

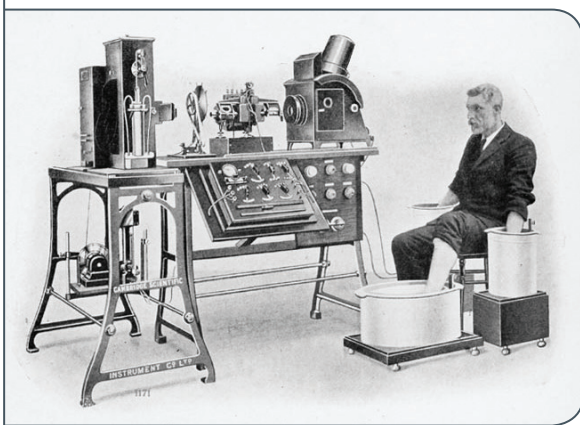
Biomarkers – Unlocking Value in Early Drug Development

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What's new about biomarkers?

The concept of using biomarkers in pharmaceutical development is not new. The presence of sweetness in urine was recognized thousands of years ago as an indication of diabetes. Blood pressure, a common biomarker of cardiovascular health status and disease risk today, was described as early as 1555 by the Polish physician Józef Struś who developed the first device. The first imaging biomarkers were x-rays, discovered by Wilhelm Roentgen in 1895, and the first ECG apparatus was invented by Willem Einthoven in 1901. Advances in analytical chemistry beginning in the 1950s and continuing through to the 1980s enabled the measurement of low levels of analytes in biological matrices, usually blood, blood components or urine. Endogenous compounds in these biological matrices became useful biomarkers in clinical practice as well as in drug discovery and development.

Figure 1. Photograph of a complete Electrocardiograph, showing the manner in which the electrodes are attached to the patient, in this case the hands and one foot being immersed in jars of salt solution.



Although biomarkers have been used across medical history, recent advances in technology have enabled a plethora of new applications for addressing questions of activity, safety, and clinical efficacy throughout the

discovery–development process. The novelty of some of these approaches (e.g. genomics, proteomics, imaging, microdosing) has created excitement and interest in biomarkers but often the expectation that ideal biomarkers must be novel or somehow exotic. In many cases, well-established biomarkers may serve just as well if not better. The primary purpose of biomarkers is to enable better decision making during drug development, and that goal should drive the technology that is chosen. Deciding which biomarkers to include and what technology to use is neither simple nor straight forward. Consortia formed by government, research institutions and pharmaceutical companies with the objective to share and validate data, such as the Critical Path Institute (www.c-path.org), have started to yield results in specific areas (e.g. renal toxicity biomarkers). Good science supported by data will convince stakeholders of the value of novel biomarkers. Overall, there is an ever-increasing breadth of methodologies and expertise available to facilitate a science-driven biomarker rationale for a particular drug development program.

Enabling go/no go decisions

The majority of biomarkers that have been used within drug development have fallen into one of the following categories: established markers of toxicity in non-clinical safety assessment studies, clinical diagnostic markers of safety and efficacy, and biochemical markers most often linked to the mechanism of action of the compound. Pharmacodynamic biomarkers have a long history of use in drug development and are typically included as the “PD” in PK/PD evaluations in early clinical research. The purpose of including the biomarkers is to optimize and accelerate drug development programs by generating informative data at every stage of the process, from lab bench to the clinic, in first-in-human (FIH) studies and in proof-of-concept Phase IIa trials. In this context, very few biomarkers are or are intended to become surrogate endpoints of clinical efficacy. Rather, they are used to help make go/no go decisions.

For small and emerging pharmaceutical companies whose survival is dependent on investor interest, and articulating and meeting clearly established milestones, biomarkers can play a pivotal role in increasing a compound's value.

Challenges with biomarker programs

Clinical relevance is of critical importance when selecting biomarkers. If a biomarker is to be used to differentiate between healthy individuals and those with a disease, one must understand how the biomarker is expressed in both of these populations: Is there population overlap? How does the population difference compare to the measurement error? These are just a few of the questions that should be addressed before initiating clinical studies. For novel biomarkers, one may need to first conduct a survey study in the appropriate population(s) to collect the data to address these questions.

Analytical assay development and validation is another important consideration and an area of focus for Celerion's Bioanalytical Services. When thoughtfully selected, biomarkers can often be translated from the preclinical stage to early clinical studies and proof-of-concept studies in patients. The analytical assays must also undergo a "translation" as the program progresses. Sometimes there is an expectation that outsourced bioanalytical assays, including PD biomarkers, should

undergo full GLP validation. However, it is not essential to implement full GLP or GLP-like assay validation for biomarker assays that will be used for exploratory research. A "fit for purpose" method validation at various phases of biomarker application should be applied. Therefore, it is important that the sponsor and the outsourcing partner have a common understanding of how the biomarker will be used in order that the scope of the assay validation can be appropriately defined and agreed upon by both parties in advance of method development. As a biomarker progresses from preclinical to clinical applications, the assay methods may need to be modified and further refined, and the performance assessed under new conditions. Frequently, a much higher degree of inter-individual variability of the biomarker response is seen in humans than in animals. Assay throughput becomes more important for clinical studies involving large numbers of subjects or patients compared to preclinical studies in smaller numbers of animals.

Celerion has developed and validated key biomarker assays which were critical in guiding the early clinical development of several compounds. In most cases, the method development was completed before the FIH dosing. Indeed, the availability of assay methods shaped the strategy of the FIH trials. Measurement of PD markers associated with the mechanism of action provided reassurance that the compounds were having the intended effects in humans. Coupled with PK assessments, results were applied for dose selection and/or to develop biomarker inclusion/exclusion criteria of patients for Phase II studies.

Results of first-in-patient studies are often a critical decision gate for advancing a compound. Some sponsors have a tendency to include numerous PD biomarkers in these studies in the hopes that one or more of these will show promising results. However, with multiple biomarkers the complexity of the study increases leading to more challenging patient recruitment and study logistics, including sample handling, particularly for multi-site trials conducted in out-patient settings. There is also the danger of over-interpreting the ensuing biomarker data that may be sparse and obtained using less robust exploratory assays. The difficulties of including esoteric non-standard assays particularly in multi-site studies spanning across different countries and/or wide geographies should not be underestimated. In the development of the biomarker strategy as well as during method development, considerable attention should be given to balancing the need to simplify

Figure 2. Considerations in evaluating a candidate biomarker

Considerations in evaluating a candidate biomarker

- **Clinical relevance**
 - Ideally, should be related to the mechanism of action of the drug and the clinical endpoint
- **Sensitivity and specificity to treatment effects**
 - Ability to detect the biomarker or change in biomarker in the target population
- **Reliability**
 - Ability to measure the biomarker analytically with accuracy, precision, robustness and reproducibility
- **Practicality**
 - Non-invasive or minimally invasive biomarkers are preferable
 - The biomarker should be suitable to implement in multi-site trials
- **Simplicity**
 - Simpler is better for translating a biomarker from lab bench to bedside

sample preparation procedures and minimize the number of clinical samples collected with the need to maximize the amount of useful information from each study. Training of clinical staff, including conducting mock procedures, and use of barcode systems for sample collection and tracking help to reduce the risk of clinical or laboratory deviations in complex biomarker studies.

Although several contract research organizations (CRO) may be involved in the execution of a study, clinical trial management, sample management, and conduct of various biomarker assays, it is beneficial to have overall project management to coordinate logistics and communicate across the various outsourcing partners. Smaller pharma companies often use the project management services of a CRO due to a lack of internal resource, however, larger companies can benefit from good program management and leadership provided by a CRO with proven success in managing biomarker programs.

Future trends

Celerion has seen an increase in FIH and other early clinical studies conducted in patients in addition to or instead of healthy volunteers. While recruitment of patients is often more challenging than recruitment of healthy volunteers, certain biomarkers are relevant only in individuals with the disease. Imaging technologies in particular are generating interest in studying biomarkers of disease progression or reversal in areas that have been traditionally difficult to study, such as neurodegenerative diseases and early indications of anti-tumor effect. The availability of imaging equipment (MRI, CT, SPECT and PET) in modern hospitals and

electronic transfer of images for centralized evaluation has increased the use of imaging technologies in clinical trials. Clinical trials involving imaging require training of participating site(s) to ensure that images are captured in a consistent and appropriate fashion. As with sample handling for biochemical markers, logistical considerations have to be carefully planned and considered in these studies.

The capacity to store and transmit digital data has increased exponentially in recent years and affects many aspects of our lives. High definition images and fast data feeds will change the way we analyze data in early clinical research. Celerion has leveraged evolving digital technologies to provide wireless instant capture of ECG signals from Bluetooth-enabled Holter monitors combined with automated analysis of the tracings on demand. This technology provides more enriched, real-time cardiac safety data during early clinical assessments of new drug candidates as well as a faster and more cost-effective approach to collecting and assessing data from thorough QTc studies. Therefore, the ability to quickly capture and analyze dense datasets is facilitating the generation of useful biomarkers from well-known signals of drug effect.

Conclusion

Biomarkers are a critical element in achieving better decisions faster in early drug development. The exploding universe of potential technologies creates opportunity to look at drug development in new ways but also challenges scientists, engineers and regulators on what to deploy when, to achieve benefits from the judicious use of new biomarkers.