JETIR.ORG ISSN: 2349-5162 | ESTD Year : 2014 | Monthly Issue
JOURNAL OF EMERGING TECHNOLOGIES AND INNOVATIVE RESEARCH (JETIR)
An International Scholarly Open Access, Peer-reviewed, Refereed Journal

A Project on Role of Biomarkers in drug development and Regulatory approval

Dr. mahesh patil, avinash shinde, vaibhav sonawane sheikh zahir, yogesh sonawane, chetan shivrame

associate professor, student

kydsct college of pharmcy

Key words: Measurable Indicator, biomarkers, cellular level, prognostic

Abstract:

Biomarkers are crucial tools in clinical practice and medical research, aiding physicians in understanding and treating various illnesses. They can guide treatment choices, track medication effectiveness, and identify susceptible individuals. Biomarkers are molecular, cellular, or biochemical changes that can be monitored and used as early warning systems for health issues. They can be derived from basic measurements like blood pressure or body weight, or from lab tests using genes or proteins. Biomarkers are essential for understanding the relationships between human biology, environmental exposures, and illness, advancing exposure science, and converting research results into practical medical and public health applications .Biomarkers are crucial for understanding the link between human biology, environmental exposures, and illness, advancing exposure science, understanding biological processes, and transforming research into practical applications.

INTRODUCTION

Definition:

A biomarker is a measurable indicator of a normal or abnormal biological process, or a condition or disease. It essentially acts as a signal, providing information about the body's internal state. These markers can be used for diagnosis, prognosis, monitoring, or predicting disease.

What are the Biomarkers?

In clinical practice and medical research, biomarkers are useful instruments that aid physicians in better understanding and treating a range of illnesses. For instance, they can direct treatment choices, track the effectiveness of a medication, and assist in identifying those who are more susceptible to specific diseases. Physiological and pathological processes or reactions to pharmacological therapies can be identified and tracked using biomarkers, which are molecular, cellular, or biochemical changes that can be precisely and consistently monitored.

A biomarker, which stands for biological marker, is an objective metric that documents the condition of a cell or organism at a certain moment in time. Biomarkers can serve as early warning systems for your health. For example, high blood lead levels, especially in children, may indicate that neurological and cognitive testing is necessary. High cholesterol is a common indicator for heart disease risk. Many biomarkers are derived from basic measurements made during a routine medical visit, such blood pressure or body weight. Other biomarkers depend on tissue, blood, or urine investigation in a lab. To record alterations at the molecular and cellular level, some employ genes or proteins. Biomarkers are essential for illuminating the relationships between environmental factors. Many biomarkers are derived from basic data such as body weight or blood pressure obtained during a routine medical visit. Other biomarkers are derived from blood, urine, or tissue tests conducted in a lab. Some examine proteins or genes to record alterations at the molecular and cellular level.

Biomarkers are essential for illuminating the relationships among human biology, environmental exposures, and illness. Scientists can employ biomarkers to advance exposure science, get a deeper comprehension of fundamental biological processes, and convert research results into practical medical and public health applications.

TYPES OF BIOMARKERS

There are numerous techniques to classify biomarkers. Learn more about the many biomarker classification systems and how they relate to the beginning, progression, and clinical outcomes of diseases by reading on. One thing to remember is that biomarkers come in a variety of forms. For example, BRCA1 expression is a predictive and prognostic biomarker for the response to treatment in sporadic epithelial ovarian cancer.

Molecular biology and genetics techniques allow biomarkers to be categorized as follows:

1.Type 0

2. Type 1

3. Type 2

Type 0

They are also known as natural history biomarkers. These biomarkers help measure the natural progression of a disease and correlate over time with recognized clinical characteristics. One example of a type 0 biomarker is the measurement of serum creatinine to monitor kidney damage or evaluate renal function.

Type 1 Biomarkers

A therapy intervention's effectiveness is demonstrated by these pharmacological activity biomarkers. Biomarkers for efficacy, which show a drug's therapeutic effects; biomarkers for mechanism of action, which give information on a drug's mechanism of action; and biomarkers for toxicity, which show a drug's toxicological effects, can be further divided into these categories. Blood glucose levels are an efficacy biomarker to monitor the effects of insulin therapy, while cytokines are a mechanism biomarker in immune-mediated disorders such as rheumatoid arthritis.

Type 2 Biomarkers

Having high cholesterol and low cholesterol can both be signs of heart disease. Both a clinical outcome of a disease and the impact of a treatment intervention can be predicted using these substitute markers, often known as surrogate endpoints. Clinical endpoints may be linked to these signs, even if there may not be a clear linkage. One Type 2 biomarker is cholesterol in heart disease; although high cholesterol is linked to a higher risk of heart disease, this relationship is not always true because some people do not go on to develop heart disease.

Prognostic, Predictive, Pharmacodynamic and Surrogate End-point Biomarkers

Biomarkers are further categorized into four classes:

1.Prognostic.

2.Predictive.

3.Pharmacodynamic.

4.Surrogate end-point.

1. Prognostic Biomarkers

"Fore-knowing or foreseeing" is the Greek definition of prognostic. Biomarkers that indicate the probability of a disease developing in an untreated person are known as prognostic biomarkers.

The PIK3CA mutation status in HER-2-positive metastatic breast cancer Prognostic is a Greek word meaning "fore-knowing or foreseeing." Biomarkers that predict the course of a disease in an untreated individual are known as prognostic biomarkers.

One example of a prognostic biomarker is the presence of PIK3CA mutations in HER-2 positive metastatic breast cancer; individuals with mutant PIK3CA have been shown to have lower disease-free survival rates.

2.Predictive Biomarkers

To determine which patients are most likely to respond favourably to a certain treatment, predictive biomarkers are employed. As a result, patients who are most likely to benefit from a certain medicine can receive it with the aid of predictive biomarkers.

A therapeutic intervention for advanced non-small-cell lung cancer is erlotinib maintenance medication. After undergoing erlotinib treatment, patients with an EGFR mutation in their tumour had a substantially poorer progression-free survival rate than patients without an EGFR mutation. EGFR mutation status is therefore a predictive indicator for erlotinib treatment response.

3.Pharmacodynamic Biomarkers

These biomarkers can tell whether a treatment is having the desired impact and aid in assessing the pharmacological effects of a medication.

PI3K inhibitors are used in the treatment of numerous cancer types. The PI3K signaling pathway has AKT as one of its downstream targets. Since AKT becomes phosphorylated when the PI3K pathway is activated, phosphorylated AKT (pAKT) can be used as a pharmacodynamic biomarker to confirm that the PI3K pathway is indeed being blocked by Pi3K inhibitor medication. If the levels of pAKT drop, the inhibitor is working.

4.Surrogate Biomarkers

For further information, refer to the section above. Surrogate biomarkers are the same as type 2 biomarkers except for their names. Blood pressure for heart disease is another instance of a surrogate biomarker.

Surrogate markers must effectively replace the clinical outcome and have effects on the substitute that forecast clinical outcomes in order to be useful, but since the biomarker is merely a surrogate, it's possible that the impact of pharmaceutical treatments on the surrogate won't have an impact on the result, which would limit its applicability.

According to the FDA Ideal Biomarkers should be:

1. specific for a particular disease and able to differentiate between different physiological states

2. safe and easy to measure

3. rapid to enable faster diagnosis

4. cheap

5. able to give accurate results

6. and consistent between different ethnic groups and genders.

Examples of Biomarkers

- Blood glucose levels: An efficacy biomarker of type 1 diabetes that is used to track how well insulin treatment is working.

- The presence of a PIK3CA mutation in HER-2 positive breast cancer: a predictive biomarker that predicts the course of the illness in patients who do not receive treatment.

According to the FDA Ideal Biomarkers should be:

1. specific for a particular disease and able to differentiate between different physiological states

2. safe and easy to measure

3. rapid to enable faster diagnosis

4. cheap

5. able to give accurate results

6. and consistent between different ethnic groups and genders.

BIOMARKERS IN RESEARCH TRENDS

1.Integration of Artificial Intelligence (AI): By 2025, biomarker analysis is expected to be even more heavily reliant on artificial intelligence (AI) and machine learning (ML). The incorporation of AI-driven algorithms will transform data processing and analysis, resulting in:

Application	Description
1.Predictive Analysis	AI will make it possible to create increasingly complex prediction models that, using biomarker profiles, can predict how a disease will advance and how a therapy will work. This skill will optimize patient management techniques and improve clinical decision-making.
2.Automated Data Interpretation	The time needed for biomarker identification and validation will be greatly decreased thanks to ML algorithms, which will enable the automated examination of complicated datasets. Workflows in clinical and research settings will be more efficient as a result.
3.Personalized Treatment Plans	Clinicians will be better able to create individualized treatment strategies that optimize effectiveness while avoiding negative effects by using AI to evaluate biomarker data and specific patient data.

2.Multi-Osmatic approaches: It is anticipated that the trend toward multi-omics integration would pick up steam. To obtain a comprehensive understanding of disease causes, researchers will progressively use data from transcriptomics, proteomics, metabolomics, and genomes. Important facets of this trend include

Aspect	**Description**
1.Comprehensive Biomarker Profiles	Multi-omics techniques will enable the identification of comprehensive biomarker signatures that reflect the complexity of diseases, facilitating enhanced diagnostic accuracy and therapy customization.
2. Systems Biology	A move toward systems biology will foster a better comprehension of the interactions between many biological processes in both health and illness. Finding new treatment targets and biomarkers requires this knowledge.
3.Collaborative Research Efforts	More cooperation between fields like clinical research, molecular

	biology, and bioinformatics will propel the creation of cutting-edge multi-omics platforms, improving the identification and validation of biomarkers even more.

3.Advancements in Liquid Biopsies: Non-invasive techniques like liquid biopsies are becoming powerful tools for early disease detection and real-time monitoring.

Advancements	Description
1.Enhanced Sensitivity and Specificity	Technological developments like exosome profiling and circulating tumor DNA (ctDNA) analysis will improve liquid biopsies' sensitivity and specificity, increasing its dependability for early disease monitoring and identification.
2.Real-Time Monitoring	Real-time tracking of the course of the disease and the effectiveness of treatment will be made possible by liquid biopsies, enabling prompt modifications to therapeutic approaches.
3.Broader Applications	Liquid biopsies are anticipated to spread beyond cancer into other medical specialties, such as autoimmune disorders and infectious illnesses, providing a non-invasive approach to disease detection.

BIOMARKERS IN DRUG DEVELOPMENT

A useful information that could lessen uncertainty in regulatory decisions during drug development could be provided by qualified biomarkers. Within the specified context of use (COU), a qualified biomarker has completed a formal regulatory process to guarantee that we can depend on it to have a particular interpretation and use in medical product development and regulatory assessment. Not the biomarker measuring technique, but a biomarker itself is qualified.

1.Early Detection and Diagnosis: Early disease detection, frequently before symptoms manifest, is made possible by biomarkers, resulting in prompt therapies.

2.Targeted Therapies: Treatments can be tailored to a patient's particular biological profile by identifying particular genetic, molecular, or cellular indicators, increasing effectiveness and lowering side effects.

3. Predictive Insights: By predicting a patient's response to a certain treatment, biomarkers assist clinicians in choosing the best course of action.

4.Monitoring and Adjustment:

They make it possible to track the efficacy of treatments in real time and make necessary adjustments to maximize results

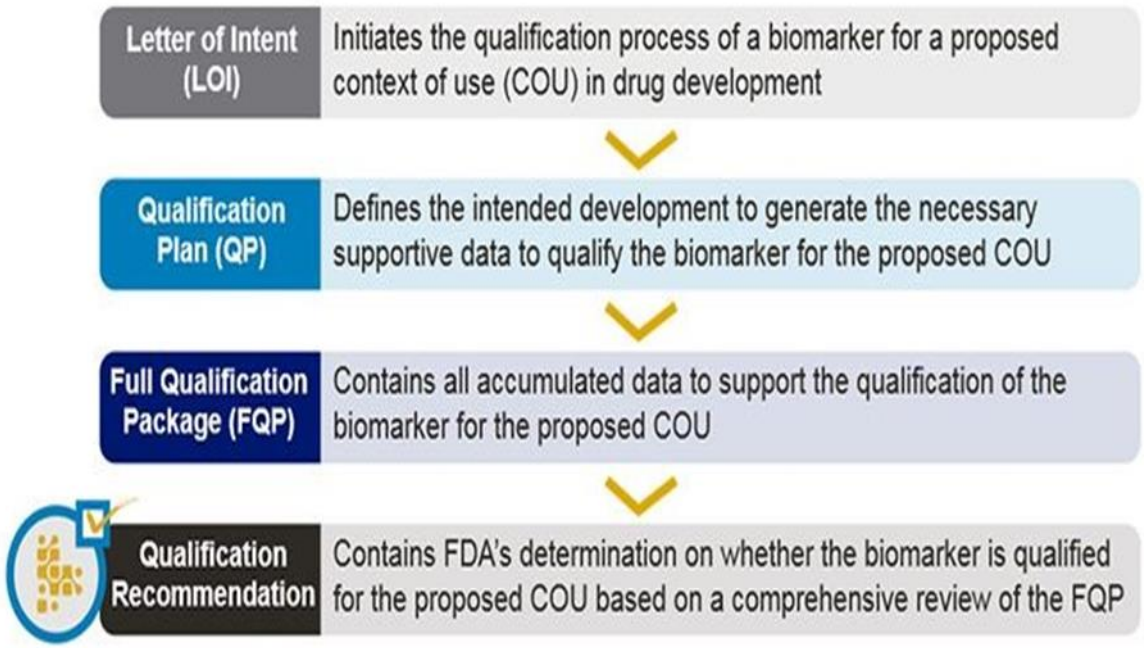
REGULATORY APPROVAL OF BIOMARKERS

- There isn't a single "regulatory approval form" that the FDA uses for biomarker guidance. Rather, they employ a three-phase submission procedure for biomarker qualification, which consists of an FDA qualifying decision, a Qualification Plan (QP), and a Letter of Intent (LOI). In medication development and regulatory evaluation, this procedure helps guarantee that biomarkers are employed effectively and consistently.

- The Biomarker Qualification Program collaborates with the requestor or requestors to guide the creation of biomarkers as part of the collaborative qualification process. To create a biomarker for qualifying, several interested

parties frequently collaborate in consortia or working groups. This method lessens the workload for individual contributors and permits the sharing of resources. As a result, even with limited funding, interested parties might be persuaded to participate in a DDT development project.

• According to the 21st Century Cures Act, biomarker qualification entails a three-step submission process to create a biomarker for regulatory use. The FDA decides whether to accept or reject submissions that are complete and of high quality, and notifies the requestor in writing along with comments and suggestions for additional biomarker development.



Stage 1: Letter of Intent (LOI): The LOI is submitted by the requestor using the suggested format. The LOI offers preliminary details regarding the proposed biomarker, such as: Need for drug development information about the biomarker's context of use (COU) and how it will be measured is what the biomarker is meant to address. After reviewing the LOI application, the FDA will evaluate the proposal's overall viability in light of existing scientific knowledge as well as the biomarker's potential relevance in addressing an unmet drug development need. The requestor may submit a Qualification Plan if the FDA approves the LOI.

Stage 2: Qualification Plan (QP): In order to give the required information to qualify the biomarker for the proposed COU in drug development, the QP is a comprehensive proposal outlining the planned biomarker development plan. It outlines the body of evidence supporting the COU, points out knowledge gaps, and suggests ways to fill them. The QP need to contain comprehensive details regarding the performance attributes and analysis methodology. If the FDA approves the QP, the organization will give the requestor

Stage 3: Full Qualification Package (FQP): The FDA will use the FQP, a thorough compilation of supporting data, to determine whether to qualify the biomarker and COU. It includes all of the information that has been gathered, arranged by subject. Based on the FQP, the FDA will ultimately decide if the biomarker qualifies. Once qualified, the biomarker can be utilized to support a novel medicine's regulatory approval under the COU for which it is qualified in any CDER drug development program.

ADVANTAGES

•Early Disease Detection: Biomarkers can assist in identifying diseases early on, when they are easier to cure, by identifying minute alterations in biological processes.

•Improved Diagnostic Accuracy: Compared to conventional techniques, biomarkers can assist in the earlier and more precise identification of diseases, resulting in more precise diagnoses.

•Predicting Disease Progression: Better planning and management are made possible by the ability of some biomarkers to anticipate the severity and course of a disease.

•Individualized Medicine: By identifying patients who are most likely to benefit from particular treatments, biomarkers can assist develop more specialized and efficient medicines.

•Reduced Invasive Procedures: The necessity for invasive procedures like biopsies is reduced because many biomarkers can be assessed from easily accessible samples like blood or urine.

•Monitoring Treatment Response: Biomarkers can be used to track the efficacy of treatments and make the required modifications, resulting in more individualized and successful therapies.

DISADVANTAGES

•Cost: Biomarker assays can be expensive, particularly for specialized tests.

•Variability: Biomarker levels can fluctuate due to various factors, making interpretation challenging.

•Sample Storage and Longevity: Some biomarkers require specialized storage conditions and may not be stable over long periods.

CONCLUSION

A systematic pathway approach to the biomarker validation process is becoming more and more necessary in light of the current explosion in the pipeline for biomarker development. therapy and biomarker co-development's future depends on determining which group will benefit from a certain therapy as biomarker research advances toward laying the groundwork for customized medicine. Because of the substantial time and money spent on their development, these biomarkers will be able to serve as surrogate endpoints and diagnostic indicators for disease screening, tracking the course of the disease and the effectiveness of treatment, evaluating patient outcomes, and spotting possible adverse effects like toxicity.

In order to eradicate biomarker failures that arise in the clinic due to subpar assays, the focus would now be on biomarker assay development and technique validation. As we look toward 2025, the future of biomarker analysis is filled with promise and potential. The integration of advanced technologies, the shift toward patient-centric approaches, and the evolution of regulatory frameworks will drive significant advancements in the field.

REFERENCES

1.Naylor S. (2003) Biomarkers: current perspectives and future prospects. Expert Rev Mol Diagn 3:525–29

2. Madenspacher JH, Stapleton RD, Suratt BT, Dixon AE, Lih FB, Lowe JM, Mould KJ, Janssen WJ, Morrell ED, Wurfel MM, Garantziotis S, Tomer KB, Fessler MB. 2018. Cholestenoic acid is a prognostic biomarker in acute respiratory distress syndrome. Journal of Allergy Clinical Immunology 143(1):440-442. [Abstract Madenspacher JH, Stapleton RD, Suratt BT, Dixon AE, Lih FB, Lowe JM, Mould KJ, Janssen WJ, Morrell ED, Wurfel MM, Garantziotis S, Tomer KB, Fessler MB. 2018. Cholestenoic acid is a prognostic biomarker in acute respiratory distress syndrome. Journal of Allergy Clinical Immunology 143(1):440-442.]

3.Carser JE, Quinn JE, Michie CO, O'Brien EJ, McCluggage WG, Maxwell P, Lamers E, Lioe TF, Williams AR, Kennedy RD, Gourley C, Harkin DP. (2011) BRCA1 is both a prognostic and predictive biomarker of response to chemotherapy in sporadic epithelial ovarian cancer. Gynecol Oncol 123(3):492–8

4.https://bitesizebio.com/26559/biomarkers-explained

5. https://blog.crownbio.com/challenges-and-future-trends-in-biomarker-analysis-for-clinical-researchwhats-ahead-in-2025

6.https://www.fda.gov/drugs/biomarker-qualification-program/about-biomarkers-and-qualification

7. https://pmc.ncbi.nlm.nih.gov/articles/PMC7563364/

8. https://en.wikipedia.org/wiki/Biomarker_(medicine)

9. https://pmc.ncbi.nlm.nih.gov/articles/PMC534923/

10.https://sonraianalytics.com/the-future-of-biomarkers

11.https://www.rootsanalysis.com/reports/biomarkers-market.html

12.https://www.fda.gov/drugs/biomarker-qualification-program/about-biomarkers-and-qualification

13.https://www.nordicbioscience.com/why-biomarkers/biomarker-regulatory-considerations

14.https://images.app.goo.gl/1kJpykvrAcDpzsys7

15.https://www.grandviewresearch.com/industry-analysis/biomarkers-industry