includes screening in vitro and/or in vivo biological activities of the new drug candidates [6]. Drug development involves the assessment efficacy and toxicity of new drugs. The field of bioanalysis is a critical tool during the process of drug discovery and development. Bio analysis plays a vital role in Over the past few decades in various stages of discovery and development, including assays for important metabolites. Bioanalytical data which is generated during bioanalysis, was gives key evidence for drug discovery and pre-clinical programs which is important for phase clinical studies [7].

Bioanalysis

The term Bioanalysis is used for quantitative measurement of a compounds (Drugs) or their metabolites in biological fluids or samples like blood, plasma, serum, urine or tissue extracts [8]. For bioanalytical estimation, the key step are sample preparation and Analysis. Sample preparation is a technique used to clean up and concentrate a sample to improve its detection. The determination of drug concentrations in biological fluids give important data to understand the drug action and pharmacokinetics in animals and man. It is the essential feature of the drug discovery and development process. For the bioanalytical assays, there is a different sample extraction technique describe Protein precipitation, liquid-liquid extraction, and solid-phase extraction [09, 11].

Method Development and Validation

Method development is the created process for identified and quantified components present in a sample matrix. Analyte components are measured by several methods and it involves many considerations such as chemical properties of the analyte, concentration levels, sample matrix, cost of the analysis, speed of the analysis, quantitative or qualitative measurement. The process of method development includes sampling, sample preparation, separation, detection, and evaluation of the results [12].

In the part of method Validation, It is accepted during the course of a typical drug bioanalysis method will undergo modifications. Changes like the addition of a metabolite, lowering of the lower limit of quantification (LLOQ) [13]. There are Three different Levels or types for method validations. First is Full validation which is necessary when the bioanalytical method is developed by the first time for a new drug entity. Second is Partial validation which is necessary when bioanalytical method transfers between laboratories or analysts, change in Instrument, change in species within matrix or changes in a matrix within a species, change in analytical Methodology, and change in sample processing procedures. The third is Cross-validation which is necessary when two or more bioanalytical methods are used to generate data within the same study [14].

Validation Parameters

Specificity/selectivity: These are two interchangeable terms used in the bioanalytical validation. Specificity describes the ability of the bioanalytical method to produce a signal analyte interfering with other components. Whereas selectivity describes the ability of a method to differentiate analyte of interest from other analytes [15].

Accuracy: Accuracy of an analytical method describes that the true value or concentration of the analyte. Accuracy determined either as % bias or % nominal.

Precision: Precision is the closeness of individual measures of an analyte when the procedure is applied repeatedly to multiple aliquots of a single homogenous volume of the matrix [16, 17].

Quantitation Limit: The quantitation limit is the limit of individual analytical procedures is the lowest amount of analyte in a sample. It can be quantitatively determined with suitable precision and accuracy.

Detection Limit: The lowest amount of analyte that can be detected but not quantified (24. Detection limit should be represent the smallest detectable amount or concentration of the analyte of interest [18].

Ruggedness: Ruggedness of an analytical or bioanalytical method is the degree of reproducibility of the test results obtained after the analysis of the same samples under the variety of normal test conditions. The ruggedness of the method is studied by changing the analytical column of a similar type [19].

Recovery: The Recovery of a bioanalytical method or Bioanalysis measures the efficiency of the extraction procedure. Higher recovery indicates that the efficient extraction procedure, higher sensitivity, and accuracy of the bioanalytical method. It can be achieved by optimization of pH, extraction procedures, and the combination of extraction solvents.

Stability: It is the chemical stability of an analyte under specific conditions. The stability test is done for the detection of any degradation of the analyte during the period of sample collection, processing, storing, preparing, and analysis. There are different types of stability studies performed during the validation of the analytical method. For the determination of stability, the conditions are dependent on the nature of the analyte, the biological matrix, and the time period of storage before analysis [20].

Drug Discovery/ Design

In the discovery stage, the aim of bioanalysis is to provide reasonable values concentration of molecules that would be used for identification and discrimination lead components. Therefore, the aim of the analyst at this stage should be to develop a simple, rapid method for identification with significant throughput [21].

During the drug discovery, it becomes necessary to quantify active metabolite (s) in both animals and humans. The Drug discovery/design consists of the identification and characterization of new targets, synthesis, and screening of new lead molecules [22]. During this, the priority given to examine a large number of compounds is determined pharmacologically active compounds and they have most suitable for drug development. When the compound is obtained, it has required biological activity. a number of analogs or chemically similar compounds will be synthesized and tested. In the next screening stage, physicochemical properties such as solubility, lipophilic study, and stability are determined. These measurements are important for predicting protein binding, tissue distribution, and absorption in the gastrointestinal tract [23]. The clinical trials provide information on the drug molecule's absorption, distribution, metabolism, and elimination. For in vivo characterization of Pharmacokinetic and bioavailability, it is necessary to administer the drug to selected Species. blood samples are collected and the drug is quantified in the harvested plasma by a suitable bioanalytical method. The hepatic subcellular fractions predict the in vivo hepatic clearance. This is the part of initial screening of lead components in a optimization program. In the execration and metabolism of xenobiotics, liver is the play major role. In this process, most drugs are cleared from the body. These tests are collectively referred to as ADME characteristics (Absorption, Distribution, Metabolism, and Elimination). These studies provide information about the overall drug disposition and progress [24, 27].

Drug Development

Drug development is the process of bringing a new pharmaceutical drug to the market once a lead compound discovered. It includes preclinical research on microorganisms and animals. It is important for new dug applications is filing for regulatory status for an investigational new drug to initiate clinical trials on humans. It may include the step of obtaining regulatory approval with a new drug application to market the drug. Drug development focuses on the evaluation of safety, toxicity, and efficacy of new drug molecules. The efficiency of drugs also depends to a large degree on the biopharmaceutical and pharmacokinetic properties of the drug [28].

Pre-clinical Phase

Lead candidates or new chemical entities are compounds that emerge from the process of drug discovery. They have promising activity against a particular biological target, which is important against a particular disease. safety, toxicity, pharmacokinetics and metabolism of the lead component in humans is initially done. drug development assess all these parameters prior to human clinical trials. Drug development must include physicochemical properties of the lead component like its chemical makeup, stability, and solubility. Manufacturers synthesis this lead component or active ingredient on scale of milligrams to manufacturing on the kilogram and ton scale. After manufacturing of bulk condition, they further examine the product for suitability to package as capsules, tablets, aerosol, intramuscular, and subcutaneous injectable. The satisfaction of drug development is necessary to full fill the regulatory requirements of drug licensing authorities. These requirements contain the number of tests that determine the toxicities of lead components to first use in humans.

The information collected during pre-clinical testing submitted to drug regulatory authorities as a new drug application. After this approval, development moves to the clinical phase [29, 30].

Clinical phase

Clinical trials involve four steps/phase

- Phase I is done with healthy volunteers for the determination of safety and dosing.
- Phase II is done using small numbers of patients having a targeted particular disease with an initial reading of

efficacy of a new drug entity.

- Phase III is similar to phase I and II but quite large. In this stage pivotal try to determine safety and efficacy with large numbers of patients with the targeted disease. If safety and efficacy are proved according to regulatory body, clinical testing may stop at this step and the lead component ready for new drug application stage.
- In Phase IV, a post-market surveillance study is done with conditions attached by the Food and Drug Administration.

Most new drug entities are fail during drug development, because of either they have unacceptable toxicity or because they have not shown the intended effect during the clinical trials against targeted disease [31, 32].

Conclusion

In conclusion, the necessity of bioanalysis and bioanalytical methods are well understood and appreciated in the discovery and development of a new drug entities. It plays a major role during the preclinical and clinical stages of drug development. The sample preparation, method development, and validation are accepted for the reliability of the analytical results. The data of pharmacokinetics, toxicology study, and drug metabolism plays a fundamental role in pharmaceutical research and development. The bioanalytical Method validation with their parameters in bioanalysis is also taken into consideration in this article. In the above review, The development and validation characteristics for bioanalytical methodology have been discussed for improving the standard and acceptance in the area of drug discovery and development.

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