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Perspective

Emergency Use Authorization of Covid Vaccines — Safety and Efficacy Follow-up Considerations

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Confidence in any Covid-19 vaccine that is made available under an emergency use authorization (EUA) will depend on the rigor of the clinical criteria, including the duration of follow-up, used to evaluate it. Recently published guidance from the Food and Drug Administration (FDA) recommends that data from phase 3 studies to support an EUA (which may result from a protocol-specified interim analysis) include a median follow-up duration of at least 2 months after completion of the full vaccination regimen.[1] This recommendation takes into consideration the likely rapid administration of a vaccine to millions of otherwise healthy Americans, and potentially billions more people around the world.

An EUA allows use of unapproved medical products (or unapproved uses of approved medical products) to diagnose, treat, or prevent serious or life-threatening diseases or conditions caused by threat agents, such as Covid-19, in response to a declared public health emergency for which there are no adequate, approved, and available alternatives. In order to issue an EUA, the FDA must determine, among other things, that the known and potential benefits of a product outweigh its known and potential risks and that the product may be effective in preventing, diagnosing, or treating serious or life-threatening diseases or conditions caused by the agent or agents identified in the EUA declaration. A favorable benefit–risk determination cannot be made for vaccines that might have only modest benefit[2] or for which there are insufficient data to assess the safety profile. At stake is public confidence in America's response to the pandemic, in Covid-19 vaccines, and in vaccines in general, all of which are essential to achieving desired public health outcomes.

Use of an investigational vaccine under an EUA would not be subject to the usual informed consent requirements for clinical investigations; nevertheless, vaccine recipients will be provided a fact sheet that describes the investigational nature of the product, the known and potential benefits and risks, available alternatives, and the option to refuse vaccination. To minimize the risk that use of a vaccine under an EUA will interfere with long-term assessment of safety and efficacy in ongoing trials, it will be essential to continue to gather data about the vaccine even after it is made available under the EUA. Continued follow-up of clinical trial participants to further refine efficacy estimates, further evaluate the potential for enhanced dis-

ease and waning of immunity, and obtain additional active safety follow-up will be essential in order to ensure public confidence in a broadly administered vaccine. The quality of the data available to inform ongoing assessment of a vaccine's benefits and risks will depend on the ability to continue evaluating the vaccine against a placebo comparator in clinical trials for as long as feasible. Moreover, evaluation of other potentially superior vaccines will depend on the ability to continue to maintain placebo controls in ongoing trials. Thus, issuance of an EUA should not, in and of itself, require unblinding of a Covid-19 vaccine trial and immediate vaccination of placebo recipients, since doing so may jeopardize approval of these products.

In setting criteria for EUAs, regulators determine the amount of data that could support a positive benefit–risk assessment, providing people who wish to receive an investigational vaccine the opportunity to realize that benefit while also providing confidence that a vaccine is unlikely to cause net harm when used in this manner.

From a safety perspective, a 2-month median follow-up (meaning that at least half of vaccine recipients in clinical trials have at least 2 months of follow-up) after completion of the full vaccination regimen will allow identification of potential adverse events that were not apparent in the immediate postvaccination period and will also provide greater confidence in their absence, if none are observed. Adverse events considered plausibly linked to vaccination generally start within 6 weeks after vaccine receipt.[3] Two months of follow-up will provide time for potential immune-mediated adverse events that began within this 6-week period to be observed and evaluated. Notably, to support licensure of a vaccine, the FDA generally requires at least 6 months of safety follow-up for serious and other medically attended adverse events in a sufficient number of vaccinees. Given that some vaccines under evaluation for preventing Covid-19 are based on technologies not previously used in licensed vaccines, arguments could be made in favor of longer safety follow-up to support an EUA. A median follow-up period of at least 2 months after the final vaccine dose is justified, however, by extensive historical experience with adverse events after vaccination, the need for a vaccine to address the current pandemic, and the magnitude of vaccine effectiveness that will be required to support a favorable benefit–risk profile for use of a Covid-19 vaccine under an EUA.

From the perspective of vaccine efficacy, it will be important to have data to assess whether protection mediated by early responses (e.g., the presence of IgM and IgG antibodies, which peak at or before 2 to 4 weeks after vaccination) has started to wane. Such an assessment is particularly relevant to coronavirus vaccines, because natural immunity to coronavirus infection is relatively short-lived.[4] Although 2 months of follow-up is insufficient to fully evaluate the duration of vaccine protection, substantial waning of protective responses might start to become apparent in the second month. Thus, a median of 2 months is the shortest follow-up period required to achieve some confidence that any protection against Covid-19 is likely to be more than very short-lived. The World Health Organization recently proposed draft guidelines requiring 3 months of efficacy follow-up data before a vaccine could be considered for its Emergency Use Listing.[5]

To support FDA approval, most vaccine clinical trials include substantially longer follow-up of trial participants to track both safety and efficacy. For example, for shingles vaccines, participants in Shingrix clinical trials were followed for a median of 3.1 years in one study and 3.9 years in another, and participants in Zostavax clinical trials were followed for a median of 1.3 years in one study and 3.1 years in another.

Recognizing the gravity of the current public health emergency and the importance of making a vaccine available as soon as possible, we believe that a median 2-month follow-up after completion of the vaccine regimen will provide the necessary safety and effectiveness data to support distribution of an investigational vaccine under an EUA. Curtailment of this minimum follow-up could destroy the scientific credibility of the decision to authorize any vaccine for use under an EUA in the United States. Appropriate conditions for issuing EUAs for Covid-19 vaccines are expected to be discussed further at the October 22, 2020, meeting of the FDA Vaccines and Related Biological Products Advisory Committee.

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