VIEWPOINT

Unwavering Regulatory Safeguards for COVID-19 Vaccines

Anand Shah, MD
Food and Drug Administration, Silver Spring, Maryland.

Peter W. Marks, MD, PhD
Food and Drug Administration, Silver Spring, Maryland.

Stephen M. Hahn, MD
Food and Drug Administration, Silver Spring, Maryland.

Audio and Video

The coronavirus disease 2019 (COVID-19) pandemic has disrupted normal life and had significant consequences for human health, with more than 4.6 million cases and more than 150 000 deaths in the US alone as of early August 2020. Preventive public health measures such as mask usage, physical distancing, and enhanced sanitation procedures are necessary to alleviate strain on the health system and reduce community transmission, while advances in therapeutic development have potentially improved clinical outcomes for patients with severe illness. However, minimizing the risk of resurgence and enabling a safe return to normal life will require a majority of the population to develop immunity against SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2, the virus that causes COVID-19). Acceptably achieving this level of herd immunity quickly will likely require the development of safe and effective vaccines.

Yet even under normal circumstances, vaccine development is a challenging endeavor that carries significant financial risk due to the high rate of failure at each stage of the development process. To expedite the development of a COVID-19 vaccine, the US government launched Operation Warp Speed in May 2020.[1,2] This endeavor is committed to compressing what can sometimes be a decade-long development process into a matter of months through up-front financial commitments that focus resources and lower the risk of innovation. The completion of phase 1 trials for several vaccine candidates in July 2020 and enrollment for forthcoming phase 3 trials are important milestones for this process.

> FDA is committed to ensuring that any vaccine is manufactured in accordance with all of FDA's quality standards and that its safety and effectiveness are verified before being authorized or licensed

Still, the emphasis on speed has provoked public anxiety about the safety and effectiveness of vaccines developed on expedited timelines. Among the concerns are that the regulatory standards for approval will be lowered under political pressure for a vaccine. In a recent poll of 1056 US adults, 31% indicated that they are uncertain about whether they would receive a potential COVID-19 vaccine and 20% indicated they would choose not to take it, with concerns about safety and adverse effects being the primary reason for avoiding vaccination.[3]

The physician leadership of the US Food and Drug Administration (FDA) (including the authors of this Viewpoint) unequivocally state that candidate COVID-19 vaccines will be reviewed according to the established legal and regulatory standards for medical products. While Operation Warp Speed is an important initiative and FDA has lent technical expertise around end point selection and safety considerations to this public-private partnership for vaccine development, there is a line separating the government's efforts to focus resources and funding to scale vaccine development from FDA's review processes, which are rooted in federal statute and established FDA regulations.[4] To offer clarity to the public, FDA issued a guidance document on June 30, 2020, which outlines key considerations for the development and licensure of vaccines to prevent COVID-19.[5]

First and foremost, FDA is committed to ensuring that any vaccine is manufactured in accordance with all of FDA's quality standards and that its safety and effectiveness are verified before being authorized or licensed. To ensure that a widely deployed vaccine is effective, FDA has specifically recommended in its guidance to vaccine developers that "the primary efficacy endpoint point estimate for a placebo-controlled efficacy trial should be at least 50%, and the statistical success criterion should be that the lower bound of the appropriately alpha-adjusted confidence interval (CI) around the primary efficacy endpoint point estimate is >30%."[5] In other words, the lower limit of a 95% CI would have to be greater than 30%.

While historically the agency has not prospectively recommended numerical end point estimates for license approval, FDA believes recommending a baseline for performance is necessary to provide confidence that broad distribution of a potential vaccine could offer immunity to the majority of the population. To properly verify efficacy, trials should also follow best practices for methodology (eg, randomized double-blind designs with placebo control). In terms of safety, adequately powered trials are necessary to detect adverse events and to evaluate safety considerations with regard to dosing. FDA generally advises the minimum population size for a prelicensure safety database for preventive vaccines to exceed 3000 patients, and to date, the anticipated enrollment for COVID-19 vaccine trials (15 000 to 20 000 patients receiving active vaccination) well exceeds FDA's recommendation. FDA recognizes that there could be rare adverse events not detected in a trial of 15 000 to 20 000 patients, so postmarketing surveillance will be critical.

Second, to achieve population-wide immunity, a COVID-19 vaccine would need to be widely deployed. It is therefore critical that the data derived from nonclinical and clinical studies clearly demonstrate that the vaccine is safe and effective for widespread use. Also acknowledging the need for broad use, FDA recognizes that

Corresponding Author: Anand Shah, MD, Deputy Commissioner for Medical and Scientific Affairs, US Food and Drug Administration, 10903 New Hampshire Ave, Silver Spring, MD 20993 (anand.shah@fda.hhs.gov).

the pandemic has disproportionately affected many populations and strongly recommends that investigators ensure sufficient representation of racial and ethnic minorities, older adults, and individuals with medical comorbidities in the clinical trials. The inclusion of diverse populations, including older individuals, in trials is necessary for a comprehensive assessment of product safety and effectiveness and to properly inform clinical decision-making. Developers will also need to consider how to provide additional safeguards for special populations, such as children and pregnant women. For children, studies should be designed in compliance with the Pediatric Research Equity Act. For pregnant women and women of childbearing potential who are not actively avoiding pregnancy, FDA encourages vaccine developers to consider the development of data early in their development programs that might support inclusion of these women in prelicensure clinical trials.

Furthermore, a discussion will need to take place prior to vaccine authorization or licensure about how postmarket surveillance will be conducted to ensure that infrastructure is in place for pharmacovigilance, especially for certain subpopulations (eg, a pregnancy exposure registry). FDA platforms such as the Vaccine Adverse Event Reporting System and the Sentinel Initiative, coupled with existing federal collaborations on vaccine safety, can offer useful starting points for postmarket surveillance of COVID-19 vaccines.[6]

These principles, along with the established standards used for preventive vaccines, will be applied as data from late-stage trials become available for FDA review. Of the available pathways, it is likely that a potential COVID-19 vaccine will be reviewed under either the traditional Biologics License Application (BLA) review process or under the Emergency Use Authorization (EUA) program. Although a vaccine could be reviewed under the Accelerated Approval program, this mechanism would not be appropriate until there is sufficiently compelling evidence demonstrating an effect of the vaccine on a surrogate end point, such as immune response, that is reasonably likely to predict clinical benefit. Issuance of an EUA for a COVID-19 vaccine may be appropriate once studies have demonstrated the safety and effectiveness of the vaccine but before the sponsor's submission of a BLA to FDA, before FDA has completed its formal review of the BLA, or both.

However, FDA recommends that sponsors of vaccine candidates—as well as sponsors of COVID-19 drugs and biologic products per the agency's previous guidance—file for review for traditional market authorization considering that any vaccine would be intended for widespread use.[7] Given the widespread potential use of a COVID-19 vaccine, transparent discussion at FDA's Vaccines and Related Biological Products Advisory Committee will be needed prior to vaccine authorization or licensure to ensure clear public understanding of the evidence supporting vaccine safety and efficacy.

The work to develop COVID-19 vaccines is a testament to not only scientific innovation, but also FDA's commitment to facilitate this effort. This is why FDA issued guidance providing clear recommendations around efficacy thresholds, population inclusion, and safety considerations prior to the initiation of most large-scale COVID-19 vaccine trials. A safe and effective COVID-19 vaccine that meets or exceeds the FDA regulatory standards will provide important momentum for pandemic recovery. Meanwhile, the continued use of evidence-based public health strategies to minimize transmission and reduce caseloads is emphasized and encouraged.

Vaccines are foundational to modern public health. Evidence from the 20th century demonstrates how the broad uptake of immunization can eliminate or reduce the risk of infectious disease outbreaks. Smallpox has been eradicated from the globe, and polio has now been eliminated from most countries. The likelihood of harm from seasonal pathogens such as influenza has also been reduced. Affirming, maintaining, and ensuring FDA's commitment to rigorous scientific review will enable COVID-19 vaccines to contribute to this important public health legacy in the months to come.

ARTICLE INFORMATION

Published Online: August 7, 2020. doi:10.1001/jama.2020.15725

Conflict of Interest Disclosures: None reported.

Additional Information: Dr Shah is deputy commissioner for Medical and Scientific Affairs, Dr Marks is director of the Center for Biologics Evaluation and Research, and Dr Hahn is commissioner, all at the US Food and Drug Administration.

REFERENCES

1. Fact sheet: explaining Operation Warp Speed. US Dept of Health and Human Services. June 2020. Accessed July 30, 2020. https://www.hhs.gov/about/news/2020/06/16/fact-sheet-explaining-operation-warp-speed.html

2. O'Callaghan KP, Blatz AM, Offit PA. Developing a SARS-CoV-2 vaccine at warp speed. *JAMA*. Published online July 6, 2020. doi:10.1001/jama.2020.12190

3. Expectations for a COVID-19 vaccine. Associated Press-NORC Center for Public Affairs. May 2020. Accessed July 30, 2020. https://apnorc.org/projects/expectations-for-a-covid-19-vaccine/

4. Collins FS, Stoffels P. Accelerating COVID-19 Therapeutic Interventions and Vaccines (ACTIV): an unprecedented partnership for unprecedented times. *JAMA*. 2020;323(24):2455-2457. doi:10.1001/jama.2020.8920

5. Development and licensure of vaccines to prevent COVID-19: guidance for industry. US Food and Drug Administration. June 2020. Accessed July 30, 2020. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/development-and-licensure-vaccines-prevent-covid-19

6. Ensuring the safety of vaccines in the United States. US Food and Drug Administration. July 2011. Accessed July 30, 2020. https://www.fda.gov/media/83528/download

7. COVID-19: developing drugs and biological products for treatment or prevention. US Food and Drug Administration. May 2020. Accessed July 30, 2020. https://www.fda.gov/media/137926/download