TO STUDY THE ROLE OF BIOMARKERS IN DRUG DEVELOPMENT

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By

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Declaration by Student

I hereby declare this dissertation tiltled Role of Biomarker in Drug development is the bonafide record of my original research work. I declare that it has not been submitted to any other university or instiution for the award of any degree or diploma . Information derived from the published or unpublished work of others has been duly acknowledged in the text .

Shabya Singh

20th June 2022

HEALTHARK

Date: 21st Jun 2022

Whom So Ever It May Concern

This is to certify that **Ms. Shabya Singh** in partial fulfillment of the requirements for the award of the degree of MBA (Hospital and Health Management) from the IIHMR University, Jaipur has successfully completed her internship at **Healthark Insights Wellness Solutions LLP** during **March 22, 2022 to June 19, 2022**.

Sincerely,
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HR Manager
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CERTIFICATE FROM FACULTY GUIDE AND SCHOOL DEAN

This is to certify that dissertation titled **To study the role of Biomarkers in drug development** is a record of the research work undertaken by Shabya Singh in partial fulfillment of the requirements for award of degree of MBA (Hospital &Health management) from IIHMR university , Jaipur under my guidance and supervision and her approach to research study has been sincere, scientific,and analytical.

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IIHMR university , Jaipur

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Date:

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Abbreviations-

WHO - World health organization
MHRA - Medicines and Healthcare Products Regulatory Agency
CTA - Clinical trial application
IND - Investigational new drug
NDA - New drug applications
BLA - Biologics license applications
MHRA - Medicines and Healthcare Products Regulatory Agency
HTS - High Throughput Screening
H2L - Hit to lead
LO - lead optimization
ADMET - Chemical absorption, distribution, metabolism, excretion, and toxicity
FAERS - FDA Adverse Event Reporting System
HTS - High Throughput Screening
ANDA - Abbreviated new drug application
IL - Interleukin

CHAPTER 1 - INTRODUCTION

The word "biomarker" was coined in 1980 and has been widely used since then. Near the end of the 1980s, the majority of environmental monitoring and research focused on chemical compounds that were considered harmful or toxic when found in modest amounts in water, sediments, and aquatic species. Chromatography, spectrophotometry, electrochemistry, and radiochemistry were employed to identify these chemical compounds. Despite the fact that these procedures were successful in clarifying the chemical makeup and amounts of the contaminants and compounds in question in the environment, the tests did not provide data on the impact of a particular pollutant or chemical on a live organism or ecosystem. Characterizing biomarkers was presented as a way to build a warning system to check on the health of a population or ecosystem before a pollutant or chemical wreaked havoc. Biomarkers can now be used and employed in the disciplines of human medicine and illness detection thanks to the advancement of biomarker studies.

A large subset of medical signals, i.e., objective indications of a patient's medical state that can be judged correctly and reproducibly from outside the patient, is referred to as a "biomarker," a blend of "biological marker." Medical signals are distinct from medical symptoms, which are limited to what patients perceive as evidence of health or illness.

There are several more precise definitions of biomarkers in the literature, which happily overlap quite a bit. The National Institutes of Health Biomarkers Definitions Working Group defined a biomarker as "a trait that is objectively measured and studied as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention" in 1998.

A joint venture on chemical safety, the International Program on Chemical Safety, led by the World Health Organization (WHO) and in coordination with the United Nations and the International Labor Organization, has defined a biomarker as “any substance, structure, or process that can be measured in the body or its products and influence or predict the incidence of outcome or disease”.

A biomarker is defined as "any substance, structure, or process that can be measured in the body or its products and influences or predicts the incidence of outcome or disease," according to the International Program on Chemical Safety, which is led by the World Health Organization (WHO) in collaboration with the United Nations and the International Labor Organization.

Biomarkers are simply the most objective, quantifiable medical signs that modern laboratory science allows us to measure reproducibly.

Medical signs have a long history of use in clinical practice—as long as medical practice itself and biomarkers are simply the most objective, quantifiable medical signs that modern laboratory science allows us to measure reproducibly.

The use of biomarkers in clinical research, particularly laboratory-measured biomarkers, is relatively new, and the best methodologies are still being discovered and refined. The main challenge at hand is finding the association between any given quantifiable biomarker and clinical endpoints that are relevant.

Biomarkers as Surrogate Endpoints

Biomarkers are regarded surrogate endpoints when utilized as outcomes in clinical studies; that is, they operate as substitutes or surrogates for clinically significant endpoints. However, not all biomarkers are intended to be surrogate endpoints, and not all biomarkers are intended to be surrogate endpoints. Surrogate endpoints are a select group of well-studied biomarkers with established clinical utility. A biomarker must have solid scientific proof (e.g., epidemiological, pharmacological, and/or pathophysiological) that it consistently and accurately predicts a clinical result, either a benefit or harm, to be deemed a surrogate endpoint.

In this sense, a surrogate endpoint is a biomarker that can be trusted to serve as a stand-in for, but not as a replacement of, a clinical endpoint.

Drug Development Process

All activities involved in changing a molecule from a drug candidate (the end-product of the discovery phase) to a product licensed for marketing by the competent regulatory authorities are referred to as drug development.

The journey will begin in a university laboratory, where researchers have used money from research agencies or the pharmaceutical industry to perform fundamental research in order to better understand disease processes at the cellular or molecular level. A better understanding of disease processes and pathways leads to the discovery of new treatment targets. This could be a critical gene or protein in the disease process that a new drug could target by blocking a crucial receptor, for example.

The following step is to verify that these compounds have an impact and are safe. Computerized models, cells, and animals are used to conduct safety and efficacy testing before any molecules are given to humans. Around half of the candidates make it past this stage of pre-clinical testing, and the remaining five to ten molecules are now ready to be tested in people for the first time. Before any human testing may take place in the UK, the Medicines and Healthcare Products Regulatory Agency (MHRA) must approve it. The company will submit a clinical trial application (CTA), which will be assessed by medical and scientific experts to determine whether enough exploratory research has been done to allow human testing to proceed.

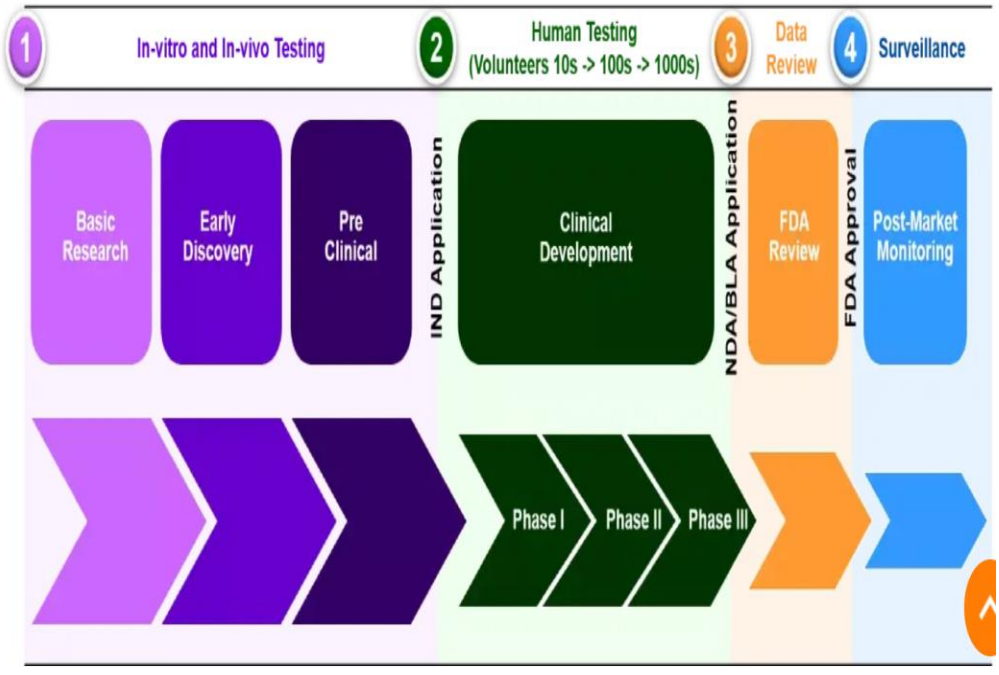

Fig 1.1 - Flowchart showing the different phases of drug development

The complexity of drug development has increased dramatically in the last 40 years, necessitating a preclinical phase, an investigational new drug (IND) application, and extensive clinical trials before getting FDA approval for marketing. Before being accepted, new drug applications (NDAs) and biologics license applications (BLAs) are normally thoroughly assessed, and drug performance is then resubmitted to regulatory agencies for post-marketing study. The major goal is to provide more efficient and safer therapies to patients as quickly as possible after a complete medical examination.

There are five critical steps in the U.S. FDA drug development process, including many phases and stages within each of them. The phases of drug development are –

- Step 1: Discovery and Development
- Step 2: Preclinical Research
- Step 3: Clinical Development
- Step 4: FDA Review
- Step 5: FDA Post-Market Safety Monitoring

Discovery and Development

Drug discovery research is used to create new medications. Traditionally, drug research, design, and development have relied on discovering active ingredients in traditional treatments or by chance. Chemical libraries containing small molecules, natural products, or plant extracts were then analysed using traditional pharmacology to discover those with medicinal effects. Reverse pharmacology has employed modern testing to uncover solutions for existing disorders since the sequencing of human DNA.

Target Identification And Validation

A target is a gene or protein (therapeutic agent) that has a significant impact on disease. Scientists and researchers then record the therapeutic characteristics of the target. Targets for drugs must be effective, safe, and useful, as well as meet clinical and commercial requirements.

To validate targets, researchers use modern tools and techniques such as disease association, bioactive substances, cell-based models, protein interactions, signalling pathways analysis, gene functional analysis, in vitro genetic manipulation, antibodies, and chemical genomics. For example, the Sanger Whole Genome CRISPER library and the Duolink PLA are excellent resources for finding drug development targets.

Hit Discovery Process

Following target validation, compound screening assays are developed.

Assay Development And Screening

The development of assays is an important part of the drug discovery process. Assays are test systems that assess the new drug candidate's effects at the cellular, molecular, and biochemical levels.

High Throughput Screening

High Throughput Screening (HTS) uses robotics, data processing/control software, liquid handling equipment, and sensitive detectors to run millions of pharmacological, chemical, and genetic tests in a matter of minutes, saving scientists hours of tedious testing. HTS is a technique for detecting active chemicals, genes, or antibodies that alter human molecules.

Hit to Lead

Small molecule hits from an HTS are reviewed and improved in a restricted way into lead compounds in the Hit to Lead (H2L) process. The lead optimization procedure is then applied to these compounds.

Lead Optimization

The lead compounds discovered in the H2L method are produced and tweaked in the lead optimization (LO) process to boost potency and reduce negative effects. Lead optimization designs the drug candidate by conducting experimental testing utilising animal efficacy models and ADMET tools.

Active Pharmaceutical Ingredients

APIs (active pharmaceutical ingredients) are physiologically active chemicals in a medication candidate that have a specific impact. The API or APIs, as well as excipients, make up all medications. Excipients are inactive ingredients that help the medicine enter the human body. HP APIs (High Potency Active Pharmaceutical Ingredients) are compounds that work at substantially lower doses than normal APIs. They're categorised by toxicity, pharmacological potency, and occupational exposure limits (OELs), and they're employed in multi-step drug development.

Pre- clinical trials

Following the discovery of a lead molecule, the preclinical phase of drug development begins with in vivo research to determine the drug's efficacy and safety. The following is what researchers discovered about the drug:

- Absorption, distribution, metabolization, and excretion information
- Potential benefits and mechanisms of action
- Best dosage, and administration route
- Side effects/adverse events
- Effects on gender, race, or ethnicity groups
- Interaction with other treatments
- Effectiveness compared to similar drugs

Preclinical Trials test the new drug on non-human subjects for efficacy, toxicity, and pharmacokinetic (PK) information. These trials are conducted by scientists in vitro and in vivo with unrestricted dosages.

Absorption, Distribution, Disposition, Metabolism, & Excretion

ADME stands for Absorption, Distribution, Disposition, Metabolism, and Excretion, and it is a pharmacokinetic (PK) procedure for determining how a new medicine affects the body. Each effect is described mathematically in ADME.

Proof Of Principle / Proof Of Concept

Studies that are effective in preclinical trials and early safety testing are known as proof of principle. In drug discovery and development programmes, the terms Proof of Concept and Proof of Principle are almost interchangeable. Following the completion of successful PoP/PoC investigations, the programme is advanced to Phase II dosage trials.

In Vivo, In Vitro, And Ex Vivo Assays

These three types of investigations are carried out on entire, living species or cells, such as animals and people, or non-living organisms or tissue extracts. The development of new medications utilizing mouse, rat, and dog models are examples of in vivo preclinical research. In vitro research is carried out in a laboratory. Animal cells or tissues from a non-living animal are used in ex vivo research. Finding efficient cancer therapy agents, measuring tissue attributes (physical, thermal, electrical, and visual), and realistic modelling for new surgical methods are all examples of ex vivo research experiments. A cell is always employed as the basis for small explant cultures in an ex vivo test, which provide a dynamic, regulated, and sterile environment.

In Silico Assays

In silico assays are computer-based or computer-simulated test systems or biological studies. With advances in computational power and behavioural understanding of molecular dynamics and cell biology, these are predicted to become more popular.

Drug Delivery

Oral, topical, membrane, intravenous, and inhalation are some of the new medication delivery techniques. Drug delivery systems are used to distribute new medications in a regulated or targeted manner. Physiological barriers in the body of an animal or a human may prohibit medications from reaching their intended target or from releasing when they should. The idea is to keep the medicine effective while preventing it from interacting with healthy tissues.

- Oral: Patients benefit from oral drug delivery because it is dependable, cost-effective, and convenient. Oral drug administration may not be able to track precise amounts to the desired location, but it is great for preventative immunizations and dietary programmes. Patients must be aware throughout administration to avoid delayed action, stomach enzyme breakdown, absorption discrepancies, or patients with gastrointestinal difficulties or distress.

- Topical: Topical drug delivery refers to the use of ointments, creams, lotions, or transdermal patches to deliver a medicine to the body through absorption. Topical distribution is better for skin or muscle disorders, and patients prefer it because it is non-invasive and allows them to self-administer the medicine.

- Parenteral (IM, SC or LP Membrane): Intramuscular (IM), intraperitoneal (IP), and subcutaneous (SC) medication delivery are all examples of parenteral drug delivery (SC). It's frequently utilised on unconscious patients since it avoids difficult-to-cross epithelial barriers.

- Parenteral (Intravenous): Intravenous injection is one of the quickest ways to absorb drugs. IV injection ensures that all of the medications are absorbed into the bloodstream, making it more successful than IM, SC, or LP membrane approaches.

- Parenteral (Inhalation): The medicine is rapidly absorbed into the mucosal lungs, nasal passages, throat, or mouth with inhalation drug delivery. The difficulty in providing the optimal dosage due to limited mucosal surface areas, as well as patient discomfort, are all issues with inhalation delivery. Fine drug powders or macromolecular drug solutions are used in pulmonary inhalation drug delivery. Because lung fluids resemble blood, they can easily collect and transfer tiny particles into the bloodstream.

Formulation Optimization & Improving Bioavailability

Formulation optimization is ongoing throughout pre-clinical and clinical stages. It ensures drugs are delivered to the proper place at the right time and in the right concentration.

Clinical Drug Development Process

Researchers go on to clinical drug development when preclinical research is completed, which includes clinical trials and volunteer studies to fine-tune the medicine for human use.

FDA Review

The new drug is sent to the FDA for a thorough review once it has been designed for optimal efficacy and safety, as well as the findings of clinical research. At this point, the FDA reviews the medicine application submitted by the drug development company and decides whether to approve or reject it.

Regulatory Approval Timeline

Depending on the applications and requirement for patients, the new medication regulatory approval timeframe may be regular, fast track, breakthrough, accelerated approval, or priority

review. The clearance process could take up to a year if standard or priority review is required. Approvals on a fast track, breakthrough, or accelerated basis may be granted sooner.

IND Application

Before beginning clinical studies, IND applications must be submitted to the FDA. Developers may begin clinical trials if clinical trials are ready to begin and the FDA has not responded unfavourably to the medicine.

NDA / ANDA / BLA Applications

Clinical trials demonstrate drug safety and efficacy, and an NDA abbreviated new drug application (ANDA) or BLA is submitted to the FDA. The FDA examines study results before deciding whether or not to grant permission. Before making a final choice, more research or an expert advisory panel may be required.

Orphan Drug

An orphan medicine is one that is designed to cure an illness that is so uncommon that financial backers are unwilling to develop it under normal marketing circumstances. It's possible that these drugs will not be approved fast or at all.

Accelerated Approval

New medications may be approved more quickly if there is strong evidence of a positive impact on a surrogate endpoint rather than proof of influence on the drug's genuine clinical benefits. The medication's expedited approval implies it can help cure serious or life-threatening diseases.

Reasons For Drug Failure

New drug applications may fail for a variety of reasons, including toxicity, efficacy, PH properties, bioavailability, or inadequate drug performance.

- Toxicity: If a novel drug's toxicity is too high in human or animal patients, it may be rejected due to safety concerns about its use after manufacture.
- Efficacy: The FDA may reject a novel medicine if its efficacy is insufficient or the evidence is inconclusive.
- PK Properties or Bioavailability: A drug's PK features, such as limited water solubility or high first-pass metabolism, can also cause it to fail FDA assessment. Inadequate action duration and unforeseen human drug interactions are two PK explanations of pharmacological failure.
- Inadequate Drug Performance: The FDA may reject the application in favour of a formulation that performs better if the new medicine achieves the desired function but only to a limited extent.

Post-Market Monitoring

Following drug approval and production, the FDA mandates drug companies to use the FDA Adverse Event Reporting System (FAERS) database to track the medicine's safety. FAERS assists the FDA in the implementation of its post-market safety surveillance programme. Manufacturers, health experts, and consumers can report concerns with licenced drugs through this service.

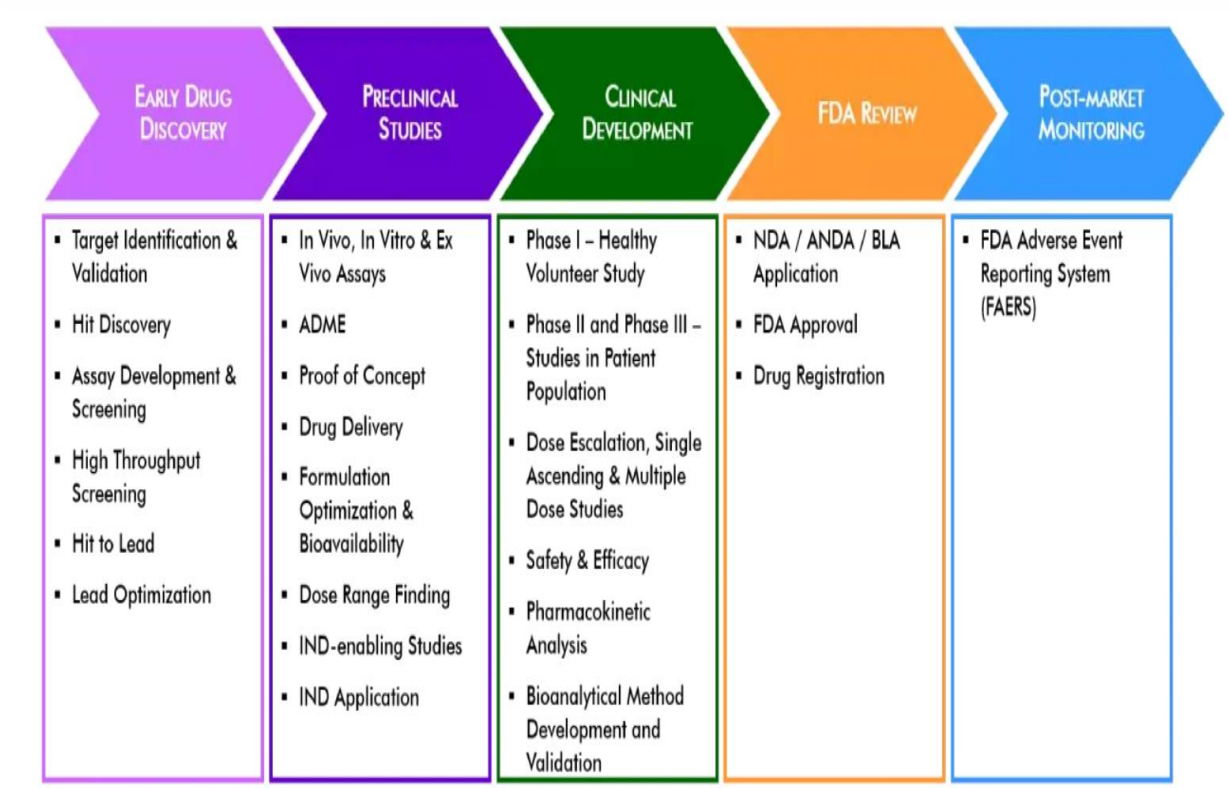

Figure 1.2 – The table shows the different phases of drug development

Research Question-

What are the roles of Biomarkers in the drug development process?

Research Objectives-

- To understand the role of biomarkers in the drug development process
- To analyze the types of biomarkers used in the drug development
- To understand the approval process by FDA for biomarkers to be used in the drug development

CHAPTER 2 - Literature review

Table 2.1- literature review

Author (years)	Study	Research Design	Salient features
Gromova, M., Vaggelas, A., Dallmann, G. and Seimetz, D., 2022. *Biomarkers: Opportunities and Challenges for Drug Development in the Current Regulatory Landscape*.	Biomarkers: Opportunities & Challenges for drug development in the current regulatory landscape	Descriptive study	Utilization of biomarkers has a potential to make drug discovery, development , and approval processes more efficient

Kraus, V., Burnett, B., Coindreau, J., Cottrell, S., Eyre, D., Gendreau, M., Gardiner, J., Garnero, P., Hardin, J., Henrotin, Y., Heinegård, D., Ko, A., Lohmander, L., Matthews, G., Menetski, J., Moskowitz, R., Persiani, S., Poole, A., Rousseau, J. and Todman, M., 2022. *Application of biomarkers in the development of drugs intended for the treatment of osteoarthritis*.	Application of biomarkers in the development of drugs intended for the treatment of osteoarthritis	Descriptive study	The biomarkers that are likely to have the earliest beneficial impact on clinical trials fall into two general categories, those that will allow targeting of subjects most likely to either respond and/or progress (prognostic value) within a reasonable and manageable time frame for a clinical study (for

			instance within 1–2 years for an OA trial), and those that provide early feedback for preclinical decision-making and for trial organizers that a drug is having the desired biochemical effect

Taylor & Francis. 2022. *Challenges with biomarkers in cancer drug discovery and development*.	Challenges with biomarkers in cancer drug discovery and development	Descriptive Study	The challenges of biomarkers in drug discovery and development may be considered at three different levels: (1) identifying the right target of the drug as biomarker; (2) validation of the biomarker test in question, and (3) development of matched biomarker-

			driven treatments
Serelli-Lee, V., Ito, K., Koibuchi, A., Tanigawa, T., Ueno, T. and Matsushima, N., 2022. *A State-of-the-Art Roadmap for Biomarker-Driven Drug Development in the Era of Personalized Therapies* (2022)	A State-of-the-Art Roadmap for Biomarker-Driven Drug Development in the Era of Personalized Therapies	Descriptive study	Biomarker-driven drug development embeds our knowledge of disease etiology into clinical trial designs with the aim of de-risking the process and improving success rates

Frank, R. and Hargreaves, R., 2022. *Clinical biomarkers in drug discovery and development*. (2018)	Clinical biomarkers in drug discovery and development	Descriptive Study	Clinically useful biomarkers are required to inform regulatory and therapeutic decision making regarding candidate drugs and their indications in order to help bring new medicines to the right patients faster than they are today.

CHAPTER 3- Study Design and Methodology

STUDY DESIGN-

This study employs systematic review study design. This study was done by collecting and analyzing relevant literature from various sources , based on "Preferred Reporting item for systematic review and Meta-analysis (PRISMA) guidelines. A method of systematic review was selected to ensure a reproducible approach to structure a critical synthesis of existing and current evidence".

The study firstly focus on extraction, interpretation and evaluation of those research results that address the formulated research question and align with the study objectives.

DATA SOURCES AND SEARCH STRATEGY-

The information was gathered in accordance with the Preferred Reporting Items for systematic Review . I have conducted a comprehensive literature search in Google and three electronic database: PubMed, Science Direct and Google Scholar. The articles between January 2002 to June 2022 , each database was searched for published articles. These dates were chosen to ensure that all of the data , from the oldest to the most recent was gathered. The Reference lists of each article included in this study were further checked for any relevant articles that were further checked for any relevant articles that were not found in the database search. Lastly we searched the bibliographies references of relevant articles to find the additional studies that may fit this review.

The search is a very sensitive step ,would need to define keywords . The search strategy retrieves the studies that need to be analyzed for inclusion and exclusion criteria .

Selection Criteria –

a) Article published between 2002 to 2022
b) Published as peer reviewed article in English language
c) Reported biomarker role in drug development
d) Included FDA qualification process for biomarker as clinical end point
e) Biomarker role in any disease related drug development

Exclusion criteria –

a) Article published in other language than English
b) Article published before 2002
c) Articles that dealt with biomarker but not in drug development
d) Article that didn't contain much information about biomarker as clinical end
e) Duplicates were not included

Keywords used for this research were " Biomarker", " Biomarker as clinical end point" , " Biomarker in drug development" , " Drug development phase" , " Surrogate end point" , " Biomarker in disease drug development" , "Pre clinical biomarker".

Study Selection – A systematic search of research publication on scientific database with key words such as Biomarker", " Biomarker as clinical end point" , " Biomarker in drug development" , " Drug development phase" , " Surrogate end point" , " Biomarker in disease drug development" , "Pre clinical biomarker".

Relevant material were chosen in accordance with inclusion criteria by auditing and identifying important articles using titles and keywords. The articles were screened on basis of title ,abstract and then full text and research papers were shortlisted in the previous phases were reexamined for the review. Cross referenced material was searched and documented for a thorough analysis.

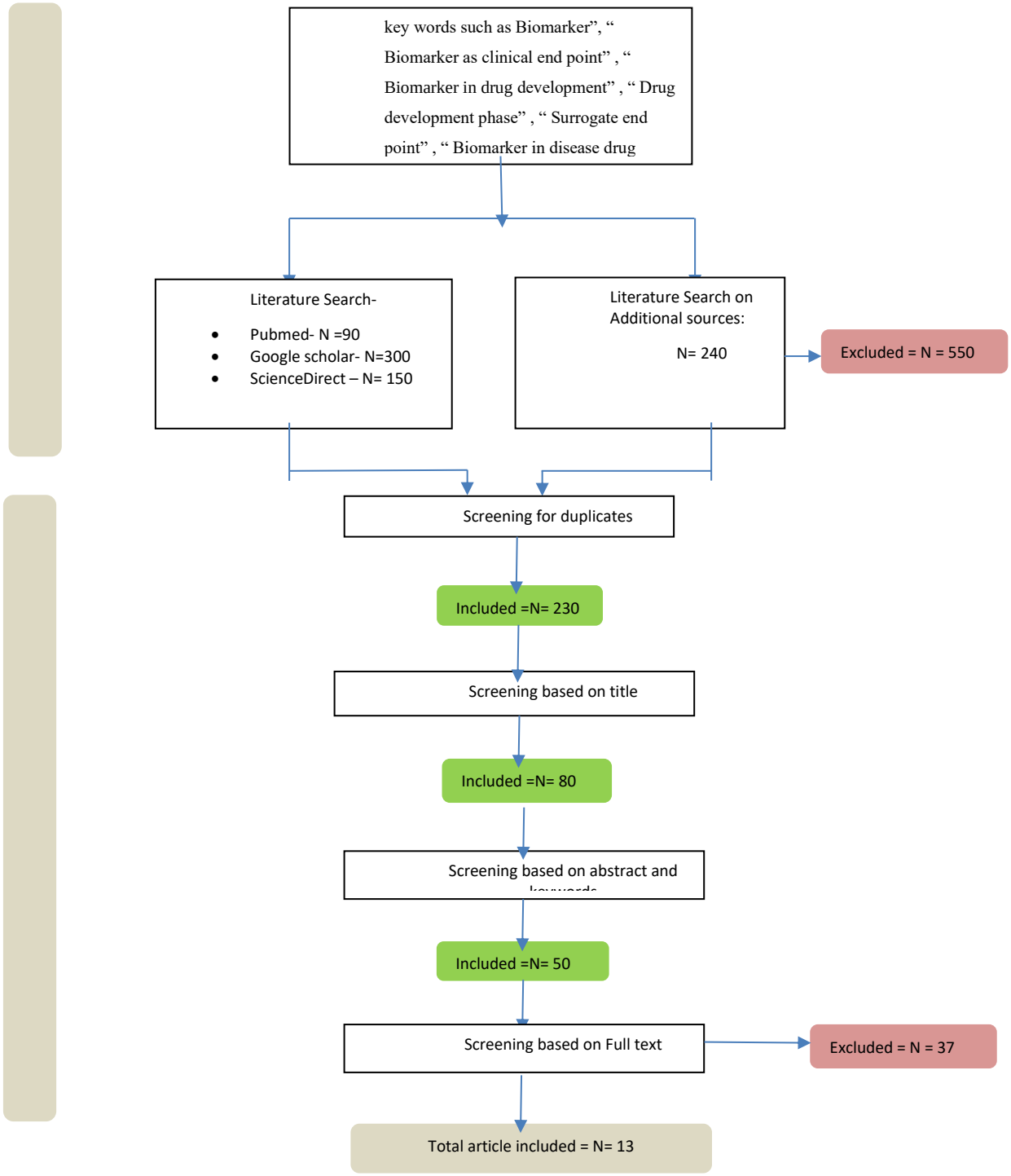

Fig 3.1 Flowchart of methodology

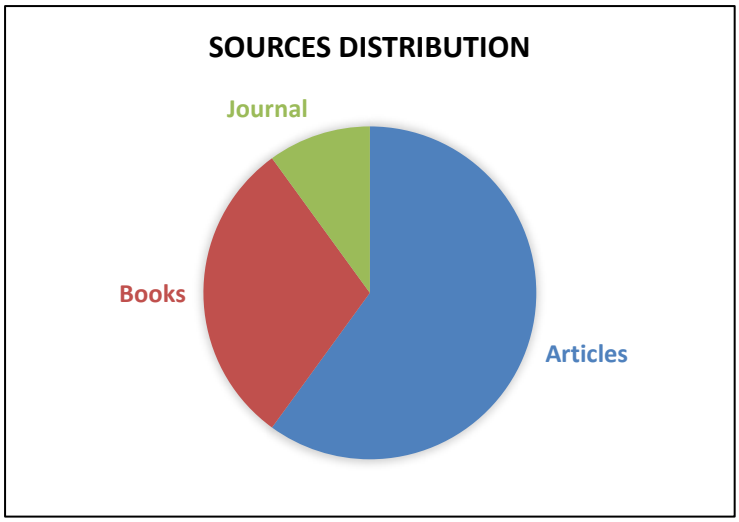

FIG 3.2- Chart showing sources distribution

CHAPTER 4 - RESULTS

Biomarkers are vital in the practice of medicine and all phases of drug research because they provide information on patient status in the clinical setting as well as critical information on pharmacodynamic activity, effectiveness, and safety. Biomarkers may even be employed as surrogate endpoints for therapeutic approval rather than a direct evaluation of a clinical endpoint in specific situations. Because of the increased usage of biomarkers, significant attempts have been made to standardize biomarker nomenclature, assessment, and validation in order to accelerate biomarker research and integration into medication development. Furthermore, recent advances in instrumentation and data computation have changed the way biomarker discovery and development are done.

To take advantage of the significant information biomarkers can provide, biomarker analysis must be strategically integrated into all stages of drug development, from early discovery to late clinical drug development, as well as post-market surveillance. Biomarker implementation, when done correctly, allows for more informed decision-making and better study design. Pharmacokinetic (PK) and pharmacodynamic (PD) investigations employing biomarkers can assist reveal the drug's mechanism of action, as well as directing clinical trial dose selection, especially during the preclinical research stages.

To improve diagnosis, monitor medication activity and therapy response, and lead the development of safer and focused therapeutics for diverse chronic diseases, robust and validated biomarkers are required. While numerous types of biomarkers have had an impact on medication discovery and development, discovering and verifying disease-specific biomarkers has proven to be a difficult task. Despite the fact that numerous obstacles remain, current attempts to uncover and develop illness-related biomarkers will aid in optimal decision-making throughout the medication development process and improve our understanding of disease processes. Furthermore, the translation of preclinical biomarkers into the clinic would pave the path for patients, healthcare providers, and the biopharmaceutical sector to benefit from tailored medicines across complicated disease areas.

Biomarkers are useful tools not only for basic and applied research and clinical applications, but also for patient stratification because they can be used to predict molecular and phenotypic changes as well as assess the efficacy and safety of therapeutic interventions in pharmacogenetically heterogeneous individuals.

Molecular, imaging, and psychometric approaches used in preclinical and clinical studies have had limited success, despite significant efforts in the development of validated biomarkers to expedite clinical trials, reduce development costs, develop precision medicine and targeted therapies, and stratify patients.

The lack of a cohesive workflow combining clinical end point biomarker discovery efforts with well-established procedures for validation has further hampered biomarker contribution to clinical diagnosis.

In addition, poor clinical trial outcomes have been attributed to a lack of understanding of immunological and tissue specific target modulation in clinical samples, as well as a thorough understanding of target modulation in preclinical in vivo disease models. This is owing, in part, to the small number of patient samples and, as a result, the clinical studies' statistical power. A systematic workflow procedure encompassing candidate biomarker development, verification, assay validation, standardisation, certification, and finally implementation as a companion diagnostic should be followed to overcome these limitations. Furthermore, better coordination between experimental, bioinformatics, and clinical tactics, as well as the participation of various stakeholders in the biomarker development process, are critical. This will necessitate a large amount of collaboration between academics, biopharmaceutical companies, and regulatory agencies.

Use of biomarkers in preclinical and clinical studies

To evaluate activity in animal models, link animal and human pharmacology via proof-of-mechanism or other observations, evaluate safety in animal models, and assess human safety early in development, biomarkers must be used from pre-discovery to late clinical drug development . Furthermore, each stage of drug development has its own set of biomarkers, some of which may or may not be applicable to subsequent phases.

Biomarkers must be reliable, repeatable, and accessible in order to be useful (i.e., present in body fluids and measurable). To identify real positives from false negatives, a biomarker must be sensitive and specific. They should show not just the presence of the disease, but also how it responds to time and treatment. Most significantly, a biomarker's detection should be clinically meaningful and give clinical advantages to the patient (e.g., increased survival and/or quality of life).

Serum chemistries, cell surface protein expression, drug PK/PD measures, drug metabolizing isoenzyme phenotype, serum transaminases, genomic expression profile, drug distribution, and receptor occupancy by imaging are examples of biomarkers in preclinical investigations.

The evaluation of dose-response and optimal regimen for desired pharmacologic action, safety indicators to identify dose-response for toxicity, and determination of the function of variances in

metabolism34 are all examples of how biomarkers are used in late drug development. Once confirmed, a biomarker can be utilised in dose selection for phase II/III clinical trials, as well as to distinguish candidate drugs from other compounds, based on the biomarker's PK/PD relationship and anticipated therapeutic index. The biomarkers that quantify the PK/PD connection also provide useful input for determining whether the mechanism is applicable to clinical trials or not. Patients can also be stratified by disease kind or therapy response using specific biomarkers.

This strategy was effectively used with the drugs trastuzumab (Herceptin) and imatinib (Gleevec) to stratify patients6 based on their pharmacogenetic polymorphisms.
Biomarkers have been used in clinical investigations for diagnosis, as a tool for disease staging, as indications of disease status, and to predict and/or monitor clinical response to therapeutic interventions (e.g., electrocardiogram, PET brain image, serum chemistries, auto-antigens in blood, bone densitometric measurement, pulmonary function test, neonatal Apgar score). Psychometric testing, pain scales, imaging investigations, culture status (antimicrobials), pulmonary function tests, serum chemistries, and EKG are all biomarkers employed in late clinical development. Furthermore, while diagnostics identify patients at a single point in time, biomarkers have the ability to give prognostic information about a patient's future health condition.

Biomarkers are often cheaper and easier to measure than ‘true’ endpoints. For example, it is easier to measure a patient's blood pressure than to use echocardiography to measure left ventricular function, and it is much easier to do echocardiography than to measure morbidity and mortality from hypertension in the long term. Biomarkers can also be measured more quickly and earlier.

Table 4.1- Types of Biomarkers

Types of biomarker(6)	Description	Examples
Predictors	These are the disease associated biomarkers	VEGF and Fibronectin can

	that can indicate whether there is a threat of disease and measure patient's responsiveness to treatment	predict clinical response to interleukin-2 (IL-2) therapy of patients with metastatic melanoma and renal cell carcinoma and high levels of these proteins correlates with lack of clinical response to IL-2 therapy and decreased overall survival of patients. Serum VEGF and fibronectin are easily measured predictor biomarkers, therefore, could serve to exclude patients unlikely to respond to IL-2 therapy Carbonic anhydrase IX –G250MN (CAIX) expression can predict responses to IL-2 in renal cell carcinoma and high CAIX staining of primary renal cell carcinoma tumors correlates with

		a significantly better survival rate after IL-2 therapy
Diagnostic	These are the biomarkers used for diagnosis of an existing disease and staging of disease biomarkers. Diagnostic biomarkers can also be used to stratify patients by disease type and response to treatment. Biomarkers that can reveal the status of the target (*e.g.*, at the level of receptor expression, genetic polymorphism, gene expression, somatic mutation, etc) in individual patients may provide significant predictive value for treatment response	Cardiac troponin for the diagnosis of myocardial infarction and staging of disease biomarkers such as, brain natriuretic peptide for congestive heart failure and measurements of carcinoembryonic antigen-125 for various cancers. Autoantibodies such as anti-cylic citrullinated peptide (CCP) are detected in patients with RA. Antinuclear antibodies and anti-Ro (SSA) antibodies are detected in patients with Sjogren's syndrome and other systemic autoimmune diseases

Prognostic	These biomarker predicts the future outcome of a disease in an individual and can predicts overall survival rate and clinical benefits from therapeutics interventions These biomarkers are often used to establish inclusion criteria for a clinical trial or for defining a patients population	The immunological data (the type , density, and location of immune cells within tumor samples) is a better predictor of patients survival than histopathological methods currently used to stage colorectal cancer. The presence of intratumoral T cells collaterals with improved progression free survival among patients with advanced ovarian carcinoma Over expression of Her -2/neu in breast cancer or EGFR expression in colorectal cancer indicate poor prognosis
Mechanistic	These biomarkers may inform and	Sequential gene profiling of basal cell

	validate the mechanism(s) of action of a particular treatment	carcinomas treated with imiquimod (a Toll-like receptor-7 agonist capable of inducing complete clearance of basal cell carcinoma (BCC) and other cutaneous malignancies) in a placebo-controlled study has revealed the early transcriptional events induced by imiquimod and provided insights about immunological events preceding acute tissue and/or tumor rejection
Pharmacodynamics	These biomarkers are signatures a certain pharmacological response to an active compound or biomarkers for monitoring the clinical response to an active compound or intervention	Hemoglobin A1C for antidiabetic treatment ,which of special interest in dose optimization studies and is used in decision making in early drug development DCEMRI(Dynamic contrast enhanced magnetic resonance

	Linking biomarker and mechanistic PK/PD models are critical to understand the relationship between dose and biomarker response . Pre clinical PK-PD models have to be validated by predicting dose efficacy relationship in clinical trial , knowing the extent and duration of target exposure and modulation is necessary to achieve effects during clinical trials. This is often achieved by preclinical PK/PD modelling by measuring plasma exposure, target occupancy and PD endpoint for target activities . To show target engagement	imaging) for the detection of changes in the permeability of tumor vasculature, FDG PET for detection of changes in Glucose metabolism and FLT PET for detection of changes in DNA synthesis

	biomarker need to be very close to the target	
Surrogate end point	These may yield information on the clinical benefit/survival at earlier stages as opposed to prolonged disease-free or overall survival analysis [1]. If validated, a surrogate biomarker may serve as a primary end point in a registration study	For example, if a treatment affects the biomarker, the biomarker will serve as a surrogate end point for evaluating clinical benefit (*e.g.*, Hemoglobin A1C) . Response rate or progression free survival in oncology or bone mineral density in osteoporosis prevention and treatment. Another example is the HIV viral load as a measure of probable clinical benefit with later confirmation of a mortality benefit

Safety	These biomarkers can predict at the time of patients's enrollment her/his likelihood to suffer major toxicity from a specific therapy Safety biomarkers measures drug induced organ(kidney , liver , etc) injuries	Albumin , total protein , B2 – microglobulin ,cystatin C , Kim -1 , and TFF3 have been selected from earlier studies as biomarker of drug induced kidney injuries.

Regardless of their definition and classification, biomarkers should be developed and employed in a way that is "fit-for-purpose," or related to the use for which they will be used. The biomarker strategy needs to be incorporated into many stages of drug development, from early discovery to late clinical drug development, because biomarkers can provide useful information during the drug development and decision-making process.

Linking biomarkers with mechanistic pharmacokinetic and pharmacodynamic (PK/PD) models, in particular in preclinical studies, can reveal the underlying mechanism of drug action, the relationship between dose and biomarker response, the impact of dose escalation studies on the time course of response, measure the duration of response and lag between plasma drug concentration and response, measure the effect of repeated doses (toleration, sensitization, reflex mechanisms), and range of doses.

Since optimal dosage selection may be the most crucial output from early clinical development, biomarkers can be used in dose selection for phase II/III trials based on biomarker PK/PD and anticipated therapeutic index. Additionally, by demonstrating a crucial reaction, biomarkers can assist in differentiating a candidate medicine from other substances (safety, efficacy).

Qualification process by FDA for Biomarkers

Various stages of drug development can lead to the discovery and creation of a wide variety of biomarkers. Depending on the scientific data that is currently available on the marker, FDA pharmacogenomics guidance defines plausible, likely, and known valid biomarker categories. For instance, a clinical end point biomarker is a characteristic or variable that indicates how a patient feels, performs, or survives, whereas a surrogate end point biomarker is designed to work in place of a clinical end point (e.g., regulatory decisions). As a result, classification as a "surrogate end point" necessitates regulatory authority registration. Only a few number of indicators can serve as substitute endpoints; for example, the FDA has approved the use of HIV 'viral' load as a substitute for AIDS. Based on epidemiologic, pharmacological, pathophysiologic, or other scientific evidence, a surrogate end point is intended to predict the clinical result (benefit or damage, or lack of benefit). Even while past debates on the use of biomarkers in drug development focused on using them as surrogate end points for effectiveness, most applications of new biomarkers may not need surrogacy (e.g., prediction of drug safety)

A qualified biomarker has gone through a rigorous regulatory process to ensure that we can rely on it to have a specified interpretation and application in medical product development and regulatory assessment, within the declared context of use (COU). It is crucial to remember that a biomarker, not the way it was measured, qualifies.

The Biomarker Qualification Program collaborates with the requestor(s) to direct the development of the biomarker as part of the qualification process. In working groups or consortia, a number of interested parties frequently collaborate to produce a biomarker for qualifying. Shared resources are possible with this method, which also lightens the workload for each collaborator. Because of this, even with limited funding, interested people might join a DDT development effort..

To qualify a biomarker for regulatory use under the 21st Century Cures Act, a three-stage submission process is required. FDA decides whether to accept or reject submissions that are full and of high quality.

The requestor is informed of this choice in writing, along with comments and suggestions for more biomarker research. Requestors have the chance to cooperate with CDER throughout this process to address various areas of the biomarker's development..

A list of qualified biomarkers as well as a summary of the requestor's qualification submissions, FDA's formal written decisions, and other requirements for transparency are included in the 21st Century Cures Act.

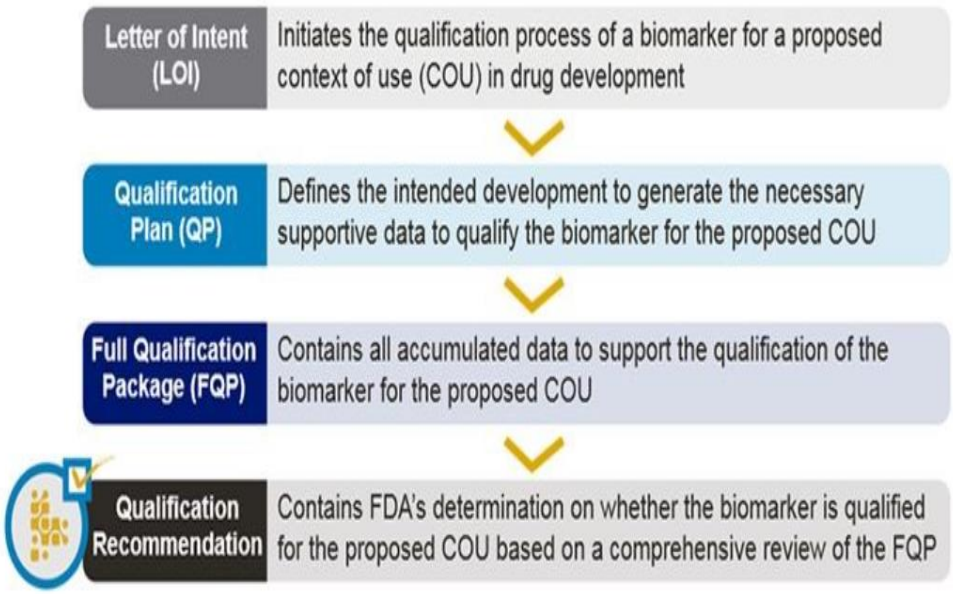

Fig 4.1 – Flowchart shows the steps required for qualification of Biomarkers by FDA

Stage 1: Letter of Intent (LOI)

The LOI is submitted by the requestor using the suggested format. Initial details on the proposed biomarker are provided in the LOI, including:

- Drug development need the biomarker is intended to address
- Biomarker information
- Context of Use (COU)
- Information on how the biomarker will be measured

The FDA will analyse the LOI submission to determine the proposal's general viability in light of existing scientific knowledge as well as the potential value of the proposed biomarker to meet an

unmet medication development need. The requestor may submit a Qualification Plan if FDA accepts the LOI..

Stage 2: Qualification Plan (QP)

The QP is a comprehensive proposal that details the planned biomarker development strategy in order to provide the essential data to support the biomarker's eligibility for the proposed COU in drug development. It outlines the information already available to support the COU, identifies knowledge gaps, and suggests ways to fill them. The QP should provide comprehensive details regarding the analytical approach and performance traits.

FDA will give the requestor instructions for the Full Qualification Package if it accepts the QP.

Stage 3: Full Qualification Package (FQP)

The FDA's determination about the biomarker and COU's qualification will be based in part on the FQP, which is a thorough compilation of supporting data. It includes all of the accumulated data, arranged by subject. Based on the FQP, FDA will make a final determination as to whether the biomarker is qualified.

Upon qualification, the biomarker may be utilised in any CDER drug development programme to support the regulatory approval of a novel medicine under the COU for which it is qualified.

Current status, challenges and future perspectives

The issue of physiologically significant splice variants that occur in individual cell populations limits the applicability of DNA microarray investigations, despite the fact that they have significantly advanced the research of global gene expression profiling of autoimmunity. Another issue is that despite being activated at the transcriptional level, a sizable number of mRNAs do not translation into proteins.

The current state of technology, the lack of high-quality reagents like monoclonal antibodies and informatics tools, as well as the challenge of identifying low-abundance markers, are the main constraints on proteomics. Because they are a bottom-up targeted approach with prior knowledge of target proteins, array and FACS platforms are limited in their ability to study systemic autoimmune diseases compared to unbiased proteomic approaches, which have had limited

success in this area. Due to the limitations of current arrays, antibodies, etc., it is impossible to predict which significant components may be overlooked.

It is necessary to develop new strategies for bioinformatics and assay platforms as well as the integration of multi-omics platforms in order to examine several datasets simultaneously, including platforms for miRNA, protein, and gene expression, as well as FACS. In addition to identifying a large number of valuable biomarkers, the investigation of systemic autoimmune illnesses using multi-omics platforms and multiplexed techniques will also highlight topics for future research and development.

Additionally, there is growing agreement that more than one biomarker is necessary for making reliable conclusions about efficacy or safety. Early detection of these biomarkers is crucial for making go/no-go judgments and at crucial points in the drug development process as a result. In this situation, a major contribution to early clinical development could be made by using multiplexed technology and a multi-omics strategy.

For the successful supply of "fit for purpose" biomarkers, it is therefore essential to comprehend the benefits of different techniques and technologies as well as their drawbacks and how they might be applied to the finding of particular biomarkers.

The robustness and reproducibility of assays is another issue in the field. This procedure should be made better by increasing the sample size and the number of replicates, as well as by including a group of bioinformatics and biostatistics scientists in the study from the design of the clinical investigation to the data analysis.

Another barrier in the field is the limited or constrained access to disease-associated tissues. Peripheral blood is now routinely used to identify DNA, RNA, protein, and other small molecule biomarkers, mostly in immunological disorders. For instance, biological characteristics of immune system cell populations are now represented by surrogates, such as global gene expression profiling.

The evaluation of mRNA or protein expression alone may not be sufficient to identify clinically relevant surrogate end point biomarkers that accurately reflect disease phenotype before, during, or after therapeutic intervention, despite the fact that global profiling of either gene or protein

expression is instructive. The majority of novel biomarkers and their links to disease came from two or more samples combined at one point in time. The approaches used are essentially snapshots of the illness state at a particular point in time, whereas the structure and function of signalling networks are dynamic. It is necessary to replace the single dimension with a multidimensional and continuous model since single measurements rarely capture all aspects of clinical outcomes.

Because outcomes affect an individual rather than a cohort as a whole, information derived from population "mean" data may not be applicable for a specific person. As a result, individual responders rather than population mean analyses should be developed and correlated with specific biomarker status in order to develop a targeted therapy. Therefore, lowering individual variations in medication exposure is essential for lowering response variability.

Combining biomarkers with an easy, affordable point-of-care diagnostic test can assist stratify patient populations for a particular disease or treatment regimen, cut down on the number of clinical trials, and generate sensitive and reliable biomarkers for a variety of purposeIt has been claimed that a trial involving 11,000 patients would have been necessary to develop trastuzumab without the inclusion of a diagnostic assay.In vitro diagnostics businesses may commercialise a biomarker after its clinical value has been confirmed; nevertheless, this choice will also be influenced by medical, regulatory, and legal considerations.

Earlier involvement of other stakeholders can shorten the time it takes for a biomarker to develop from discovery through validation and submission to regulatory authorities for qualification. For the development of therapeutically applicable biomarkers, a lot of work has gone into the founding of projects like "The Biomarker Consortium," whose members include government, business, industrial, academic, and patient organisations.

Finally, the use of biomarkers may generate several social, ethical, and legal issues because they may have unfavourable effects on people (such as negative professional repercussions, stigmatisation, insurance eligibility, and/or financial credits). These problems should be resolved by collaboration between scientists, doctors, ethicists, legal academics, policymakers, and marketers.

Chapter 5 - Conclusion

There has been minimal success in the identification and validation of robust biomarkers as alternative endpoints to clinically significant endpoints due to technical difficulties and inadequate experimental design. The discovery of validated and qualified biomarkers should proceed much more quickly with better experimental and clinical design, more standardised multi-omics and multi-parametric technology and analysis platforms, and a collaborative effort between scientists, clinicians, the biopharmaceutical industry, and regulatory authorities.

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