

VIEWPOINT

Biomarkers and Surrogate Endpoints

Developing Common Terminology and Definitions

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Biomarkers, surrogate endpoints, and clinical outcome assessments provide **an essential set of tools needed to translate scientific concepts into diagnostic and therapeutic approaches and technologies**. Recently, biomarkers have been promoted as offering significant potential for accelerating basic science, drug discovery, and medical product development, as well as improving clinical care.¹ **Examples of common biomarkers include breast cancer genes 1 and 2, prostate-specific antigen, and hepatitis C virus ribonucleic acid**. Although new analytical approaches and omics-based technologies have yielded a rapidly expanding array of biomarkers, precisely how and when they should be used has not been clearly described.

Progress has also been slowed by the challenges presented by an evolving understanding of the complexity of biology, its dynamic reciprocal links with environment, and the challenges of determining whether biomarkers are fit for different purposes. This latter issue has proven to be especially difficult in the context of efforts to use biomarkers as surrogate endpoints in clinical development programs.² **Examples of biomarkers used as surrogate endpoints for this purpose include (1) blood pressure reduction, used to support the approval of drugs intended to treat hypertension; (2) hemoglobin A_{1c}, used to support the approval of drugs intended to treat diabetes mellitus; and (3) HIV-RNA reduction, used to support the approval of drugs to treat HIV**. However, an even more fundamental issue is the problem of terminology.

Recognizing that unclear terminology and definitions impede progress, the Joint Leadership Council of the Food and Drug Administration (FDA) and the National Institutes of Health (NIH), in the spring of 2015, identified the harmonization of terms used in translational science and medical product development as a high priority. Members from multiple FDA centers and NIH institutes formed a working group to focus on the creation of the Biomarkers, Endpoints, and other Tools (BEST) resource,³ which would include a glossary of terms that could serve as a point of consensus for all stakeholders and provide the clarity needed to drive progress in biomedical research and clinical care, with the understanding that the glossary could be continuously extended and elaborated. The group considered existing terms and definitions, including those appearing in the literature or used in FDA guidance documents, as the basis of their work.

The current glossary focuses on providing the necessary context around biomarkers and clinical assessments, as well as delineating and illustrating their various potential or actual roles in research and medical product development. The initial focus of the glossary is on medical products (eg, drug and medical devices), with the goal that the proposed definitions can also be adopted by communities that use biomarkers for other

aspects of public health (eg, food safety, tobacco-containing products). Although greater emphasis has been given to biomarker definitions and uses in the current version, future iterations will more fully explore uses of clinical assessments in biomedical research.

This emphasis is particularly important because, although biomarkers play crucial roles throughout various stages of medical product development, translational science research, and health care, the lack of clear terminology is distracting and disruptive for stakeholders attempting to use biomarkers, which are understood 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. Molecular, histologic, radiographic, or physiologic characteristics are types of biomarkers. A biomarker is not an assessment of how an individual feels, functions, or survives."³

Biomarkers can help identify populations more likely to benefit from a given treatment or intervention. However, problems may arise when the terms *biomarker* and *surrogate* are used interchangeably, even though few biomarkers have met the rigorous criteria required to be used as surrogate endpoints to support medical product approval. A surrogate endpoint is defined as

"...an endpoint that is used in clinical trials as a substitute for a direct measure of how a patient feels, functions, or survives. **A surrogate endpoint does not measure the clinical benefit of primary interest in and of itself, but rather is expected to predict that clinical benefit or harm based on epidemiologic, therapeutic, pathophysiologic, or other scientific evidence**. From a US regulatory standpoint, surrogate endpoints and potential surrogate endpoints can be characterized by the level of clinical validation: validated surrogate endpoint, reasonably likely surrogate endpoint, candidate surrogate endpoint."³

Surrogate endpoints can be used in a trial intended to show efficacy and support marketing approval or new indications for a medical product. To ensure that the medical product has the expected effect, validation of a candidate surrogate endpoint for this purpose requires 2 key elements: (1) substantive data supported by a clear mechanistic rationale; and (2) clinical data providing strong evidence that an effect on the surrogate predicts clinical benefit. This is important because despite being excellent biomarkers in many cases, most candidate surrogates have been shown not to predict clinical benefit with enough accuracy to provide a reliable basis for clinical decision making.² This is illustrated by the failure of antiarrhythmic agents in the Cardiac Arrhythmia Suppression Trial (CAST) to improve survival by depressing ventricular ectopic beats; in this case, the drugs were effective in suppressing ectopic

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beats, but caused increased mortality.⁴ Clear, comprehensive definitions are needed across the spectrum, and critical concepts and constructs should be identified for consistent use, albeit with full recognition of their situation-specific applications.

To succeed, several considerations had to be accommodated during the glossary's development. **First and most important is the recognition that biomarkers serve multiple purposes.** For example, biomarkers are regularly used in clinical practice to define disease, select therapies, choose drug dosage, and establish prognosis. They can be used at an early stage in the clinical development cycle of a medical product to enrich the populations of small trials with patients who are most likely to benefit from the investigational therapy or to choose patients more likely to have the study endpoints of interest. In the later stages of clinical development, biomarkers that have been validated as surrogates (eg, Hemoglobin A_{1c}; blood pressure) and therefore are known to predict an effect on clinical events or future outcomes can be used to support regulatory decision making. Although these various categories are not mutually exclusive, there is no reason to assume that any single biomarker will perform and be applicable in every possible setting. For example, a biomarker valuable for establishing prognosis may not have value as a surrogate endpoint to measure effectiveness.

Second, novel biomarkers are being identified at a rate that has outstripped the collective capacity to fully evaluate and validate their use across the potential applications (previously described). It is now possible to measure an enormous number of biomarkers—but each must be investigated sufficiently to define its operating characteristics for diagnostic or prognostic predictions or surrogacy. Ultimately, clear definitions and better public access to information will enable the appropriate evaluation of biomarkers, reduce or eliminate redundant efforts, and focus attention on research capable of answering critical questions.

Third, differing levels of evidence will be needed to support biomarker use, depending on the setting and intended application. For instance, relying on a biomarker for use in supporting a regulatory marketing decision on a medical product's effectiveness (ie, as a validated or reasonably likely surrogate endpoint) will require a higher level of evi-

dence than would be needed to support the use of a biomarker in enriching a patient population for clinical trial enrollment. This is because in the first example, the biomarker is the basis for a regulatory decision and is directly related to the demonstration of safety and efficacy. However, the second example only uses the biomarker as a tool in facilitating trial conduct.

Despite the inherent challenges of this effort, significant progress is being made. Recently, **the FDA issued 2 guidance documents for industry: one on the qualification of medical device development tools⁵ and the other on qualification for drug development tools, including biomarkers and clinical outcome assessments.⁶** As described in the latter draft guidance, FDA qualification of a medical product development tool specifically refers to the regulatory conclusion that within the stated context of use, the tool can be relied upon to have a specific interpretation and application in medical product development and regulatory review. For example, the FDA's Center for Drug Evaluation and Research has qualified galactomannan in serum and/or bronchoalveolar lavage fluid as a sole microbiological criterion to classify patients as having probable invasive aspergillosis (IA) as defined by the European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and Infectious Diseases Mycoses Study Group in 2008, for enrollment in, and analysis of, clinical trials conducted to evaluate the efficacy and safety of drugs for the treatment of IA. In addition, the Biomarker Consortium of the Foundation for the NIH is supporting a broad array of biomarker identification, classification, and validation efforts in multiple areas.

This glossary is envisioned as a dynamic document that will foster a shared understanding among all who study and use biomarkers and clinical assessments, and it may potentially accelerate the pace of development, validation, and qualification of these tools to support medical product development and health care delivery. Developing common terminology and definitions will enhance the ability to confront other challenges inherent in the development, validation, qualification, and appropriate application of biomarkers, clinical assessments, and other tools and work to realize their promise for improving research and clinical care.

ARTICLE INFORMATION

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