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Fully Enrolled Confirmatory Studies Can De-Risk Novel Accelerated Approval Endpoints – FDA Official

by Sarah Karlin-Smith

Oncology Center of Excellence Deputy Director Paul Kluetz talks about what might make a drug a good candidate for a Project Frontrunner-type development program and how sponsors might benefit from FDA's experience with OCE's first Project Pragmatica pilot.

A novel endpoint for a cancer drug's accelerated approval is more likely to get the go ahead from the US Food and Drug Administration if the sponsor has a fully accrued post-marketing study underway at the time of application, Oncology Center of Excellence Deputy Director Paul Kluetz said.

Kluetz noted this is one way in which an Oncology Center of Excellence project can help "de-risk" aspects of a drug's development. In this instance he was discussing Project Frontrunner, which is pushing sponsors to study cancer treatments in earlier lines of care first, rather than starting with the most refractory setting, and pushing for more randomized trials for cancer accelerated approvals. In some cases, the agency envisions the same study being used for accelerated approval and post-market confirmation. (Also see "*Cancer And Accelerated Approval: FDA To Crack Down On Single-Arm Trials, Refractory Disease Focus*" - Pink Sheet, 10 Jun, 2022.) and (Also see "*'On-And Off-Ramps' For Cancer Accelerated Approvals: FDA Suggests Earlier Randomized Trials*" - Pink Sheet, 21 Sep, 2022.)

Kluetz's remarks at the Prevision Policy/Friends of Cancer Research Biopharma Congress in February were made in response to comments from Sunita Zalani, *Merck & Co., Inc.*'s VP of Oncology and In-Vitro Diagnostics in Global Regulatory Affairs and Clinical Safety. Zalani said the company wants more guidance on the types of endpoints that might be appropriate for Frontrunner applications. For example, she asked whether it might be possible to use a composite endpoint of imaging plus circulating tumor DNA for accelerated approval.

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Kluetz didn't comment directly on any of the endpoints Zalani brought up, but instead emphasized that FDA would be more likely to accept such novel endpoints in the Project Frontrunner context, since the expectation would be that a well-designed confirmatory trial is also ongoing to confirm the surrogate's findings.

"I think if you have that certainty of the randomized trial already up and under way, you could imagine how that might de-risk the acceptability of endpoints that have not been used before, because that trial is clearly underway, it's powered for the endpoint that we'd like to see," he said. So it's context specific, "but it's certainly a much easier sell to say we're going to use something relatively new, here's the data, here's the rationale, we believe it's going to work, and we're going to deploy the [post-marketing requirement] to evaluate it."

These types of decisions will be made on a case-by-case basis by the relevant review divisions, Kluetz noted.

"But I can tell you that it is a less risky proposition to have a novel endpoint in a setting where you have a powered randomized trial fully accrued with an [overall survival] endpoint," he said.

Context Specific, Not Disease Specific

When asked if there are cancer types that make the most sense for a Project Frontrunner application, Kluetz suggested sponsors think more about the context rather than the specific disease, noting a Frontrunner approach will work well in settings where there are many available therapies, the effect size looks large and where the treatment approach makes sense with respect to the natural history of the disease.

"I don't think it's a disease specific thing. I think it's a context specific thing. What are the available therapies? How safe? What does the safety profile look like? What's the magnitude you think you're going to have? What's the delta for the response rate?" Kluetz said.

FDA oncology review divisions "will also be on the lookout for those sorts of situations," and pitch the approach to sponsors where the FDA believes it makes sense, he added.

De-risking Simple Trials…

Kluetz also emphasized FDA's role in de-risking sponsor's involvement in simple, pragmatic trials as a key reason for OCE's Project Pragmatica.

The first Pragmatica collaboration involves the National Cancer Institute, Merck and *Eli Lilly and Company* testing a combination of the companies' pembrolizumab and ramucirumab in advanced non-small cell lung cancer. (Also see "*Project Pragmatica: US FDA's OCE Initiative Aims To Encourage Simple Clinical Trials*" - Pink Sheet, 21 Nov, 2022.)

Merck's Zalani said the company needs "more dialogue and clarity on what the data elements would be to support the benefit-risk evaluation by the FDA and global agencies as we take this for registration." The company is still in discussions with FDA on the kind of labeling that could be obtained from this type of pragmatic study, she said.

"Probably our biggest role in a lot of these things is to de-risk a little bit of the idea that it would be acceptable for us to review," Kluetz said.

FDA identified this first Pragmatica trial as a particularly unique case where you could "really strip a trial down," Kluetz said. Part of the goal is to learn from this level of strip down and the various pragmatic elements incorporated in the Merck/Lilly study so that FDA then knows "how to operationalize them in other sorts of trial contexts which may not be so perfectly tailored for such a simple trial," he said.

...Along a Continuum of Pragmaticism

People sometimes think a study is either a pragmatic trial or a randomized-controlled prospective trial and there's nothing in between, Kluetz said.

But while there may not be that many Pragmatica Lung super stripped down trials, "we should, as we learn from this trial, be able to deploy aspects of the pragmatic elements into more and more trials," Kluetz said. Doing so will help sponsors and FDA achieve other goals, such as improving accrual rates, decreasing attrition and improving diversity, he said.

Safety Barriers to Going Global

The simple nature of the first Project Pragmatica trial means the safety data collections exclude ex-US participants. That helps FDA encourage US-based participation, but is not ideal for sponsors who want regulatory approval worldwide.

Zalani said she can "envision future studies in which enrollment in global regions becomes necessary," so the company is looking for some global harmonization in terms of protocol development and submission requirements from large, simple trials.

She questioned if there is a way for the Pragmatica pilot to be engaged in Project Orbis, the OCE's effort to allow other countries to review participating applications at the same time as US regulators. (Also see "*Project Orbis Nears 30 Approvals In Oncology; Could China Be Added?*" - Pink Sheet, 8 Sep, 2021.)