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BIOMARKERS IN EARLY DRUG DEVELOPMENT

The EMA glossary defines a biological marker, or biomarker, as 'an objective and quantifiable measure of a physiological process, pathological process or response to a treatment (excluding measurements of how an individual feels or functions)'. Similarly, the FDA defines a biomarker as 'a defined characteristic that is measured as an indicator of normal biological processes, pathogenic processes, or responses to an exposure or intervention, including therapeutic interventions. A biomarker is not an assessment of how an individual feels, functions, or survives'.

Under these (somewhat) vague definitions, biomarkers are very diverse types of measures which quantify physiological processes, from cellular to organism level, with the purpose of a biomarker defining its respective category (see below 'Types' and 'Categories').

Although the term biomarker is relatively new, using these as a proxy for certain conditions has been clinical practice for centuries, with a famous example being salty sweat in children with cystic fibrosis. Some biomarkers, such as heart rate/pressure, urine analysis or blood cholesterol levels, are very commonly used as indicator of organ-level disfunction. With the rise of -omics and other advances in molecular biology, new biomarker studies have shown potential for early diagnosis and/or prognosis, and in some cases the promise of effective and/or personalized treatment of many diseases (see 'Efficacy Biomarker Identification').

In clinical trials, biomarkers can serve as intermediate milestones in the strategic development of a novel (or repurposed) therapeutic by helping to determine if a given candidate has the potential to be disease-modifying (see 'Biomarkers in (Early) Clinical Development').

While this blog-entry focuses more on the use of biomarkers as surrogates for efficacy. It is very important to emphasize, in line with the rather broad definitions of biomarkers given above, that biomarkers can be used for many potential purposes. Hence, it is useful to define biomarkers by their properties (type) and purpose (catergory), and, thus, be as specifics as possible in what aspect of drug development can be assisted by a given biomarker.

Biomarker Types and Categories

The technical type of biomarker is often based on their (quantification) technique or procedure, namely whether they are molecular, histologic, radiographic, or physiologic. Molecular biomarkers comprise methods of biophysical or quantitative measurements from biological samples, such as plasma, cerebrospinal fluid, bronchoalveolar lavage or biopsies (e.g. blood sugar levels); histological biomarkers reflect biochemical or phenotypical alterations in cells, tissues or fluids (e.g. Grading and staging of cancer); radiographic biomarkers are obtained from imaging studies (e.g. Bone mineral density); lastly, physiologic biomarkers measure body processes (e.g. Blood pressure).

An example for categorising biomarkers by their clinical application is provided by the BEST (Biomarkers, EndpointS, and other Tools) Resource published by the FDA (link here), as listed below, with their respective definition, with examples given:

Susceptibility/Risk

A biomarker that indicates the potential for developing a disease or medical condition in an individual who does not currently have clinically apparent disease or the medical condition. Examples: LDL cholesterol levels in blood as a risk factor in heart disease or BRCA2 mutations for breast cancer.

Diagnostic

A biomarker used to detect or confirm presence of a disease or condition of interest or to identify individuals with a subtype of the disease. Example: Sweet chloride measurement in individuals with cystic fibrosis.

Monitoring

A biomarker measured repeatedly for assessing status of a disease or medical condition or for evidence of exposure to (or effect of) a medical product or an environmental agent. Example: blood glucose level and its response to therapeutic (candidates) in individuals with diabetes.

Prognostic

A biomarker used to identify likelihood of a clinical event, disease recurrence or progression in patients who have the disease or medical condition of interest. Example: In cancer, a stage of disease score is employed to assign chance of relapse to individuals.

Predictive

A biomarker used to identify individuals who are more likely than similar individuals without the biomarker to experience a favorable or unfavorable effect from exposure to a medical product or an environmental agent. Example: Preserved Ejection Fraction in cardiovascular indications to estimate progression towards need for heart transplant.

Pharmacodynamic/Response

A biomarker used to show that a biological response, potentially beneficial or harmful, has occurred in an individual who has been exposed to a medical product or an environmental agent. Examples: In individuals with Gauchers disease, levels of ^{4}glucocerebroside are measured to quantify effect of enzyme replacement therapy.

Safety

A biomarker measured before or after an exposure to a medical product or an environmental agent to indicate the likelihood, presence, or extent of toxicity as an adverse effect. Examples: bilirubin can be used to monitor for hepatotoxicity, or creatinine as a marker for nephrotoxicity.

Biomarker Identification and use in (early) clinical development

Careful consideration needs to be paid on how the above categories can be used in clinical practice, by first defining the purpose of the biomarker employed, and determining whether a given biomarker is fit for purpose (FFP), and evidence available to support its use (validation), but this merits a blog-entry by itself. As a recap, as introduced above, examples of biomarker purposes include safety (e.g. a biomarker established during non-clinical safety/tox studies), patient eligibility screening (e.g. diagnostic), patient stratification (e.g. prognostic) and monitoring of response to therapeutic intervention (e.g. pharmacodynamic/response).

For the example given here, we assume a hypothetical biomarker will provide a path to test a mechanistic hypothesis as postulated by experiments in preclinical disease models i.e. would categorise as PD/Response biomarker. One of the main appeals of such biomarkers, is that in contrast to more conventional approaches of using clinical endpoints alone (e.g. quality of life or mortality), these biomarkers can provide objective data during early drug development to inform later clinical development strategy.

In this perspective, the ambition is to use a biomarker-driven approach to shorten clinical trial time and speed up product development, and ultimately increase chances of regulatory approval.

Ideally, when considering choosing a potential biomarker for use in a clinical trial setting, this should be part of discovery efforts. In practical terms, in the context of repurposing medicines, when screening approved medicines with a (novel) disease model (in vitro or in vivo), it is useful to establish how a given model represents a given disease, and how the models' outcome measure relates to for example disease onset, progression or regression. This allows alignment with clinical outcome measures.

Hence, it is of primary importance to determine the suitability of a biomarker in providing (supporting) evidence of a specific hypothesis to be explored during (early) clinical trials. During non-clinical work, potential[5] biomarkers should be evaluated for their clinical application categories (as listed in 'Categories'). For early clinical trials, perhaps the most relevant categories are safety, but also efficacy. The importance of safety biomarkers should be self-explanatory in its importance, with in vivo experiments potentially identifying specific signals related to adverse effects of a therapeutic candidate guiding clinical trial design.

Efficacy biomarkers identified in non-clinical work can be useful in establishing early signs of disease-modifying potential. For example, a biomarker can establish, directly or indirectly, that the (molecular) mechanistic or phenotypical outcome measures used in the disease model are indeed modulated by the candidate therapeutic agent in a clinical setting. These non-clinical observations should be considered when designing a clinical trial, including evaluation of appropriately powering a study to test a specific hypothesis.

Also, regulatory considerations on validity of a biomarker, including its standardisation, are integral part of choosing a specific efficacy biomarker.

Overall, in the context of early clinical development, an ideal biomarker responds in a relatively short timeframe indicating potential improvement. These can sometimes be characterized as pharmacological target engagement biomarkers: to give an example, in a therapeutic designed to modulate enzymatic activity against a substrate, the biomarker can report directly (e.g. Enzymatic inhibition or potentiation), or indirectly (reduced or increased levels substrate) on the desired molecular mechanism of action.

These biomarker observations can potentially 'gate' clinical development, by providing supportive evidence that a therapeutic candidate has disease-modifying potential. Furthermore, these early studies can establish a relation or correlation to other clinical outcome measures, and hence providing additional lines of evidence in support of further clinical development.

Here at 3D-PharmXchange, we keep up to date with the constantly evolving field of biomarkers in drug development and have ample experience with designing strategic development plans to include biomarker-driven approaches. We have hands-on operational expertise in selecting and implementing biomarker measures in non-clinical studies and clinical trials, as well as a proven track-record of accurately evaluating feasibility, costs, and risks. As part of our multidisciplinary drug development approach, we carefully weigh all these factors to meet the clients' goals, and strongly believe that biomarkers can play a pivotal part in being successful/accelerating drug development: from de-risking early drug development (e.g. as mechanistic proof-of-concept), all the way to registration trials based on biomarkers. We look forward to hearing about your project and are available to discuss your biomarker needs!