PINK SHEET
CITELINE REGULATORY

22 Oct 2020 | **News**

US COVID-19 Advisors Vexed By Vaccine Post-EUA Placebo Controls, But Agree On Need

by Sarah Karlin-Smith

FDA indicates it expects sponsors and other government agencies to come up with ways to fulfill its request for placebo-controlled studies post-emergency use authorization of COVID-19 vaccines, but neither it nor vaccines advisory committee see a clear way to do this.

Coronavirus vaccine sponsors may be stuck with the US Food and Drug Administration's call for placebo-controlled follow up of COVID-19 vaccines after they receive emergency use authorization. The agency's Vaccines and Related Biological Products Advisory Committee reaffirmed the need for such data to support a full biologics license application during its 22 October meeting.

Yet neither the FDA nor the advisory committee offered companies much advice on how to achieve this outcome, which they acknowledged would be challenging.

The FDA has told sponsors that an EUA request should include strategies to ensure follow-up in ongoing trials and to handle loss of follow-up due to withdrawal of participants. The agency is also concerned that the placebo-controlled nature of other ongoing COVID-19 vaccine trials could be compromised once one vaccine gets an EUA.

"I don't have any specific remedies to offer," said Doran Fink, Center for Biologics Evaluation and Research deputy director of the Division of Vaccines and Related Product Applications in the Office of Vaccines Research and Review. "At this time, we have asked the vaccine manufacturers and the other government agencies who are involved in conducting these trials to think carefully about how they would ensure clinical trial retention," Fink told the VRBPAC.

This was not the response sought by industry.

PINK SHEET
CITELINE REGULATORY

Pfizer Inc., *Janssen Pharmaceuticals Inc.* and the Biotechnology Innovation Organization, along with some disease groups all sent comments to the FDA ahead of the advisory committee indicating that continuing placebo-controlled studies after an EUA may not be feasible. Industry pointed to ethical obligations to notify trial participants of authorized or approved vaccines and asked the agency and committee to think about creative and acceptable solutions to collect the necessary data. Janssen pressed the FDA and the committee to come up with statistical approaches or other solutions, such as an external control if there is considerable cross-over from placebo arms. (Also see "*COVID-19 Vaccine Sponsors Want US FDA To Find Alternatives For Control-Arm Data After First EUA*" - Pink Sheet, 20 Oct, 2020.)

Read more from the meeting:

- (Also see "*COVID-19 Vaccines: Advisory Committee Picks Apart US FDA Guidance On Efficacy Endpoints*" - Pink Sheet, 22 Oct, 2020.))
- (Also see "*Patient Warehousing Emerges As Another COVID-19 Vaccine Confidence Problem*" - Pink Sheet, 22 Oct, 2020.)

But the only thing coming close to advice on this at the advisory committee session was some level of confidence that many people in the trials wouldn't be eligible for a vaccine under an initial EUA anyway and that sponsors may not have as much of an ethical obligation as claimed to allow trial enrollees to crossover to obtaining a vaccine outside their trial.

The FDA's Philip Krause said that in general the vaccine trials now ongoing do not have crossover to placebo built into the protocol, so companies don't necessarily have an obligation to provide placebo patients with a vaccine when it becomes available.

Krause, the deputy director of CBER's Office of Vaccines Research and Review, added that not all trial participants will be the ones who will be first in line to get a vaccine after an EUA, particularly given the expected limited supply, so that may keep more patients in the study.

And he said that while he is not a bioethicist, people have other ways to protect themselves from COVID-19 besides with a vaccine so that may limit the obligation to offer placebo patients vaccine.

"For those that say there's an ethical reason, I think that's perhaps overstating the case," Krause said.

A number of advisory committee members seemed to agree with the assumption that many placebo patients simply wouldn't have quick access to a vaccine post-EUA even if they wanted to drop out of studies because they wouldn't be the types of recipients targeted under the EUA. But

those comments didn't align with both the advisors and the the FDA's push for trials to study as much as possible the populations most at risk of COVID-19 and most at risk of poor outcomes such as minorities. Such high-risk populations would presumably be prioritized early for vaccination.

Plus, groups working on laying out vaccine allocation principles, like the US National Academy of Medicines, have indicated that participants in vaccine trials should ethically receive vaccination as soon as possible – placing them in the highest priority group. (Also see "*COVID Vaccine Distribution Plan From National Academies Leaves Room For Adjustments Based On Trial Results*" - Pink Sheet, 1 Sep, 2020.)

Amanda Cohn, the chief medical officer at the National Center for Immunization and Respiratory Diseases at the US Centers for Disease Control and Prevention, asked if there was a way to avoid unblinding trials and still inform study participants that if they were in a recommended group in an EUA they could consider getting vaccinated.

"I do worry about telling a person that they should not go get vaccinated when they are in one of the prioritized groups," she said.

But fellow advisory committee member Sheldon Taubman, the panel's consumer representative and staff attorney at the New Haven Legal Assistance Association, pointed out that if this kind of notification required sponsors to make trial participants aware of whether they were on placebo or vaccine, the potentially resulting behavioral changes could bias the study, regardless of whether placebo patients drop out.

The committee's industry representative, *Merck & Co., Inc.*'s Vice President and Therapeutic Area Head for Vaccines Clinic Research Paula Annuziato, said that her company and others have experience conducting placebo-controlled studies for approved and available vaccines, but didn't go into any detail on how sponsors have successfully recruited or kept patients in such studies.

She did reiterate industry comments that companies will have to update informed consent documents and make participants aware of the potential ability to receive a vaccine outside of a clinical trial once a product is cleared by the FDA.

Annuziato also cautioned the FDA and the committee that the level of public attention focused on the search for a COVID-19 vaccine and thus any clearance of one by FDA may make the continuation of placebo-controlled studies extra challenging.

The advisory committee acting chair was perhaps the most unconcerned about this possibility saying that observational data has been used for effectiveness studies.

“So what looks logistically difficult, maintaining the blind for very long periods of time, may be both not feasible and not necessary as we go forward,” said Arnold Monto, a professor of public health and epidemiology at University of Michigan.