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HOW TO SUCCESSFULLY DEVELOP AND VALIDATE MOLECULAR BIOMARKERS FOR USE IN CLINICAL TRIALS

In our previous blog, entitled "Biomarkers in early drug development", we highlighted the different types of biomarkers and their applications in (early) drug development. We discussed that biomarkers have the potential to speed up and enhance the chances of success of a clinical development program. A biomarker can, for example, define a patient subset most likely to respond to a novel drug compound, or act as an early indicator of efficacy or safety. In the ideal situation, a biomarker (or panel of biomarkers) is developed in parallel with the (novel) drug compound as it moves through the development pipeline. Implementation of a biomarker strategy helps make sure that the biomarker is fit-for-purpose (FFP) for its intended use and can, for example, test hypothesis, bridge pre-clinical and clinical data or inform clinical study design.

Selecting the right biomarker is essential to its usefulness in a drug development program. The process of biomarker selection and development can be divided into three main categories: 1) discovery and selection, 2) analytical method development and validation and 3) clinical validation. The extend of validation that is needed is dependent on the context of use (CoU) of the biomarker. For example, for an exploratory or early biomarker basic analytical validation often is sufficient. These types of biomarkers are typically used to obtain proof of concept or assist with dose selection, but are not used to confirm clinical efficacy of a drug compound. A fully qualified biomarker (the complexity of which merits a separate blog) can be used as a surrogate clinical endpoint and has the potential to significantly shorten trial duration and costs. This is because it generally takes less time to see an effect on a surrogate than on the true clinical endpoint. However, for a biomarker to be approved as a qualified biomarker by regulatory authorities, extensive analytical and clinical validation is needed. This step has proven challenging; over recent decades many potential biomarker candidates were identified, but only a small fraction has progressed to clinically useful surrogate endpoints or diagnostics.

Molecular biomarker discovery and selection

The selection of, and criteria for, an ideal biomarker have been briefly touched upon in our previous blog. To recap, a biomarker should show a quantifiable response within a relatively short timeframe and be related to a disease relevant clinical endpoint, the mode of action of the drug compound or be indicative of the presence of drug compound within the target compartment. When selecting the right biomarker for a clinical development program it is important to consider several sources, ranging from (in house) performed experiments to a thorough literature review, all keeping in mind the intended CoU.

Many molecular biomarker candidates are originally identified in discovery experiments using omic techniques like (epi)-genomics, proteomics or metabolomics. This is especially the case when looking for molecules that can be used as markers of drug efficacy or safety, or as a screening tool to predict or monitor disease development.

A thorough statistical analysis of the data generated is important to select the most ideal candidates for further investigation. It is important to always keep the intended CoU in mind, as, for example, a promising candidate identified in pre-clinical model systems may not always suitable biomarker if the ultimate goal is to measure it in human biofluid, like plasma or CSF.

Analytical method development and validation

Once a biomarker candidate is selected, the process of analytical method development and method validation starts. As mentioned, many molecular biomarker candidates are discovered and selected using omics techniques. These platforms often present data in a semi-quantitative way, but do not offer an absolute quantitative measure. Analytical method development starts with choosing the right method for quantification of a biomarker. Sometimes a validated analytical method is already available, but in many cases a novel method will need to be developed. This is often the case when the biomarker candidate is a molecule not previously associated with a disease or drug mode of action, nor analyzed in routine clinical chemistry laboratories. Bioanalytical CROs offer method development and validation services for biomarkers, but depending on the CoU, method development and (partial) validation can also be performed in house.

The goal of analytical method validation is to demonstrate that the technical performance of the developed method is as expected. This ensures that the generated data is trustworthy and reproducible. Contrary to the field of bioanalysis or routine laboratory diagnostics, the field of biomarkers is not highly regulated. It is specifically mentioned that biomarkers are out of scope of the M10 Guidance for Bioanalytical Method Validation and Study Sample Analysis. The reason provided is that biomarker types, their applications and analytical techniques, are so diverse, it is impossible to capture in a single guidance document. Therefore, it is important to consider the CoU and performance criteria for the selected biomarker and develop it to be FFP to that need. A method is considered FFP when its analytical performance is sufficient to support the intended purpose of the data. A biomarker method that is used as an exploratory marker has to adhere to less stringent criteria then a biomarker used to enrich a clinical study with subjects most likely to respond to drug compound. Deciding what FFP looks like and which validation parameters are most crucial requires extensive technical and methodological knowledge and a strategic mindset.

Biomarker clinical validation

Clinical validation of a biomarker is the process of proving that a biomarker is clinically useful and linked to a clinical endpoint. This process is required for full biomarker qualification, for example via the FDA biomarker qualification program. It is important to say that clinical validation is a process that is time consuming and should be part of the biomarker strategy early on. The data that is required for proof of clinical validity is extensive, should preferably come from several independent sources and provide a high level of evidence that the biomarker is indeed clinically relevant and predictive of a clinical endpoint.

Data supporting biomarker clinical validity may come from literature, cohort studies and/or clinical trials. This data should, amongst others, characterize the relationship between the biomarker and the clinical endpoint and provide a biological rationale for its use. Data generated in clinical trials (starting in early phase but progressing to confirmatory trials) is ideally suited to demonstrate a correlation between the biomarker and the clinical outcome. The latter is important when the ultimate goal is, for example, to implement the biomarker as a companion diagnostic to a drug compound once it is on the market. It is important to note that although biomarker clinical validation is important, the degree of clinical validation should always be in line with the CoU of the biomarker.

What can 3D-PharmXchange do for you?

The process of selecting and validating biomarkers, as well as determining which level of validation is required for a biomarker to be FFP and useful for your clinical program, is a complex process. 3D-PharmXchange has expertise in developing a biomarker strategy as part of each clinical development program. We can assist in selecting the right biomarkers and determining the optimal level of validation for it to enhance a clinical development program in a cost-effective manner. Within our company we have the technical expertise necessary to advise in the selection, development and validation of a method that is FFP and can also assist in selecting and overseeing the right bioanalytical vendor to perform validation and sample analysis. We have extensive expertise in biomarker driven clinical trial design and can help in generating data that is acceptable as proof of clinical validity and can help you compile and submit for approval as a qualified biomarker. Please reach out if you would like to discuss further.

Stay updated with the latest insights and developments by subscribing to our blog and following us on Linkedin. Let's work together to bring innovative therapies to the market.

Keywords: *Molecular biomarkers, Biomarker strategy, Biomarker validation, Clinical biomarkers, Analytical method development, Clinical validation biomarkers, Biomarker qualification program, FDA biomarker qualification, Companion diagnostics, Bioanalytical CROs, Fit-for-purpose biomarkers, Biomarker-driven clinical trials, Drug development biomarkers, Biomarker method validation, Early drug development, Omics techniques biomarkers, Biomarker clinical endpoints, Biomarker discovery process, Disease-relevant biomarkers, Biomarker strategy consulting*