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Biomarker Editorial: The Many Lives of the Biomarker

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Biomarkers became “legitimate” at the joint NIH/FDA/industry meeting held at the National Institutes of Health in April of 1999. Definitions were made distinguishing different types of biomarkers and numerous interesting applications were presented. This was considered to be a milestone in terms of creating the biomarker industry as a business. It is often forgotten that biomarkers have been around for as long as life science or biomedical research has been performed. A recent diagnostics conference presentation focused on the future of imaging as a biomarker/diagnostic in drug development and biomedical research. The audience was reminded that X-rays have been used as a medical diagnostic for over 120 years! The only difference was that the term *biomarker* was not used. They were called biological or clinical endpoints, diagnostics, outcomes, and so on.

Since this 1999 NIH meeting, the pharmaceutical industry has spent hundreds of millions of dollars searching for, identifying, and developing new biomarkers. The regulatory agencies in virtually all countries have embraced the importance of biomarkers in drug development and, to a lesser extent, in drug approval. Many technology companies have sprung up focusing on developing specific biomarkers, biomarker technology platforms, and multiplex assays. In addition, many biomarker services have grown out of existing contract research organizations and

central labs and companies focused on delivering biomarker contract services. There have been many detailed reports, reviews, chapters, and even books published about biomarkers. In fact, a parallel industry to the pharmaceutical/biotech industry has been created. Biomarkers have even entered the consumer markets. Companies such as Nestlé, Procter & Gamble, and Unilever all recognize that biomarkers provide an opportunity to legitimize the science behind their products.

Multiple technologies, highly integrated in other industries, have been translated into life sciences and biomedical research. Techniques such as spectroscopy (visible, fluorescence, IR, acoustic spectroscopy, mass spectroscopy) have all been published upon as potential platforms for methodologies. Likewise, it is valuable to consider all platforms when discussing biomarkers. Too often individuals discuss biomarkers and imaging as two separate entities—imaging is a technology that provides a biomarker endpoint.

However, with all of this activity, internal resources, and finances spent on biomarkers, one often hears debates as to the value of biomarkers. Do we have too many? Do we need them for this or that application? If we consider that we have always used them in biomedical and life sciences research, then there is no argument as to their value. So, what is the problem? There

are numerous answers, and depending on one's perspective, the priorities shift. One of the most common challenges is the issue of "validation" or, more recently, "qualification." Back in the late 1990s, there was an FDA Science Forum session on emerging technologies and how they would be incorporated into drug development. Much of the discussion revolved around the issue of validation. It was concluded that it is very difficult to define a generalized pathway for validation of biological/biochemical technologies. Methodologies such as H & E staining, which had been used for over 100 years, had never been validated. The previously cited X-ray has been standardized in terms of the instrument, but even today with more sophisticated imaging modalities such as MRI, PET, and ultrasound, there is considerable skepticism regarding the requirements for validation. While validation can be established for chemical-based assays, this is considered to depend on development of SOPs (standard operating procedures) of technical factors to enhance sensitivity and specificity. In the case of a clinical biomarker, there are two forms of validation: the technical or analytic, which refers to the instrumental related aspects, and the clinical validation. The discussion at the FDA Science Forum suggested that rather than validation it should be more of reaching a "comfort zone," referring to the clinical validation. Basically, what this means is that there is no substitute for experience. So, the more a test is used, the more it will be viewed as being "validated." Another term that has been proposed instead of validation is *qualification*. We can define the technical or analytic validation very well, and in fact, many of the research instruments are at a higher specificity and sensitivity than many of the diagnostic devices.

Another concern is the risk of using an unvalidated biomarker in a new application for a drug in development. Is it the drug or the biomarker that is responsible for the positive or negative response? The author of this editorial has heard many people say that biomarkers just raise more questions. This then comes back to the "comfort zone" concept. Of course, the person developing

the biomarker completely believes in whatever result is obtained, while the researcher working on the drug development may be more reluctant to "kill" a compound due to a result from a new biomarker as he/she/they have already invested much in terms of resources and costs in the compound. This results in a situation wherein other established biomarkers are used to provide confidence in the new biomarker, which would appear to defeat the purpose. Interestingly, the drug developer tends to be risk-averse, often reluctant to use new biomarkers. The author has heard comments in which a commercial person has said, "Just go and use the biomarker, as the compound will fail anyway. At least we can gain confidence and knowledge in the biomarker." This is a difficult challenge.

Another concern to management is the cost versus benefit of the biomarker. Should biomarkers be developed internally or externally? If you ask the internal biomarker person, you know what the answer will be? This is a complicated issue made even more difficult as there is no business model for biomarker development. There have been numerous models focusing on evaluating the benefit, but they have not been run as a business. A senior pharmaceutical executive had said at a conference, "It is easier to kill the lead chemist than the lead compound." I would argue it is easier to kill both of these than the biomarker lead or biomarker itself.

Much has also been talked of in terms of translational biomarkers. The focus has been on translating from preclinical to clinical. Imaging biomarkers/methodologies are providing some excellent examples. However, I would emphasize that the translation from clinical trials to clinical practice is severely neglected. Here the translational biomarker relates to the translation of a clinical endpoint or surrogate to a diagnostic. While biomarkers are being used for patient selection/segmentation, the clinical endpoint is often different from the diagnostic/diagnosis used in clinical care. This is a lost opportunity as it does make sense to establish the conditions for clinical care during the clinical trials process, particularly phase III. This is something that needs collaboration among

pharmaceutical companies, regulatory agencies, and the technology companies.

The following articles provide some excellent insights by some of the thought leaders in biomarker research and application. In addition, there is a diversity of different perspectives as the representation is from academia, industry, and government. We must focus on such applications as these provide the positive examples that we need to continue to develop the biomarker industry. Considerable work needs to be done to continue to develop this evolving business, and

it will be interesting watching its progress. It relies very heavily on the pharmaceutical industry, which is undergoing its own considerable difficulties. With the FDA Critical Path activity, many consider that the biomarker industry will be part of the way to the new “promised land” of the pharmaceutical industry. In the meantime, we all need to continue to improve our level of knowledge of the “biomarker space” so that the challenges for their acceptance and their subsequent impact on the drug development process will be continually advanced.