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14 Jul 2022 | **Analysis**

Biomarker Work Needs To Start Early In Drug Development Programs, US FDA Says

by Sue Sutter

Companies often do not focus on biomarker development and validation until too late in the game, FDA officials said at a recent Duke-Margolis meeting; experts cited the need for precompetitive work and public-private collaborations with an emphasis on early engagement, data sharing and transparency.

When it comes to biomarker and surrogate endpoint development, the US Food and Drug Administration has a plea for industry: "think early."

Work on establishing biomarkers and surrogate endpoints needs to start early in a drug development program and requires planning and a substantial resource investment. However, companies often do not focus on biomarker development and validation until late in the game and it is sometimes too late, experts said at a recent Duke-Margolis Center for Health Policy meeting on translational science in drug development.

"If you're talking about putting a biomarker in a clinical program, you should already have done it," said John Wagner, chief medical officer of Koneksa Health.

A common mantra throughout the two-day meeting was the need for more precompetitive work and public-private collaborations on biomarker and surrogate endpoint development, with an emphasis on early engagement, data sharing and transparency as a way to overcome challenges in this space.

Think Ahead About Confirmatory Evidence

Translational science, including biomarkers and surrogates, can play key roles throughout drug development and in regulatory decision-making. However, a lack of adequate planning and

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forethought can hinder the utility of biomarkers and surrogates in bringing a new drug across the regulatory finish line.

FDA Office of New Drugs director Peter Stein discussed the role for biomarkers and surrogate endpoints in the context of the agency's substantial evidence of efficacy standard, which in some instances allows for use of a single adequate, well-controlled trial plus confirmatory evidence as the basis for approval.

Pharmacodynamic or mechanistic information that is intended to serve as confirmatory evidence must be robust, using biomarkers that are well understood. A biomarker's relationship to the clinical outcome of importance also must be well understood, Stein said.

> ***It is essential to plan for confirmatory evidence early in the drug development program and "not after the fact, not when we have a single trial that doesn't provide the weight of evidence that we might get from a highly persuasive single trial." – FDA's Peter Stein***

"Sponsors often focus on the design of the adequate, well-controlled trial," Stein said. "This is especially the case in rare diseases, where only [one] trial is often feasible. And it's common that we have discussions that focus on the design of that single trial, with relatively limited discussion of confirmatory evidence which would be needed to go along with that trial."

Approval based upon a single adequate, well-controlled trial requires highly persuasive evidence, essentially comparable to two positive trials, which is a very high bar, Stein said. Consequently, it is essential to plan for confirmatory evidence early in the drug development program and "not after the fact, not when we have a single trial that doesn't provide the weight of evidence that we might get from a highly persuasive single trial."

Work to enhance the analytic and clinical support for proposed biomarkers or other mechanistic evidence must start early and requires meaningful resource investment, Stein said. "I'd emphasize it's important to meet with FDA divisions to talk about what might be confirmatory evidence where the program is intended to have just a single trial."

Biomarker Development Runway

Koneksa's Wagner, who also serves on the executive committee of the Foundation for the National Institutes of Health's Biomarkers Consortium, said a sponsor needs a "runway" for

development and validation of the biomarker itself.

Although it is important to separate the stages of early and late clinical development, “one unifying theme is that if you're talking about biomarkers, you need to start working on especially a novel biomarker quite a while ahead of time.”

For example, a PET imaging biomarker for a neuroscience drug may actually be its own drug development program that needs to be started years ahead of the clinical work, he said.

“In early clinical development, the biomarker usage is really, from a sponsor perspective, up to the sponsor. And if the evidence hits the level of confidence that the sponsor requires, it can probably be used in that clinical study,” he said. “Later on, it's more of a conversation with regulators, and then that also is a need for that long runway in order to make sure that everything is done well in advance.”

The late-in-development use of biomarkers, “whether it's a biomarker that's used mechanistically for confirmatory evidence or for decision-making or it's a surrogate endpoint, is going to need some kind of work that's done to make sure that it's analytically valid and clinically valid. If that's not been done, it's going to take a while to do that,” Wagner said.

Seeking Reliability, Not Perfection

Center for Biologics Evaluation and Research director Peter Marks discussed efforts the center is making to ensure that analytical and clinical validation of biomarkers is sufficiently robust. In particular, he noted the agency’s work with the FNIH and the National Center for Advancing Translational Sciences on the Bespoke Gene Therapy Consortium, which is aimed at developing platforms and standards to help speed the development of customized gene therapies for rare diseases. (Also see "*AAV Vector Consortia Address Quality Assays, Endpoints*" - Pink Sheet, 8 Nov, 2021.)

“We don't always know exactly how to do it right, but we definitely know how to do it wrong,” Marks said. “The idea is to perhaps come up with a playbook that tries to help those who are trying to develop such models think about what they need to do right up front, in order to try to get it right or to most likely get it right.”

“For some of these very small populations we don't need perfection, but we need something that we feel is reliable,” Marks continued. “Focusing on getting that quality data on something is really ... important. It's a little easier with gene therapy because there you can make an intervention that you are pretty sure it's going to hopefully have an effect. And if you don't see a change appropriately in that biomarker, you know that you've chosen unwisely. So I think we need to try to help develop some paradigms, and then allow those to be reused.”

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The consortium is taking a precompetitive approach "rather than having every time someone needs to develop a biomarker be a new birth, which is something of what goes on right now," Marks said.

Early Engagement …

Wagner and other panelists cited several keys to promoting and enhancing the use of biomarkers and other translational medicine approaches in drug development: early engagement; partnerships; and transparency.

"The concept of early engagement is important, and it's early engagement on the innovator side, whether the innovator's at the NIH or an academic or in industry, early engagement with the science, because it always takes longer than you expect to develop a biomarker," Wagner said. "It's Murphy's Law of biomarkers."

Early formal and informal engagement with regulators also is needed because "it's so important to have the dialogue, not just dumping off a package. It's a back and forth."

> *"It always takes longer than you expect to develop a biomarker. It's Murphy's Law of biomarkers." – Koneksa Health's John Wagner*

Several FDA officials emphasized the agency's willingness and desire to engage with sponsors early in a program to discuss biomarker development.

Sponsors are often reluctant to engage early with the FDA on biomarkers because they do not have everything together or know how things will look in the end, said Nicole Gormley, director of the Division of Hematologic Malignancies II.

"Even in those formative stages when thinking about assays and how you're going to look at them or how you're putting together the meta-analysis if that's what you're doing with trials," the FDA and its review divisions can provide input and guidance on what would be most helpful from a regulatory perspective, she said.

"Since people have to drag us along anyway, they should get started early on that part," said Norman Stockbridge, director of the Division of Cardiology and Nephrology.

… Partnerships and Data Sharing …

Many panelists said precompetitive collaborations are needed to drive biomarker development.

“The ability of a neutral party to act as a convener, I think, is very helpful when it comes to building scientific consensus,” said Patrick Archdeacon, associate director for therapeutics in the Division of Diabetes, Lipid Disorders and Obesity. He noted that such precompetitive collaborations are about more than just sharing financial resources, they also involve sharing and pooling data across trials, often among entities who normally would be competitors.

When it comes to establishing collaborations, it is important to try to figure out where there is common ground and mutual priorities among stakeholders, Friends of Cancer Research president and CEO Jeff Allen said. FOCR currently is leading a collaborative effort to collect data from multiple clinical trials to determine if circulating tumor DNA, a blood biomarker, can accurately predict whether a cancer therapeutic is working. (Also see "*ctDNA Can Be Used For Patient Selection and Enrichment, But Not As Early Efficacy Endpoint, US FDA Says*" - Pink Sheet, 4 May, 2022.)

Allen talked about the importance in such collaborations of early agreement on common data elements to be prospectively collected in trials.

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“Unfortunately when many organizations are designing their individual trials, it’s not with the goal of … ultimately aggregating and validating some sort of a biomarker in these instances,” Allen said. “Oftentimes you’re sort of left with the data that you have by bringing the willing data partners to contribute the data together. So really trying to align on that up front I think could be helpful into the future to figure out where there are standardizations that can be put into place and where they may not be able to happen.”

However, such collaborations and data-sharing projects are no easy feat to accomplish, and negotiations can get bogged down in legal issues and privacy concerns, experts said.

The European Union’s General Data Protection Regulation was cited as hindering data sharing. The data privacy regulations have been seen as an obstacle to conducting clinical trials due to strict requirements on protecting subjects' personal data and ensuring that data are used only in

the manner for which consent was given. (Also see "*Companies Urged Not To View EU Privacy Law As A Barrier To Conducting Decentralized Trials*" - Pink Sheet, 13 May, 2022.)

However, Henrik Zetterberg, professor of neurochemistry at the University of Gothenburg, Sweden, and University College London, said he believes data sharing will become easier in the context of GDPR.

Part of the problem was that different European universities had taken different interpretations of the GDPR text and how rigorously to implement it, Zetterberg said. However, entities are learning how to deal with GDPR in a more pragmatic way. In addition, "EU has formed a committee to look into this also to harmonize how different member states are implementing GDPR so that it will still be possible to do international research."

"I think we are entering a phase where it will be easier to access data," Zetterberg said.

Experts also cited the importance of developing strong ties to the patient and advocacy communities, who can assist in the discovery and validation of biomarkers as well as the enrollment of clinical trials.

… And Transparency

Panelists said there needs to be more publication of translational science findings, both the good and the bad.

"One very simple thing … that we can do to promote the increased translational science … in drug development is publication, and publication not just of success but of failure so that we can guide folks where things are going right and where they're going wrong," Wagner said.

It is rare to share information about failures, or things that ultimately did not work or where wrong predictions were made, said Estelle Marrer-Berger, senior translational safety leader at *Roche Holding AG*. "This kind of data, I think, should be shared as well as our success stories."

Whatever You Do, Do It Early

Lynne Yao, director of the FDA's Division of Pediatric and Maternal Health, said that regardless of what the biomarker or surrogate is or how it is intended to be used, a data package has to justify that use.

"So much of it requires the up-front work," Yao said. "I'm the regulator. … I'm not the one that's got to dig up the capital to figure out how to do this early work. But the reality is if you don't do the work early, you're not going to get it on the back end. You're not going to be able to validate a biomarker after the trial is over."

“My plea to everybody is to think early,” she said.