

Regulatory Decision-making on COVID-19 Vaccines During a Public Health Emergency

Jerry Avorn, MD

Program on Regulation, Therapeutics, and Law (PORTAL), Division of Pharmacoepidemiology and Pharmacoeconomics, Department of Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts.

Aaron Kesselheim, MD, JD, MPH

Program on Regulation, Therapeutics, and Law (PORTAL), Division of Pharmacoepidemiology and Pharmacoeconomics, Department of Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts.



[Viewpoint page 1282](#)



[Author Audio Interview](#)

Corresponding

Author: Jerry Avorn, MD, Program on Regulation, Therapeutics, and Law (PORTAL), Division of Pharmacoepidemiology and Pharmacoeconomics, Department of Medicine, Brigham and Women's Hospital, Harvard Medical School, 1620 Tremont St, Ste 3030, Boston, MA 02120 (avorn@post.harvard.edu).

Vaccine development and use depend on data-driven assessment of benefits and risks, first by regulatory bodies, and then more subjectively, millions of times over, by individual physicians and patients. Some vaccines have transformed public health (polio, smallpox, measles), whereas others have failed to work (HIV, malaria) or were later found to have important unexpected adverse effects (rotavirus, the 1976 influenza vaccine).

Regulatory review of the numerous coronavirus disease 2019 (COVID-19) vaccine candidates will occur under intense clinical, economic, and political pressure. In early August 2020, President Trump predicted that a vaccine could be available before election day. Less than a week later, Russia claimed to have developed its own vaccine and was beginning widespread administration without completion of the large-scale testing that Western countries routinely require, bringing efficacy-risk questions to even wider public attention. Acknowledging the pressure the US Food and Drug Administration (FDA) faces on this front, its leadership has stated that no vaccine would receive formal approval unless it met the agency's published standards.¹

As with drugs, the efficacy and safety of a vaccine are not binary. Each will fall along a gradient and be subject to varying definitions over time. In its June 2020 guidance document, the FDA established its expectation that an approved vaccine would reduce the occurrence or severity of disease in at least 50% of recipients, a standard similar to that for annual influenza vaccines.² But that criterion could change. If the pandemic surges further, should a vaccine be approvable if it prevents infection in a lower proportion of people? What if the vaccine substantially reduces the severity of illness, but not in half of recipients?

The FDA also cited the possibility of less conventional approaches. One approach would allow "accelerated approval" of a vaccine based only on antibody levels or another biochemical marker rather than actual clinical outcomes. This could occur if "additional understanding of SARS-CoV-2 immunology, and specifically vaccine immune responses that might be reasonably likely to predict protection against COVID-19, is acquired."^{2(p18)} For many years, the agency has shown increasing willingness to approve medications based on their capacity to affect surrogate measures such as laboratory test results, rather than demonstrating an effect on clinical disease.³ Such approvals have been made for drugs with extremely limited patient outcome evidence in oncology and muscular dystrophy, among other conditions. Some have argued that extreme clinical need warrants backing away from the FDA's historical standards requiring clinical benefit. This trend coincides with increasing political popularity of the libertarian "right to try" movement for medications, which advocates that patients should be able to access treatments not approved by the FDA. This approach was likely reflected in the presi-

dential reasoning about unproven COVID-19 treatments: "Try it; what do you have to lose?"

Alternatively, the FDA has noted that it could implement an Emergency Use Authorization (EUA) to make a COVID-19 vaccine available even before its full evaluation is completed. This would have seemed implausible but for the agency's issuance of another COVID-19-related decision in March. In the context of the president's persistent advocacy for hydroxychloroquine, the agency issued an EUA making millions of doses available for this purpose. That decision was eventually rescinded but led to considerable use of the drug, which continues, and the widespread misperception that the FDA had "approved" hydroxychloroquine for this use.

The FDA vaccine guidance acknowledged that an EUA issued before completion of planned clinical trials "could reduce the ability to demonstrate effectiveness of the investigational vaccine in a clinical disease endpoint efficacy trial to support licensure."^{2(p19)} A similar issue arose with convalescent plasma donated by COVID-19 survivors. The Trump administration established a program to provide convalescent plasma through an "expanded access" program outside ongoing randomized clinical trials, likely reducing enrollment in the studies required to determine if this therapy is effective and safe. A planned FDA EUA for plasma was initially blocked by senior government scientists who cited the lack of adequate efficacy data.⁴ President Trump then expressed concern that influences within the FDA were trying to delay COVID-19-related approvals until after the election to harm him politically.⁵ Immediately thereafter, the FDA reversed its decision on convalescent plasma and authorized an EUA for it, apparently without additional trial outcome data to justify this move.⁵

Other concerning regulatory decisions by the FDA at a time of enormous pandemic-driven pressure included its early hesitancy to approve tests to determine the presence of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), followed by widespread authorization of other tests with widely varying accuracy.

Just as the question "Does the vaccine work?" does not have a simple yes/no answer, neither does the question "Is the vaccine safe enough?" This will depend on the incidence and prevalence of COVID-19 in a given place and time, as well as the quality of available therapeutics. What about a vaccine that is effective in reducing infection but produces a severe allergic reaction in 1% of recipients? Or one that causes anaphylaxis in 1 in 1000 recipients, or 1 in 10 000? The extremely rare but potentially catastrophic possibility of immune enhancement must also be considered, in which disease is made substantially worse in some patients who receive a vaccine even as it protects others. Finding severe rare adverse events will require the study of tens of thousands

of patients, but this requirement will not be met by early adoption of a product that has not completed its full trial evaluation. This concern is even greater for new molecular approaches that have never been used in any prior vaccine, produced by manufacturers that have never brought a vaccine (or any other product) to market.

Based on suggestive trends in a biomarker such as antibody levels before clinical trial end-point data are complete, might the FDA be pressured in October to authorize limited “emergency” use of a not-yet-approved vaccine in a high-risk subset of the population (for example, health care workers or nursing home residents) on the grounds that the need is too pressing to wait for the usual assessment of efficacy and safety? FDA Commissioner Stephen Hahn, MD, has maintained that any vaccine “authorized for widespread use [emphasis added] will meet the appropriate standards for quality, safety, and efficacy”⁶ and noted a distinction between “emergency use” and “final approval,” suggesting that the criteria for an EUA could well differ from those for standard approval. The late-August plasma EUA decision is cause for alarm in this regard.

Standards for efficacy and safety must be high for any product designed to be administered to millions of healthy individuals in the hope that it will prevent illness in a fraction of them. The calculus is particularly challenging when such infection is often asymptomatic, sometimes mild, but in some cases severe or fatal. The stakes are significantly higher if the decision must be made at a time when the public is experiencing increasing anxiety over the pandemic, by a federal agency under the jurisdiction of a president facing an imminent election who is not known for his understanding of or respect for scientific rigor.

The public is not likely to focus on subtle distinctions between antibody levels and clinical end points, or on the difference between emergency authorization and full FDA approval. An October EUA based on suggestive surrogate markers may give rise to an unjustified sense of “mission accomplished”—a risky strategy for the nation. Vaccine use under an EUA could also miss the opportunity to learn about the safety and risks of the vaccine in its earliest use, a problem that has occurred with remdesivir,⁷ and could undermine the completion of randomized trials, as well as the public’s use of established measures, such as masks and distancing, that actually do prevent disease.

If the FDA declined to issue an October EUA for a COVID-19 vaccine, the agency could conceivably be directed to do so by the secretary of Health and Human Services, or possibly by the president. Such political intervention occurred in 2011, when the secretary of Health and Human Services reversed an FDA commissioner’s decision to make the “morning after” contraceptive pill available over the counter to patients of all ages.⁸ This type of political interference should not occur again.

The approval or emergency authorization of any COVID-19 vaccine will just mark the start of a second, equally crucial phase: its deployment across an enormous population. This will be the largest vaccine launch to take place in a period of unprecedented “vaccine hesitancy” by the public. In one large recent survey, only 44% of 34 269 respondents said they were willing to get a COVID-19 vaccine.⁹ If an approved vaccine reduces disease risk by 50%, and is used by less than half the population (as occurs each year with influenza immunization), it is unlikely to achieve the herd immunity that many anticipate from a product expected to “reopen the country.” If premature authorization leads to overestimation of its effectiveness, or failure to anticipate a serious adverse effect, either misstep could damage the already delicate trust many people in the United States have in immunization programs. The resulting damage to public acceptance could represent a dangerous “adverse effect” of any vaccine program, potentially undercutting all the excellent science and expense that preceded it.

The FDA has established a well-developed, science-based approach to vaccine approval and surveillance. It has rigorously presented sensible plans for evaluating COVID-19 candidate products^{1,2,7} but also noted the possibility of approaches using an EUA or accelerated approval based on surrogate measures even before ongoing randomized trials are completed. The political and economic pressures on the agency in October will be unprecedented. But the nation’s health will be far better served by reliance on the usual rigorous approach to vaccine evaluation. Premature rollout before the planned trial data are even collected would not be a medical breakthrough; it could represent a major public health misstep.

ARTICLE INFORMATION

Published Online: August 31, 2020.

doi:10.1001/jama.2020.17101

Conflict of Interest Disclosures: None reported.

Funding/Support: This work was supported by grants from Arnold Ventures and the Harvard-MIT Center for Regulatory Science to Dr Kesselheim.

Role of the Funder/Sponsor: The grant funders had no role in the preparation, review, or approval of the manuscript or the decision to submit the manuscript for publication.

REFERENCES

- Shah A, Marks PW, Hahn SM. Unwavering regulatory safeguards for COVID-19 vaccines. *JAMA*. Published online August 7, 2020. doi:10.1001/jama.2020.15725
- Development and licensure of vaccines to prevent COVID-19: guidance for industry. Published June 2020. Accessed August 25, 2020. <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/development-and-licensure-vaccines-prevent-covid-19>
- Zhang AD, Puthumana J, Downing NS, et al. Assessment of clinical trials supporting US Food and Drug Administration approval of novel therapeutic agents, 1995-2017. *JAMA Netw Open*. 2020;3(4):e203284. doi:10.1001/jamanetworkopen.2020.3284
- Weiland N, LaFraniere S, Fink S. FDA’s emergency approval of blood plasma is now on hold. *New York Times*. Published August 19, 2020. Accessed August 26, 2020. <https://www.nytimes.com/2020/08/19/us/politics/blood-plasma-covid-19.html>
- Bose N, Roston A. Trump hails FDA’s authorization of plasma treatment for coronavirus, after slamming agency. Reuters. Published August 23, 2020. Accessed August 26, 2020. <https://www.reuters.com/article/us-health-coronavirus-usa-trump/trump-hails-fdas-authorization-of-plasma-treatment-for-coronavirus-after-slamming-agency-idUSKBN25J00D>
- Hahn SM. FDA commissioner: no matter what, only a safe, effective vaccine will get our approval. *Washington Post*. Published August 5, 2020. Accessed August 25, 2020. https://www.washingtonpost.com/opinions/fda-commissioner-no-matter-what-only-a-safe-effective-vaccine-will-get-our-approval/2020/08/05/e897d920-d74e-11ea-aff6-220dd3a14741_story.html
- Sarpawari A, Kaltenboeck A, Kesselheim AS. Missed opportunities on emergency remdesivir use. *JAMA*. 2020;324(4):331-332. doi:10.1001/jama.2020.11932
- Center for Reproductive Rights. Federal judge orders FDA to broaden access to emergency contraceptive. Published April 5, 2013. Accessed August 25, 2020. <https://www.reproductiverights.org/press-room/federal-judge-orders-fda-to-broaden-access-to-emergency-contraception>
- Kamisar B, Holzberg M. Poll: less than half of Americans say they’ll get a coronavirus vaccine. *NBC News*. Published August 18, 2020. Accessed August 25, 2020. <https://www.nbcnews.com/politics/2020-election/poll-less-half-americans-say-they-ll-get-coronavirus-vaccine-n1236971>