Non-imaging biomarkers and regulatory aspects of imaging biomarkers

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**Biomarkers**, characteristics that are objectively measured and evaluated as indicators of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention,¹ can aid in understanding diseases, diagnosing diseases, predicting progression, regression, or treatment outcome of diseases, monitoring early signs of toxicity and signaling the potential for severe toxicity.²,³ Biomarkers cover a wide range of measurements from protein levels to basic physiological measurements (such as blood pressure) and morphologic measurements (such as cartilage volume by magnetic resonance imaging). Most non-imaging, non-physiologic biomarkers are based on ‘-omic' technologies (genomics, proteomics, and metabolomics) and involve quantitative measurements of DNA, RNA, protein or metabolites by *in vitro* analysis of body fluids or *ex vivo* analysis of tissues.⁴

Although biomarkers have been used in clinical practice, drug development and regulatory evaluation of new drugs for many years, there is currently an increased focus on them as a means to accelerate and reduce the costs of developing more effective, more affordable, and safer therapeutics for patients. Biomarkers can provide information critical to both internal decision-making (i.e., establish presence and/or coverage of target, evaluate biological and/or clinical activity, dose selection for later phase trials, stratify study populations, conduct interim analysis of efficacy and/or safety) and establishing efficacy and/or safety for regulatory approval as a substitute for a clinical characteristic or variable reflecting patient feeling, function or survival (i.e., a **surrogate endpoint**). Although there are many biomarkers under development, it must be emphasized that there are currently very few surrogate endpoints that are recognized by the FDA. The only current examples include: blood pressure, intraocular pressure, HgBA1c, psychometric testing, tumor shrinkage, ACR criteria, bone mineral density and pain scales.

In order for biomarkers to be useful, in addition to evaluating their analytical performance (e.g., sensitivity, reproducibility, etc.),⁵ it is critical to link what is measured with biological and/or clinical endpoints to ensure it is suitable for the intended use. Although this has often been referred to as biomarker ‘validation’, there has been considerable confusion with the use of ‘validation’ in this context primarily due to the implication of an either/or status irrespective of the intended use of the biomarker. In order to recognize that demonstrating a biomarker is suitable for use in drug development is a process rather than an endpoint, the FDA recently introduced the concept of **qualification** of biomarkers.⁶

As one would expect given the motivation for the FDA introducing the term qualification, the rigor required to qualify a biomarker depends on its intended use(s). First, the technology must be sufficiently safe for animals or humans, depending upon its purpose. If the biomarker is used for internal preclinical decision-making, qualification includes establishing that the method accurately measures the desired information and is technically reliable (i.e., reproducible and precise). Qualification of biomarkers used for internal decision-making in clinical studies requires that the technical reliability in a clinical setting and the value added are documented by a combination of preclinical studies, clinical studies (with or without an experimental drug), and the biomedical literature. If biomarkers are used for regulatory licensure decisions, in addition to
the requirements for internal decision-making, qualification requires a broad-based
demonstration of the performance in late-stage clinical trials (e.g., Phase 2-3), generally
conducted at multiple institutions by more than one company, and acceptance by the appropriate
regulatory agency.

The accumulation of evidence that may ultimately qualify a biomarker as a surrogate endpoint
can also be viewed as stages in the development of that biomarker. In the initial stage of
‘exploration’, evidence is accumulated to show that the biomarker actually measures the
biological process of interest, but there is no consistent information linking the biomarker to
clinical outcomes in humans. In the next stage of ‘demonstration’, the accumulating evidence
demonstrates a link with clinical outcomes in a limited number of clinical studies, but the results
have not been reproducibly demonstrated. This category corresponds to ‘probable valid
biomarkers’ in nomenclature suggested in a draft guidance from the FDA for submitting
pharmacogenomic data (it should be noted, this draft was created before the FDA introduced the
concept of qualification). As evidence accumulates from multiple prospective clinical trials
linking the biomarker with clinical outcome, it moves into the ‘characterization’ stage. This
category corresponds to ‘known valid biomarkers’ in nomenclature suggested in the FDA
pharmacogenomic guidance. Finally, a stage of ‘surrogacy’ is reached when a holistic
evaluation of all of the available data make it obvious that the biomarker provides a suitable
substitute for a clinical endpoint. As noted above, this designation of surrogate end point
requires agreement with regulatory authorities.

It is important to note that biomarkers are often used in clinical practice independent of being
recognized by the regulatory agencies as surrogate endpoints and can be of considerable value in
the drug development process long before they reach the stage of surrogacy. They can be used in
preclinical studies and for hypothesis generation even during the exploration stage. If the
biomarker provides unique or more precise information compared to existing technologies,
biomarkers in the demonstration stage can be very valuable. Their use to assess target coverage
or biological activity in a limited number of subjects over a short period of time can have a
significant impact on our ability to identify ineffective molecules earlier, eliminating the need for
long, large and expensive clinical trials doomed for failure. For molecules that demonstrate
target coverage/biological activity, information from biomarkers can help to better design studies
for the next step of clinical development.

References
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