The FDA's push for better biomarkers

By Lauren Martz, Staff Writer

Despite the huge output of preclinical papers on new biomarkers, few result in validated agents that contribute to clinical trials. The FDA turned to stakeholders from industry and academia last week to discuss the challenges in the space and hear proposals for how to address them. Meeting attendees agreed that clarity and standardization of the regulatory process involving biomarkers is critical for advancing the use of biomarkers.

"Our goal with biomarkers is to know exactly the right way to treat each patient," said meeting moderator Mark McClellan. He added that although there have been scientific advances in targeted therapeutics and biomarkers, that progress has not accelerated drug development.

McClellan is director of the healthcare innovation and value initiative at the **Brookings Institution**. He was FDA commissioner from 2002 to 2004 and Centers for Medicare & Medicaid Services administrator from 2004 to 2006.

Briggs Morrison, CMO and EVP of global medicine development at **AstraZeneca plc**, said, "The goal is to speed up drug development. Biomarkers are an important tool, but up to this point we have done a poor job of developing, qualifying and using biomarkers in drug development."

He added, "We understand the molecular basis for 4,000 diseases, yet we may have 2 handfuls of biomarkers and a few more companion diagnostics."

Several industry representatives said that the primary problems in biomarker development are the variability in assay conditions and the lack of regulatory clarity surrounding the development and use of predictive and prognostic biomarkers.

Janet Woodcock, director of the FDA's **Center for Drug Evaluation and Research**, agreed that there is a problem with standardizing and validating biomarker-based assays and argued that it will take cooperation between the FDA, industry and academia to move the field forward.

The FDA's biggest challenge in the space, she said, is to define the evidentiary criteria needed to validate new biomarkers. "We can't just make them up. There has to be a scientific process. At this point, defining the criteria is still haphazard. FDA can't do this alone, and there is not a lot of scholarly activity," she said.

Woodcock noted that in addition to validation criteria, the FDA faces three other major challenges related to biomarkers: how to regulate next-generation sequencing, how to design trials for genetically defined rare diseases and their subsets and how to address the lack of organized trial networks and other translational infrastructure.

Because sequencing is an integral component of biomarker discovery and many companies now offer sequencing services, regulation of new techniques is important for creating standards. In genetically defined rare diseases, biomarkers could help stratify patient populations and subsets, but it is difficult to establish statistical significance for a biomarker and design trials to meet statistical significance because of the low numbers of patients. Similarly, building biomarkers into programs and strategies designed by trial networks and adaptive trials can help select patients for trials and organize clinical data, but more networks and collaborative trials are needed.

The topics of genetically defined rare diseases and translational infrastructure were also addressed at the meeting. Regulation of next-generation sequencing was not further addressed.

Regulations, reproducibility and reporting

Preclinical biomarker assays produce widely varying and inconsistent data quality, said meeting participants. New regulations, improved reproducibility and increased reporting of assay details were highlighted as first steps for increasing the generation of clinically useful biomarkers.

Mya Thomae, VP of regulatory affairs at **Illumina Inc.** and a panelist at the meeting, told *SciBX*, "There are currently no regulations that would help standardize preclinical biomarker discovery or assay design, although FDA is willing to answer questions at these stages of development."

She added, "The regulations start to come into play when biomarker-based assays are used to determine which drugs should go to which subjects during a clinical trial."

Lisa McShane, mathematical statistician at the **National Cancer Institute** and a presenter at the meeting, told *SciBX* that because of the lack of regulation and standardization, "the quality of assays in early stage biomarker studies is often suboptimal. Assay reproducibility is a minimum requirement for testing in humans, but for many assays we don't even have sufficient information about that."

McShane added, "Assays measuring biomarkers should produce the same results at different labs that offer it. We shouldn't need to worry about reproducibility based on test variations."

Morrison noted that technology standardization also needs to be considered for clinical tests measuring different markers. "It is hard for physicians and hospital labs that need all of the different technologies approved with different companion diagnostics. For clinical utility, we need some common technology," he told the panel.

Illumina's Thomae told the meeting that although companies are working together and with the FDA to advance therapeutic

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development, the industry and the regulatory framework is fragmented. “The diagnostics industry is diverse, and there are different models of how [the diagnostics] are delivered. We need centralized technologies and sample handling to give consistent results. Coalescing around next-generation sequencing might help,” she said.

Thomae told *SciBX*, “Clear regulatory guidance from FDA would level the playing field for all companies developing biomarker-based assays regardless of which technologies they use to identify biomarkers.” According to McShane, assay performance can be affected by the type of specimen, the handling of the specimen and the nature of the biomarker itself. Whereas some assays are highly robust, she said, others are fickle.

She added, “There are initiatives through the NCI that lay out best practices to handle specimens, and small studies have been performed to see how handling might affect results.”

McShane said that the first step to address specimen control should be to get researchers to report how the samples were collected, handled and stored. “If you pick up a biomarker paper, it is amazing how often this information is not included.”

Daniel Hayes, a professor of breast cancer research and clinical director of the Breast Oncology Program at the **University of Michigan Comprehensive Cancer Center**, agreed with the need for better reporting. “Journal articles almost never show how the specimens used got there and how they were measured,” he said at the meeting.

NCI has already taken measures to improve documentation and dissemination of assay conditions with the release of the Biospecimen Reporting for Improved Study Quality (BRISQ) guidelines in 2011. The challenge, said McShane, is to get journals to follow the guidelines.

Scarce resources

In addition to outlining the need for improved validation and clearer guidelines, attendees called for increased funding and greater accessibility to sample specimens.

McShane told *SciBX*, “The problem is that this is not the sexy kind of research, and it is hard to get funding. It is costly for a company or an academic investigator, but ultimately it may be very important if it can better ensure assay reproducibility that could improve the likelihood of clinical trial success.”

“The challenge is that it may not make sense to spend the time and money to rigorously validate a biomarker early in discovery, but if the assay is unreliable then the research results may be misleading,” added Thomae.

At the other end of the development spectrum, “there is poor reimbursement for biomarkers,” Hayes said. “Payers are used to paying \$50 for a test, so when we tell them that an important test costs thousands of dollars, it isn’t paid. This is even though the cost of a cancer therapy regimen is much more and the regimen may not be effective without the test.”

McShane added that in addition to a lack of funding, there is not a sufficient supply of biological specimens for developing and validating biomarkers.

“There is a limited amount of tumor tissue, and this is the material that we have for assessment. We want to get the most information out of the limited material as possible. Broad-spectrum -omics panels such as next-generation sequencing and gene expression profiling can get a lot of information out of small samples,” she told *SciBX*. Another solution to the limited resources issue could be to create pooled resources for researchers such as biobanks of patient-derived xenografts.

“Patient-derived xenografts might be closer to representing how biomarkers behave in humans than cell lines, which are used to screen drugs with mixed success. These resources need to be built up. The NCI and other institutions are carrying out major efforts to build up these programs. These kinds of resources aren’t easily accessible, and it takes a dedicated program to acquire them,” said McShane.

For rare diseases or biomarkers with rare prevalence, the resource issue is even more of a problem, attendees said. And with the availability of genetic sequencing, more genetically defined disease subsets are emerging that can be classified as rare or ultra-rare diseases, said Woodcock.

McShane told *SciBX* that it is difficult to get enough samples to perform statistically rigorous biomarker validations in these situations. The NCI has helped investigators find specimens to study rare diseases and subsets.

Dietmar Berger, global head of oncology at **Roche’s Genentech Inc.** unit, added that adaptive, master protocol trials such as the I-SPY and Lung-MAP trials could help address the issue of using biomarkers for rare disease subsets through large-scale tumor genotyping, which can more efficiently match patients with certain tumor mutations to the appropriate trials than traditional individual trial designs. The trials stratify patients to receive different therapeutics based on tumor genotypes.

Biomarkers beyond oncology

To date, the majority of biomarker-based diagnostic and prognostic development has centered on oncology. Although data from DNA sequencing and proteomics suggest biomarkers could also be powerful tools in other diseases, the regulatory infrastructure is even less well established in those areas.

AstraZeneca’s Morrison said at the meeting that this is also a matter of regulatory mindset. “Most of the conversation is around oncology,” he said. “It is challenging to convert other divisions of the agency to this way of thinking. Some parts are very progressive but others are not.”

Tracy Bush, director of companion diagnostics regulatory affairs at the Roche Diagnostics unit, told *SciBX*, “The sets of FDA guidance are not written to be specific for any therapeutic area. The major companion diagnostic co-development has been in oncology, though. Oncology is where we first identified the targets and where it all started. All but one of the approved companion diagnostics on the FDA’s website are for oncology.”

She added, “The pathways and best practices that have been developed are based on the drug/diagnostic pairs that first went

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through the process, which are in the oncology space. We encourage the FDA to continue sharing its learning and best practices between branches of the agency that are used to doing these things and other branches that haven't dealt with companion diagnostics."

In addition to the issues affecting the development of biomarkers for clinical development, the meeting covered both the use of biomarkers as surrogate clinical trial endpoints and clinical pathways for diagnostic development.

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