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Biomarkers on a roll

A consortium of industry, nonprofit institutions and regulators outlines a rolling biomarker qualification process, providing the first clear path for translation of such markers from discovery to preclinical and clinical practice.

This issue presents the results of the first set of studies by the Predictive Safety Testing Consortium (PSTC), a collaborative effort of scientists from 15 pharmaceutical companies and 2 biotech companies, four academic institutions, the Critical Path Institute, the Food and Drug Administration (FDA) and the European Medicines Agency (EMEA; now EMA). These studies provide data supporting the utility of seven renal biomarkers in safety testing in the preclinical setting. They have now been formally accepted by the US and European regulatory authorities, with a decision expected from the Japanese Pharmaceuticals and Medical Devices Agency next month.

From an industry standpoint, drug-induced toxicity is a serious issue, killing 30% of compounds overall, from leads in the preclinic all the way to marketed products. The availability of better preclinical toxicity biomarkers thus remains a key strategic goal.

What makes a good safety biomarker? In essence, there are three important technical attributes: first, the marker must be present in peripheral body tissue and/or fluid (e.g., blood, urine, saliva, breath or cerebrospinal fluid); second, it must be easy to detect or quantify in assays that are both affordable and robust; and third, its appearance must be associated as specifically as possible with damage of a particular tissue, preferably in a quantifiable manner. Existing renal damage biomarkers such as serum creatinine (SCr) and blood urea nitrogen (BUN) meet the first two criteria. However, regulators have now accepted that in preclinical testing, at least, six other renal drug safety biomarkers—Kim-1, albumin, total protein, β2-microglobulin, cystatin C and clusterin—outperform the traditional markers in specificity and sensitivity.

A 'good' biomarker, therefore, can be defined technically. But a more interesting question is, what makes a 'qualified' biomarker? In other words, what does it take to convince a regulator of a biomarker's utility? This is the question that the PSTC set out to answer.

Under the coordination of the nonprofit Critical Path Institute, the PSTC was formed in 2006 and has grown to encompass around 190 industry and government scientists. After preliminary discussions among all the participants, 23 urinary biomarkers were selected and 33 studies in rats conducted at Novartis, Merck and FDA then correlated the levels of seven biomarkers as well as SCr and BUN with different histopathological assessment for different kidney lesions. Between June 2007 and January 2008, these data were presented to the authorities, which by April 2008 had accepted that these biomarkers outperformed the current standards.

Agreeing upon multiple nephrotoxicity biomarkers at the same time is, of course, an important achievement in its own right. But the larger contribution of the PSTC is that there is now a formal, standardized regulatory review process for the qualification of biomarkers. A biomarker can be qualified by the regulatory authorities as long as there is appropriate data support. In the case of the PSTC's nephrotoxicity biomarkers, the FDA and EMEA regard the tests as 'fit for purpose' in preclinical research only because the data presented are from animal toxicity testing. Under the new 'rolling' qualification process, the aim is that some or all of these urinary biomarkers could subsequently be 'qualified' for clinical drug-induced nephrotoxicity once further supportive human data are submitted. Similarly, other groups at the PSTC are hoping to generate preclinical data in the coming months on drug-induced hepatotoxicity, myopathy, vascular injury and nongenotoxic carcinogenicity in rodents.

Importantly, the PSTC process is both cooperative and transparent. One group of regulatory representatives acted as advisors to the pharma teams. Separate teams within the regulatory agencies then assessed the data submissions, providing specific feedback on the need for more experimental data at additional time points, proper blinding of the samples during the assessment of kidney tissue sections by pathologists and additional types of statistical analysis of the data set.

This leaves the question of why it has taken so long for regulators and industry to agree upon standards for such a fundamental piece of data. After all, all of the newly qualified markers had been known to be associated with kidney damage for years, some of them for decades. Furthermore, the limitations of BUN and SCr have long been appreciated.

One explanation is the inadequacy of biomarker research and development. The literature throws up dozens of new potential biomarkers each month but too many of these studies lack sufficient rigor for translation into drug development, let alone regulatory qualification. Too often, studies lack adequate description of the sampling, data generation or statistical analyses. Others are underpowered or inadvertently biased or identify biomarkers on the basis of portions of cherry-picked data.

But a larger part of the answer lies in the fact that cooperative relationships between regulators and drug companies are a relatively new development. The April 2008 announcement of the approval of the PSTC's renal biomarkers was the first ever cooperative decision by the FDA and EMEA made on the basis of a joint data submission. Pan-industry research collaborations are also new. The FDA's Critical Path Initiative started in 2004, the PSTC in 2006 and the Innovative Medicine Initiative in 2007 (operationally in 2008). Until the formation of these structures with a clear mandate to address toxicity markers, industry had no framework to engineer cooperative initiatives. The PSTC provides that framework, allowing participants to work under a legal agreement that covers intellectual property, confidentiality and material transfer.

The PSTC is undoubtedly a major step forward in rationalizing the development of toxicity biomarkers. Industry now has a clear path to qualify biomarkers in the preclinical and clinical settings. The jury remains out on whether pioneer pharmaceutical companies will share knowledge on *novel* biomarkers with their competitors. But for existing biomarkers that are widely accepted within industry and detailed in the literature, the PSTC shows how open and cooperative precompetitive research among large pharmaceutical companies can benefit the entire industry.