

BIOMARKER STRATEGIES TO ENHANCE EARLY-PHASE DRUG DEVELOPMENT

In drug development, biomarkers are a highly relevant approach for enhancing the precision and utility of early-stage studies. When added to clinical trials as substitutes for a direct clinical outcome, they are thought to provide insight into the true outcome. They can help enrich clinical trials by stratifying participant populations and providing targeted data.

Biomarkers have proven to be effective surrogate endpoints. For instance, a reduction in low-density lipoprotein (LDL) cholesterol indicates a lower likelihood of cardiovascular events. Likewise, Hemoglobin A1c (HbA1c) is a validated surrogate endpoint for the reduction of microvascular complications associated with diabetes mellitus.

In this issue, we review common biomarker strategies by category, selected disease indications (including immunological treatments, central nervous system (CNS), ophthalmology, and cardiometabolic), and by modality within the indications.

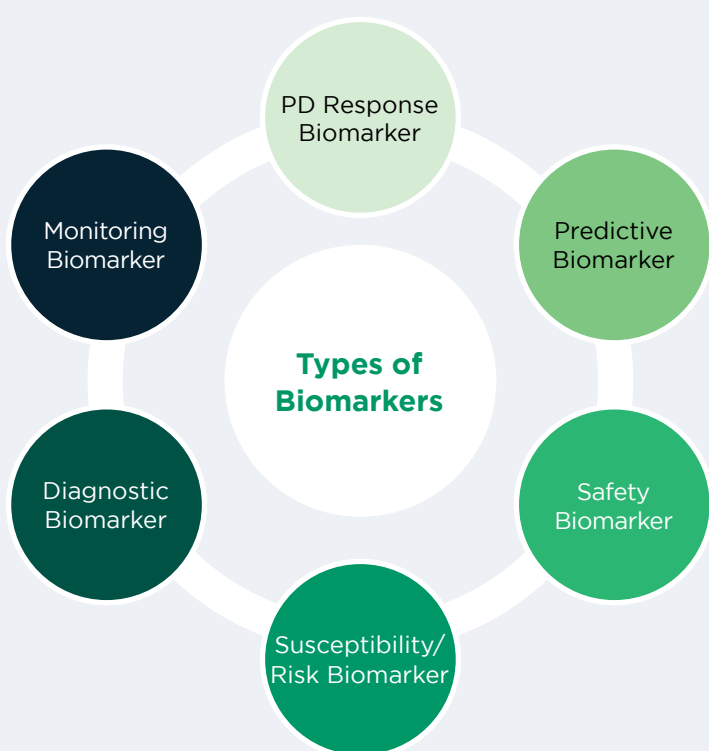
BIOMARKERS IN EARLY-PHASE DRUG DEVELOPMENT

The National Institutes of Health Biomarkers Definitions Working Group 2001 defines biomarkers as “a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention”. This definition has since evolved and expanded to include molecular signatures of pharmacodynamics and therapeutic response.

Biomarker Categories

Biomarkers provide useful insight across different categories during early-phase drug development.

Figure 1. Types of Biomarkers in Early-Phase Drug Development



- Pharmacodynamic (PD)/Response biomarkers measure biological responses to treatment. They provide an objective, rapid, and quantitative measure of a drug's biological activity, contributing to optimal dosage selection and potentially reducing the time and cost of trials.

- Predictive biomarkers help identify sub-populations that are likely to respond and are crucial for enriching Phase II trials by targeting efforts for recruitment and enrollment and providing additional insight into study data, from nonclinical through clinical trials.

- Safety biomarkers detect nonclinical signs of toxicity and support early go/no-go decisions and relevant program adjustments.

- Susceptibility/Risk biomarkers identify gene mutations that may indicate the potential for a seemingly healthy individual to develop a specific condition in the future.

- Diagnostic biomarkers detect or confirm the actual presence of a disease or a medical condition, and/or identify the specific subtype of a disease that is present.

- Monitoring biomarkers are measured serially over time, to evaluate the safety or toxicity of a therapeutic candidate, to detect changes in the state of a disease, or provide evidence of exposure to a medical substance.

BIOMARKERS BY DISEASE INDICATION

Different treatments may require distinct biomarkers when the therapy acts on a unique biological mechanism, target, or pathway. Selecting the appropriate biomarker for your program is essential for robust data collection and analysis.

Multiplex biomarker panels allow for measurement of multiple proteins, cytokines, or metabolites from a single biological sample. These panels accelerate programs by providing comprehensive, multi-pathway insights into target engagement, PD, and early toxicity.

Some of the most common indications, and the rationale and purpose for their related biomarkers, are described below.

CNS-Active Agents

- **Fluid Biomarkers:** Cerebrospinal fluid (CSF) or plasma levels of amyloid-beta, p-Tau, and neurofilament light chain (NfL) to monitor neurodegeneration and target engagement, via MSD multiplex panels that include multiple CNS biomarkers.

Metabolic Diseases

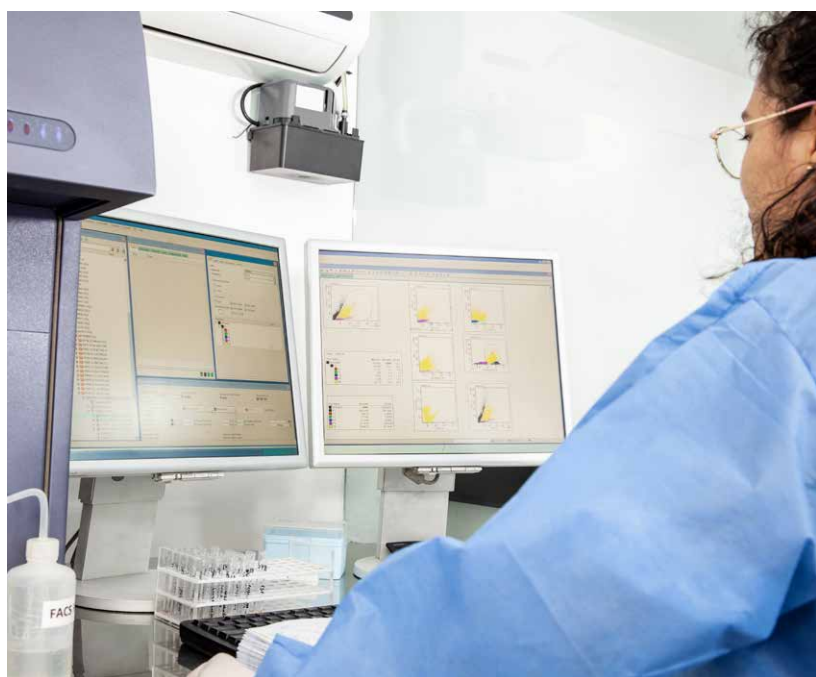
- **Biomarker Profiles:** Specialized panels (e.g., GLP-1, specific lipid panels) to differentiate drug effects. Some multiplex panels measure numerous biomarkers from a single sample.

Immuno-Oncology (IO) Agents (Checkpoint Inhibitors, Vaccines)

- **Predictive Biomarkers:** PD-L1 expression by MSD.
- **PD Biomarkers:** Peripheral cytokine levels, humoral responses by ELISA/MSD or cellular responses by ELISpot, immunophenotyping by flow cytometry, gene expression profiling of the tumor microenvironment.

Ocular Diseases

- **Analyzing specific proteins and cytokines** in tears. Molecules like Matrix Metalloproteinase-9 (MMP-9), Human Leukocyte Antigen-DR (HLA-DR), and lactoferrin quantify surface inflammation and dry eye disease activity.
- **Assessing retinal drug interaction** in vitreous humor via cytokines, chemokines, and Vascular Endothelial Growth Factor (VEGF)



Within the specific disease indications, different treatment modalities are possible, and each have their own biomarker strategies. Some examples include:

Biomarkers for Cell and Gene Therapies

- **Target Protein Transgene Expression:** Detection of protein product in target tissues/fluids by ELISA/MSD or flow cytometry.
- **Vector Copy Number (VCN):** qPCR or ddPCR for quantification of vector DNA in peripheral blood or tissues.
- **Immune Response:** Total anti-drug antibodies (ADA) and neutralizing antibodies (NAb) to the vector (e.g., AAV) and transgene product. In some cases, T-cell responses may also be needed against the vector and the expressed transgene. Screening subjects for pre-existing immunity against the gene therapy product is usually performed and used for exclusions from study enrollment.
- **Toxicity Biomarkers:** Focusing primarily on liver enzymes and kidney function to monitor gene therapy vector accumulation.
- **Disease-Specific Pathologies:** Selection of biomarkers depends on the disease being targeted.

Biomarkers for Small Molecules

- Target engagement and mechanism of action (MOA) by LC/MS
- Early safety and toxicity biomarkers found in blood or urine
- Dose ranging and optimization
- Participant selection and stratification

Biomarkers for Large Molecules

- Target engagement and MOA by LBA, flow cytometry, or hybrid-MS/MS
- Early efficacy and safety biomarkers, mostly in blood
- Immunogenicity monitoring through various platforms
- Participant selection and stratification



OPERATIONALIZING BIOMARKER SELECTION

The right biomarker strategy can translate promising biological signals into reliable, decision-enabling tools that can be used across discovery, clinical trials, and regulatory interactions. Such a strategy requires a structured approach that integrates scientific validation, analytical rigor, and clinical relevance.

In early-phase drug development, exploratory biomarkers are often assessed at the nonclinical phase, and only some with predictive outcomes are selected for later phases.

Key Considerations for Selecting Early-Phase Biomarkers

The following is an overview of how to identify, qualify, and implement biomarkers to inform patient selection, demonstrate target engagement, and ultimately support more efficient and data-driven development decisions.

- **A Clearly Defined Context of Use (COU):** This includes specifying the analyte, patient population, timing, and how the results will inform go/no go decisions. A COU statement typically includes detailed information about the decision the biomarker is supporting, how the biomarker is measured, the analytical method involved, various performance characteristics, and the specific clinical context where the biomarker is intended for use.

By defining a distinct COU, adjusting the assay's validation level, timing, biological matrix, and assay performance, the same biomarker can be used for different purposes. By planning and documenting such uses, a single biomarker can guide target engagement, patient stratification, and safety monitoring across multiple trials and phases.

- **Biological Plausibility and Translation:** Choose markers with a solid theoretical basis, supported by nonclinical evidence showing translation from animal models to humans. Engage early by involving clinical, laboratory, and regulatory experts during protocol development.
- **Accessibility and Feasibility:** Choose biomarkers that are easily quantified in accessible, patient-friendly matrices (e.g., blood). If using more complex matrices, ensure your drug development partner has the relevant knowledge to properly analyze such samples. Define criteria for success by specifying in advance what constitutes a meaningful change to avoid over-interpretation.
- **Align With "5 Rs" Framework:** Select markers that ensure accurate tissue and target engagement. The 5 Rs of biomarker selection are reproducibility, reliability, risk prediction, response indication, and relevance.
- **Focus on Target Engagement and PD:** Early-phase priorities are identifying PD markers that confirm the drug attains its target, and that engagement leads to downstream biological changes. PD biomarkers can serve as surrogate endpoints, if validated as consistently and accurately predictive of a particular clinical outcome. Biomarkers based on the mechanism underlying a complex disease such as obesity, if validated as an endpoint, can potentially reveal more about a treatment's efficacy than broader endpoints such as body weight, while still providing key safety data.

- **Fit-for-Purpose Validation:** Unlike late-phase trials, early-phase studies may use a fit-for-purpose (FFP) approach, balancing the need for rigorous analytical performance and speed with the exploratory nature of the study. FFP validation of early-phase biomarkers is an iterative, tiered process that tailors analytical rigor to the specific decision-making context, such as dose selection or proof-of-mechanism. It ensures that assay reliability matches the needs of the study, transitioning from exploratory towards more robust assays as clinical development proceeds.

Assays may be refined throughout the study, often moving from research-grade to more standardized procedures. This approach avoids the excessive time and cost of fully validating exploratory markers while ensuring that critical, data-driven decisions are supported by reliable, well-characterized data. This tiered approach varies depending on the phase of a trial.

- **Exploratory**, early nonclinical or clinical studies intended for product characterization and information gathering that are not linked to regulatory submissions can rely on **qualified methods** which cover appropriate range, parallelism, precision, and sensitivity for the context of use.
- **IND-enabling** nonclinical studies with safety endpoints dictate the safety profile of the developmental drug and require increased rigor regarding assay robustness to support critical decision-making and regulatory submissions. Full bioanalytical validation in accordance with [ICH M10](#) guidance is required.
- **Later-stage clinical studies** where biomarkers are used for PD assessments, including primary or secondary endpoints, also require bioanalytical validation in accordance with [ICH M10](#) guidance. When biomarkers are used for diagnostic purposes and results dictate patient enrollment eligibility, clinical validation and [CAP/CLIA](#) certification is required. In cases where the same biomarkers are used for more than one COU, both bioanalytical and clinical validation are needed to meet different regulatory requirements.

In the last decade, there has been a regulatory shift, with drug developers needing to meet additional requirements for any data supporting patient-specific treatment. Those requirements are mandated by the [IVDR](#) and [CAP/CLIA](#). [Recently proposed updates to CLIA](#) are aimed at shifting the industry toward formalized evidence, digital traceability, and stringent risk-management controls for diagnostic and prognostic biomarkers.

Avoid These Common Pitfalls:

- Over-investing in fully validating a biomarker for a compound with an uncertain future.
- Using biomarkers for purposes beyond their COU. For example, using a diagnostic assay for screening patients for exclusion, and as a biomarker for PD assessment to monitor changes from baseline. This may lead to bioanalytical issues, as the assay sensitivity has not been demonstrated under the validation.
- Poorly defining the analytical procedures and sample handling. This can lead to compromised sample integrity, inaccurate data, and high rates of sample rejection. Commercially available kits are not appropriate for bioanalysis and need to be modified for the COU.
- Overlooking the need for reproducibility in the laboratory conducting the test; it is important to test the assay kit lot-to-lot variability to ensure consistent performance.

The goal is to select markers that support go/no go decisions with reliable data by allowing for rapid failure of unviable candidates or providing strong confidence for advancing promising ones.

HOW ALTASCIENCES CAN HELP

We integrate biomarker strategy, bioanalysis, and clinical conduct into a single, seamless program to generate robust data that supports faster, more confident go/no-go decisions. The Altasciences Acceleration Platform provides:

- A single, integrated team of experts
- Rapid turnaround of high-quality data
- A coherent translational story from nonclinical to clinical
- CLIA-certified clinical laboratories

We support you with expertise in these critical areas:

Translational and Biomarker Strategy

- Selecting/implementing the appropriate biomarkers for your drug's modality
- Defining fit-for-purpose validation
- Ensuring alignment with your clinical endpoints and regulatory path
- Demonstrating expertise in data interpretation

Advanced Bioanalytical Capabilities

- Robust assays across platforms (ligand binding, LC-MS/MS, multiplex, flow cytometry, cell-based assays, etc.)
- Experience with complex and low-abundance biomarkers (CSF, various tissues, etc.)
- High-quality, regulatory-ready data

Integrated Clinical Conduct

- Expertise with clinical trial design leveraging biomarkers
- First-in-human (FIH) trials with PD endpoints and adaptive biomarker-driven trials
- Early-phase units designed for intensive PK/PD and biomarker sampling
- Real-time data flow to support adaptive decisions
- Seamless transition from nonclinical to FIH to proof-of-concept
- Model-informed drug development (MIDD)
- Exposure-response modeling
- Quantitative systems pharmacology (QSP)
- Translational and multimodal data integration, combining genomics, proteomics, and imaging
- In-house regulatory team

RELATED RESOURCES

Scientific Publications

[The Altascientist—Cytokine Release Assays](#)

[Brochure—Key Biomarkers of Immunomodulation: Complement Factors and Cytokines](#)

Fact Sheets

[Translational Biomarker Assays](#)

[Comprehensive Bioanalytical Services](#)

Webpage

[Translational Biomarkers](#)

Posters

[Comparison of Baseline Levels of Biomarkers Commonly Used to Assess Drug Candidate Safety, Efficacy, and Mechanism of Action in Cynomolgus Monkeys of Cambodian, Chinese, or Cambodian-Chinese Mixed Origin Bred in a U.S.-Based Research Facility](#)

[Validation of an SC5b-9 Commercial Kit for Preclinical Biomarker Analysis](#)

[Parallelism Challenges When Using Commercial Kits for Biomarker Quantitation](#)

ABOUT ALTASCIENCES

[Altasciences](#) is an integrated drug development solution company offering pharmaceutical and biotechnology companies a proven, flexible approach to [preclinical](#) and [clinical pharmacology](#) studies, including [formulation, manufacturing, and analytical services](#). For over 30 years, Altasciences has been partnering with sponsors to help support educated, faster, and more complete early drug development decisions. Altasciences' integrated, full-service solutions include [preclinical safety testing](#), [clinical pharmacology and proof of concept](#), [bioanalysis](#), program management, medical writing, biostatistics, clinical monitoring, and data management, all customizable to specific sponsor requirements. Altasciences helps sponsors get better drugs to the people who need them, faster.

© 2026 Altasciences. All Rights Reserved.