IIHMR UNIVERSITY

Role of Biomarkers in Drug Development

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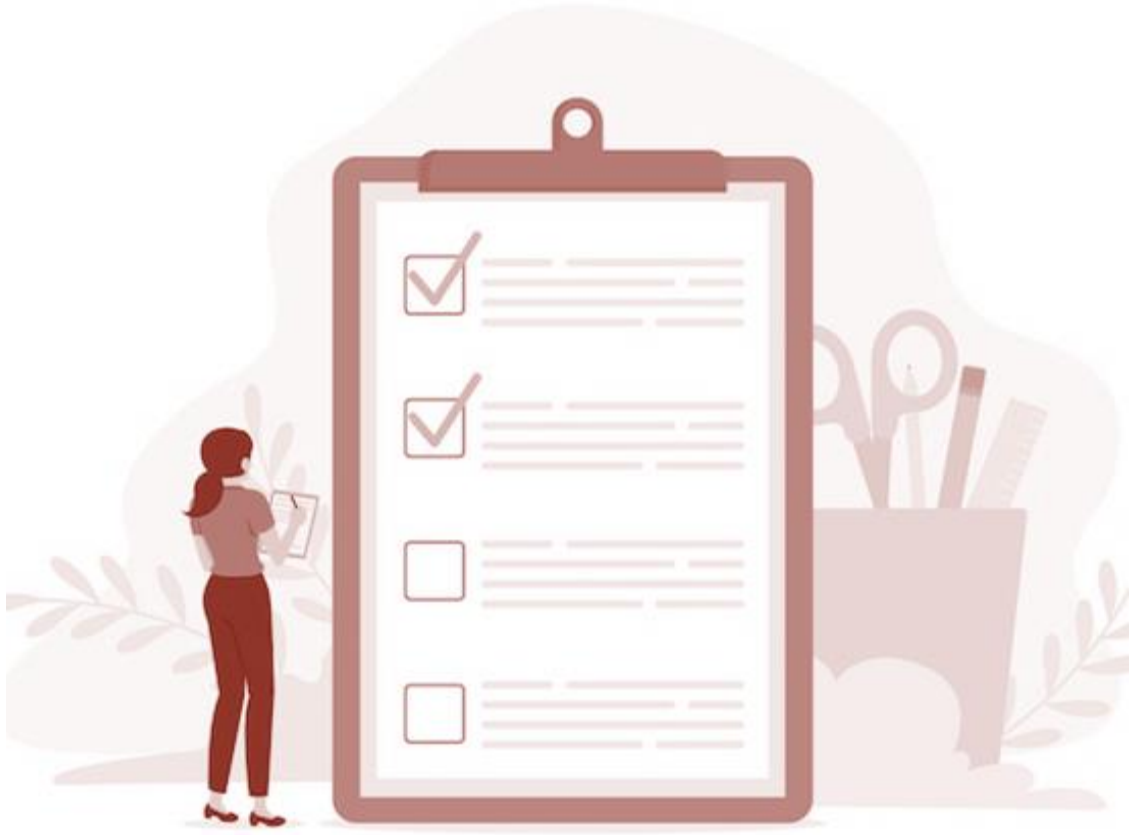


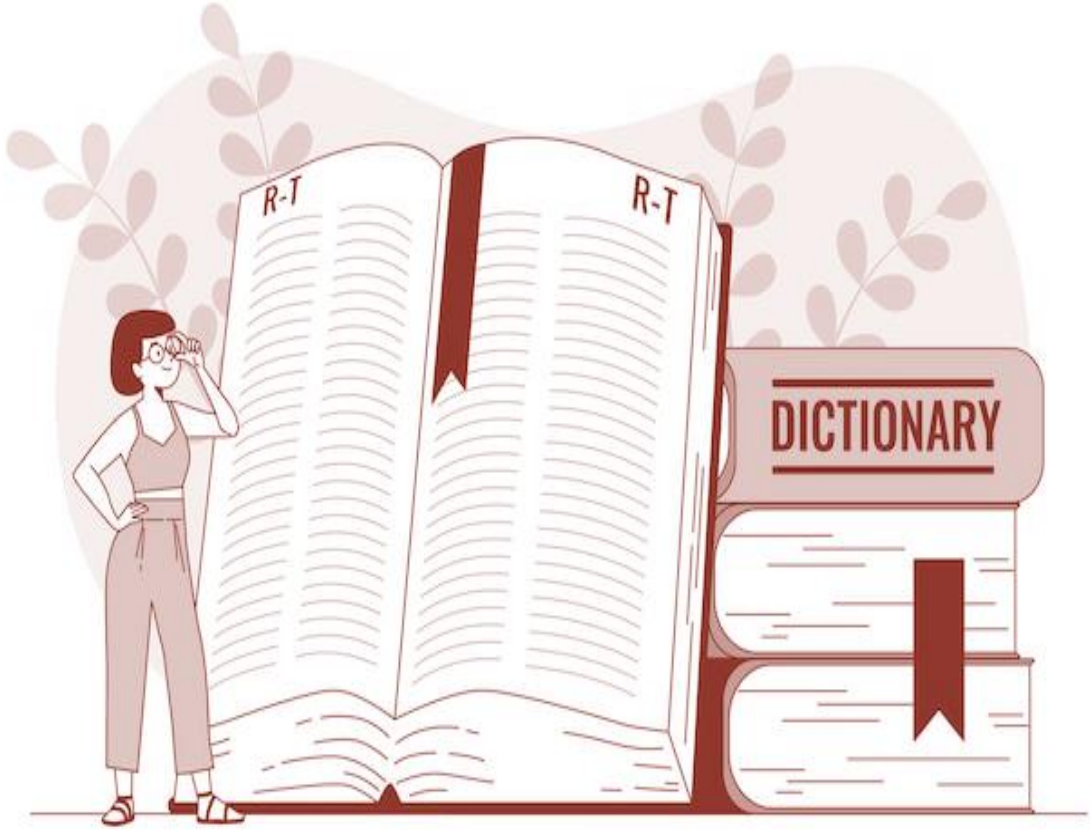
WHAT IS BIOMARKER?

- 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, "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"**

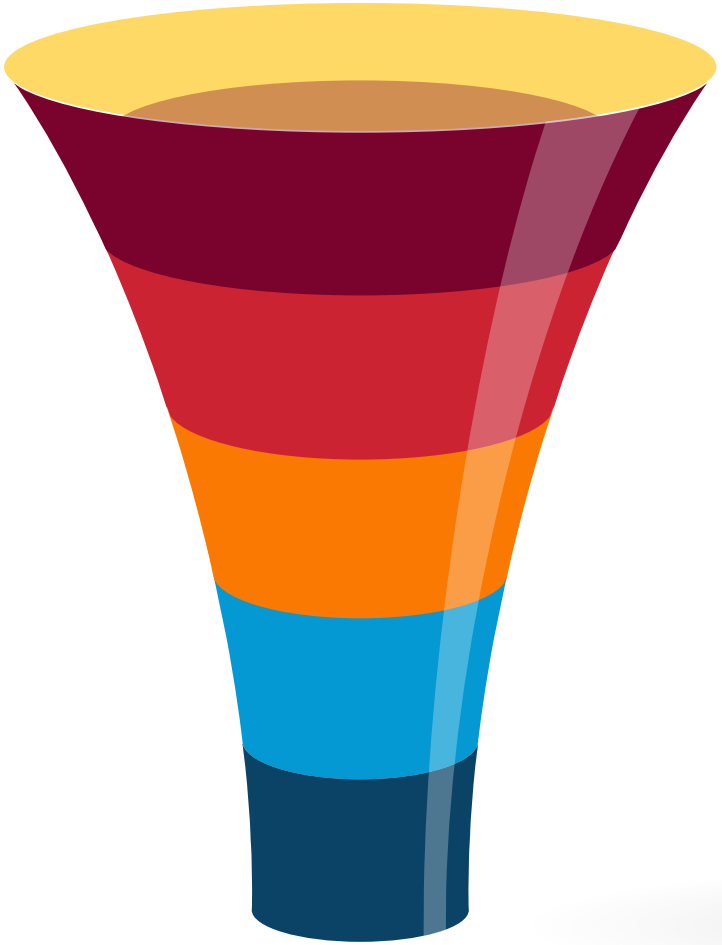
- Biomarkers (short for biological markers) are biological measures of a biological state. By definition, a biomarker is "**a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes or pharmacological responses to a therapeutic intervention**"

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
- 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 as 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



1

Drug discovery & 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.

2

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. Scientists discover about doses, side effects, MoA etc about the drug

3

Clinical Trials

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..

4

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..

5

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.

RESEARCH QUESTION

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

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

METHODOLOGY(1/1)

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"
- 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.
- 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

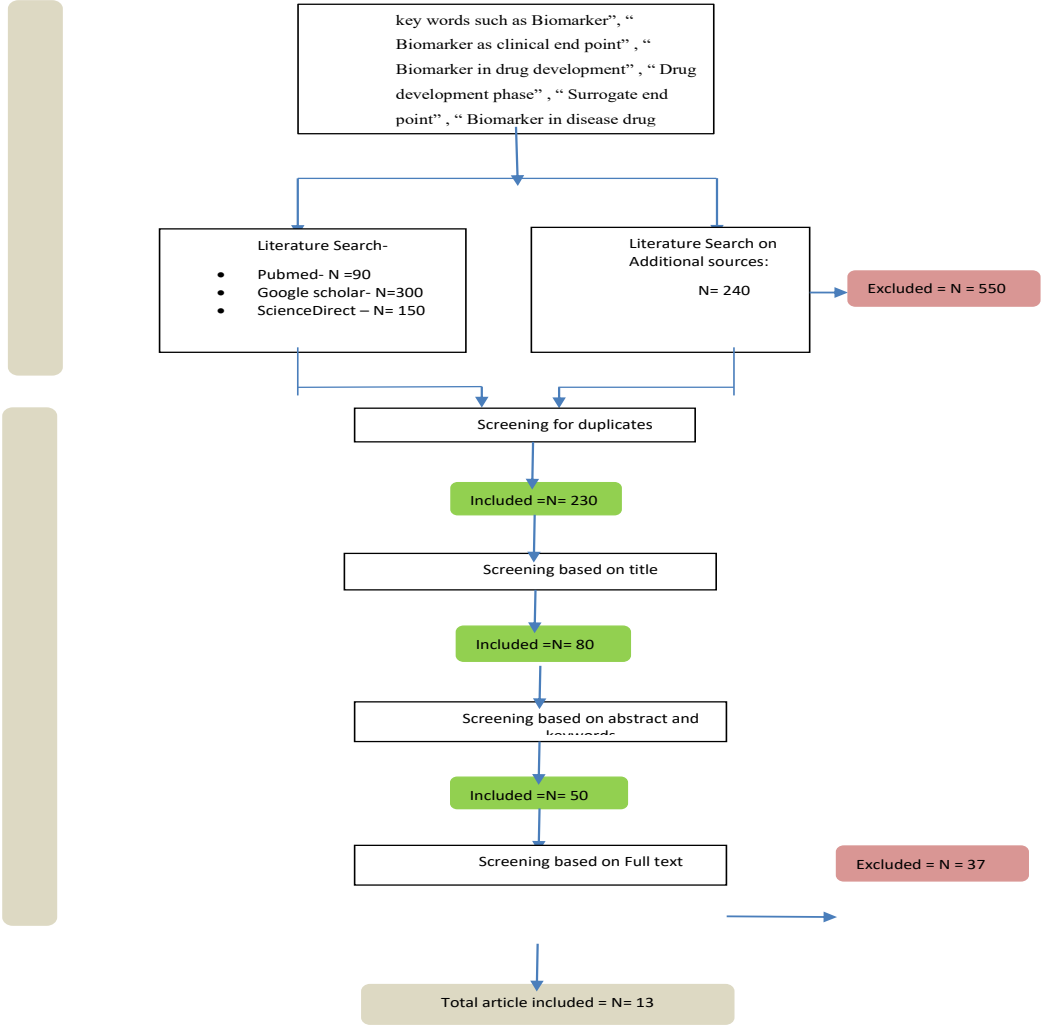
e) Duplicates were not included

METHODOLOGY(1/2)

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.

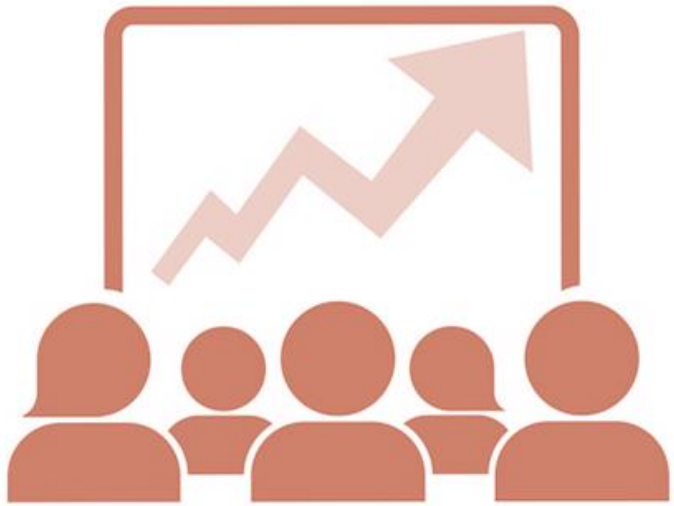


RESULT(1/1)

- 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 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)

- 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.



RESULT(1/2)

Types	Description	Example
Predictor	These are the disease associated biomarkers that can indicate whether there is a threat of disease and measure patient's responsiveness to treatment	**VEGF and Fibronectin** can predict clinical response to i**nterleukin-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
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	**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.
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	**Over expression of Her -2/neu** in breast cancer or EGFR expression in colorectal cancer indicate poor prognosis
Mechanistic	These biomarkers may inform and validate the mechanism(s) of action of a particular treatment	Sequential gene profiling of basal cell carcinomas treated with **imiquimod** 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
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	if a treatment affects the biomarker, the biomarker will serve as a surrogate end point for evaluating clinical benefit (***e.g.,* Hemoglobin A1C**)
Safety	These biomarkers can predict at the time of patients's enrollment her/his likelihood to suffer major toxicity from a specific therapy	**Albumin , total protein , B2 – microglobulin ,cystatin C , Kim -1 , and TFF3** have been selected from earlier studies as biomarker of drug induced kidney injuries

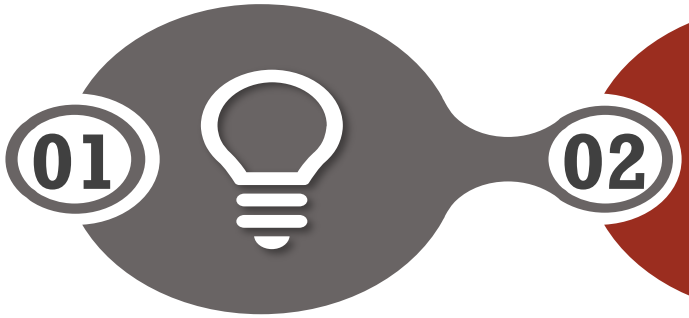
RESULT(1/3)

Qualification process by FDA for Biomarkers

- 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.

- 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

Letter of Intent



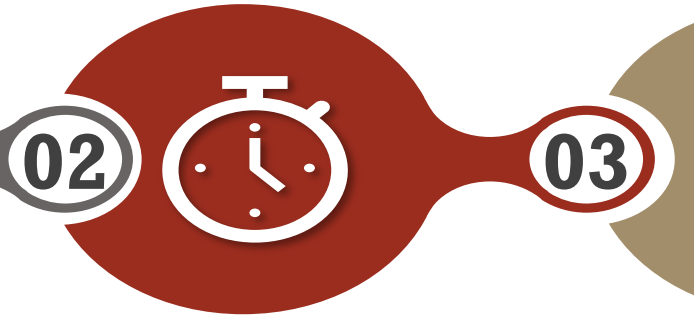
The LOI is submitted by the requestor using the suggested format. Initial details on the proposed biomarker are provided in the LOI, including:

- 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.

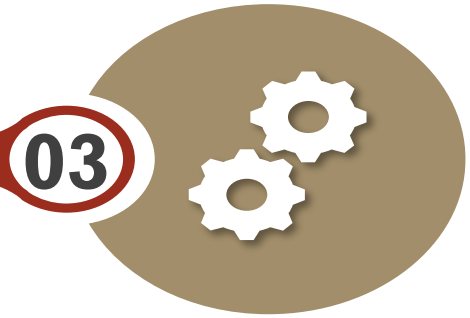
The requestor may submit a Qualification Plan if FDA accepts the LOI.

Qualification Plan



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.

Full Qualification Plan



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.

CHALLENGES AND FUTURE PERSPECTIVE

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

- 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

- 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

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 standardized 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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Thank You