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COVID Vaccines: Is Expanded Access A Better Option Than Emergency Use Authorization?

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Executive Summary

Given concerns about completing Phase III trials, advisory committee member asks whether US FDA has considered ‘the possibility of an expanded access protocol,’ but agency official points to added complexity that comes with the pathway; bioethics experts talk to the *Pink Sheet* about pros and cons of expanded access vs. EUA pathways.



CONCERN ABOUT COMPLETING CLINICAL TRIALS HAS LED TO QUESTIONS
ABOUT WHETHER EXPANDED ACCESS MIGHT BE A BETTER PATH THAN
EMERGENCY AUTHORIZATION FOR COVID-19 VACCINES.

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The US Food and Drug Administration’s insistence that COVID-19 vaccine sponsors find a way to continue randomized, placebo-controlled Phase III trials after an emergency use authorization is granted has some experts questioning whether an expanded access program would be preferable to an EUA.

The prospect of an expanded access program as an alternative to an EUA arose at the 22 October meeting of the Vaccines and Related Biological Products Advisory Committee. The panel was convened to debate general issues related to the development of COVID-19 vaccines but did not discuss the matter of expanded access in depth.

(Also see "COVID-19 Vaccines: Advisory Committee Picks Apart US FDA Guidance On Efficacy Endpoints" - Pink Sheet, 22 Oct, 2020.)

Outside the FDA, some experts say expanded access seems likely to raise many of the same concerns as an EUA, while others hold the view that a limited expanded access program would be preferable to emergency authorization and more likely to result in the completion of randomized Phase III trials of vaccine candidates.

Focus On Completing Phase III Trials

FDA officials are worried that use of a COVID-19 vaccine under EUA would interfere with long-term assessment of safety and efficacy in ongoing trials and potentially jeopardize product approval for the first vaccine as well as subsequent ones. Consequently, the agency has placed a high priority on ensuring that placebo-controlled trials are able run their course, with minimal loss to follow-up, even if an EUA is granted.

The FDA's position was strongly endorsed by the vaccines advisory committee, although neither the agency nor panel members offered any clear suggestions on how sponsors could achieve this outcome. (Also see "US COVID-19 Advisors Vexed By Vaccine Post-EUA Placebo Controls, But Agree On Need" - Pink Sheet, 22 Oct, 2020.)

In contrast, vaccine developer Pfizer Inc. has said it would have an ethical responsibility to inform study participants about any COVID-19 vaccine granted an EUA and the eligibility requirements for that vaccine. (Also see "COVID-19 Vaccine Sponsors Want US FDA To Find Alternatives For Control-Arm Data After First EUA" - Pink Sheet, 20 Oct, 2020.) If Pfizer's vaccine receives an EUA, the company proposes to amend its ongoing study to allow voluntary crossover of eligible subjects in the placebo arm to the vaccine arm.

"Operationally speaking, an expanded access protocol would add some complexity, and that is why emergency use authorization is being considered primarily as the mechanism for addressing the public health emergency that has been declared." – FDA's Doran Fink

At the meeting, Doran Fink, deputy director of the Division of Vaccines and Related Products Applications, reiterated the agency's view that issuance of an EUA, in and of itself, is not grounds for unblinding ongoing trials and offering vaccine to placebo recipients. (Also see "COVID-19 Vaccines: Lost Placebo Control Could Mean Lost Approval, US FDA Officials Say" - Pink Sheet, 16 Oct, 2020.)

Fink reviewed agency guidance that states an EUA request should include strategies for ensuring ongoing vaccine trials are able to assess long-term safety and efficacy in sufficient numbers of subjects after authorization to ultimately support licensure. Sponsors also should address how ongoing trials will handle loss of follow-up for subjects who withdraw from study to receive the vaccine under an EUA. (Also see "After EUA, COVID Vaccine Sponsors Need Plans For Continuing Trials" - Pink Sheet, 6 Oct, 2020.)

Advisory committee member Michael Kurilla, director of the division of clinical innovation at the National Institutes of Health's National Center for Advancing Translation Sciences, asked whether the agency had considered "the possibility of an expanded access protocol," instead of an EUA, for the specific populations that would have been the focus of an EUA.

An expanded access protocol is another regulatory mechanism for providing access to investigational vaccines, Fink responded.

"I think if we were to consider an expanded access protocol of the same size and scope as what is being considered for an emergency use authorization, then the benefit/risk considerations and the data to inform those benefit/risk considerations that allow that type of use would be highly similar," Fink said.

Unlike with an EUA, use under expanded access would be carried out under the agency's investigational new drug regulations, he said.

"Among many other things, those regulations require use of an institutional review board and also obtaining informed consent from recipients of the investigational vaccine," Fink said. "Operationally speaking, an expanded access protocol would add some complexity, and that is why emergency use authorization is being considered primarily as the mechanism for addressing the public health emergency that has been declared."

Expanded Access Criteria

Marion Gruber, director of the Office of Vaccines Research and Review, provided more details about the expanded access mechanism later in the meeting, saying she was doing so in the interests of transparency given Kurilla's earlier question. "I just wanted to inform the committee of this additional provision to make investigational products available."

The expanded access regulations are intended to facilitate availability of investigational drugs to patients with serious or life-threatening diseases or conditions when there are no satisfactory alternatives, and the primary purpose of an expanded access program is to treat the patient's disease or condition, Gruber said. Under expanded access, the potential benefits of the product must justify the potential risks, and providing the investigational product must not interfere with clinical development of the product for that specific use, she said.

Although there are three categories of expanded access, Gruber focused on the treatment IND/treatment protocol category, which is the only one intended for widespread use of a product. Under this category, the following requirements must be met:

The drug is being investigated in a controlled clinical trial under IND designed to support a marketing application;

The sponsor is pursuing marketing approval;

For a serious disease, there is sufficient clinical evidence of safety and effectiveness to support expanded access use, ordinarily from Phase III trials, but there could be compelling data from Phase II trials; and

For an immediately life-threatening disease, available evidence provides a reasonable basis to conclude that the investigational drug may be effective and would not expose patients to unreasonable and significant risks; such evidence ordinarily would come from Phase II or III trials but could be based on more preliminary clinical evidence.

The panel's acting chairman, Arnold Monto, University of Michigan, asked whether expanded access has been used for vaccines.

The expanded access regulations and provisions apply to biologics and vaccines, Gruber said, noting this pathway previously has been used to help stem a meningococcal type B outbreak among college students. (Also see "Expanded Access Data Can Support Approval Decisions, US FDA Says" - Pink Sheet, 21 Nov, 2018.)

Between 2013 and 2014, more than 15,000 students and staff at Princeton University and University of California-Santa Barbara were vaccinated with two doses of Novartis AG's (now GlaxoSmithKline plc) meningococcal group B vaccine Bexsero under an expanded access IND granted by the FDA and sponsored by the Centers for Disease Control and Prevention. (Also see "Pfizer's Meningitis B Vaccine Beats Novartis To Market, But ACIP Remains Key To Uptake" - Pink Sheet, 3 Nov, 2014.)

In addition, yellow fever vaccine is currently available in the US only under expanded access, Gruber noted. Sanofi Pasteur is the manufacturer YF-Vax, the only yellow fever vaccine licensed in the US. However, the product supply has been depleted as the manufacturer transitions to a new production facility.

The company received FDA approval to make another yellow fever vaccine, Stamaril, available under IND in the US. Stamaril is registered and distributed in more than 70 countries and is comparable in safety and efficacy to YF-Vax, according to CDC's website. (Also see "The Quality Lowdown: Risk And Opportunity" - Pink Sheet, 6 Sep, 2018.)

An Idea 'Worth Considering' ...

Bioethics experts were mixed on the utility of the expanded access pathway, in lieu of an EUA, for investigational COVID-19 vaccines.

"Expanded access is worth considering as a possibility but also raises a lot of challenges and questions," Robert Klitzman, professor of psychiatry and director of the masters of bioethics program at Columbia University, told the *Pink Sheet*.

Expanded access was not designed to make an investigational product available to potentially hundreds of millions of people, Klitzman said, questioning how this would be accomplished and what such a program would look like for a COVID-19 vaccine.

Expanded access is not "clearly the answer. It's worth considering what it might look like, but it still raises many questions and challenges and has many of the disadvantages that the emergency use authorization would have." – Columbia University's Robert Klitzman

While the intended purposes of expanded access is treatment of seriously ill patients with no other options, in this case the investigational product is a prophylactic vaccine that would be administered to healthy people, some of whom may never get the disease caused by the novel coronavirus, he said.

In addition, the FDA's minimum efficacy threshold of 50% for a COVID-19 vaccine is "fairly low," Klitzman said, also raising concerns about how effective the vaccines will be at generating antibodies, how protective those antibodies will be, and how long that protection will last.

Sponsors likely still would face a challenge in completing ongoing Phase III trials even if a vaccine were available through expanded access, he said. "We desperately need evidence of effectiveness of vaccines, and so to impair clinical trials has a steep cost."

Klitzman said he does not think that expanded access is "clearly the answer. It's worth considering what it might look like, but it still raises many questions and challenges and has many of the disadvantages that the

emergency use authorization would have.”

However, FDA officials’ comments about expanded access being a more cumbersome process because of the need for IRB approval and informed are not reasons to dismiss the pathway, Klitzman said. “I think those are not legitimate excuses not to consider it.”

... Or One That Is Clearly Preferable To EUA?

Alison Bateman-House, assistant professor in the department of population health at New York University, said it would be shortsighted to grant an EUA prior to completion of the pivotal trials. She told the *Pink Sheet* a limited expanded access program would be preferable to an EUA and would better ensure the completion of ongoing randomized, blinded Phase III trials.

“I would strongly advise for the use of expanded access, rather than an EUA, for any non-trial access to a COVID-19 vaccine candidate,” Bateman-House said. “While presumably the FDA would not be agreeing to such a product being used outside of clinical trials unless it deemed its potential benefit to outweigh its potential risk in the recipient, there is a pressing need to complete the trials that will provide definitive evidence of safety and efficacy. Widespread non-trial access as could happen under an EUA would prevent, or at least slow, completion of those trials.”

“A cohort expanded access program provides the framework for provision of an investigational product with the least possible demand on physician time.” – NYU’s Alison Bateman-House

A sponsor-run cohort expanded access program could allow early access to a promising vaccine candidate for a population or subpopulation at high risk of disease that was ineligible for the Phase III trials, and for whom the risk/benefit calculus still supports investigational use, she said. This type of program would look like a trial but with minimum eligibility criteria, as determined by safety concerns, and its protocol would be reviewed by the FDA and an IRB.

“A cohort expanded access program provides the framework for provision of an investigational product with the least possible demand on physician time. It also increases knowledge of and access to the investigational product via expanded access, so that you do not see only rare individuals with well-informed physicians pursuing this option for their patients,” she said.

Expanded access would provide more limited access than would an EUA, but this is appropriate, Bateman-House said. “Anyone who is not excluded from the trials should participate in a trial in order to get access to an unapproved vaccine candidate.”

A 'Bridge' To Trial Completion

Jesse Goodman, the FDA's former chief scientist and director of the Center for Biologics Evaluation and Research, suggested expanded access could serve as a “bridge” from a Phase III interim endpoint to the final study results.

This would provide a way for “high-risk people who are motivated to get the vaccine while the trials are continuing to get to their true endpoints rather than their interim endpoints,” said Goodman, who is now

director of the center on medical product access, safety and stewardship (COMPASS) and an attending physician for infectious disease at Georgetown University.

Such an expanded access program potentially could lead to an EUA if safety and efficacy continue to be demonstrated once the trials reach their conclusion, and the authorization could be issued while a biologics license application is being filed and reviewed. This approach “wouldn’t destroy the trials,” Goodman said, although he acknowledged that any large-scale expanded access program would be complex.

Sarah Karlin-Smith contributed to this story.