

STATEMENT OF JESSE L. GOODMAN, MD, MPH July 14, 2020

Good morning Chairman Krishnamoorthi and other committee members. I am Dr. Jesse Goodman, an infectious diseases physician and Professor at Georgetown. I was formerly FDA's Chief Scientist and in that capacity helped lead many US and global public health responses. Before that I directed FDA's Center for Biologics Evaluation and Research, which assesses and monitors vaccines for the US. I appreciate the opportunity to be here today. While public health measures, diagnostics, and treatments can save lives, only vaccines offer the potential to provide widespread immunity and stop this outbreak before it burns through the world's population. For this reason, there are unprecedented efforts, both in the US and globally, to accelerate vaccine development, with the remarkable result that only 6 months from identifying the virus at least 15 candidates are being studied in humans with at least three slated to begin large Phase 3 trials soon. However, vaccine development and manufacturing are complex, success is never assured, and while we can speed the process, we must not cut corners. We must ensure COVID vaccines are safe and effective, and maintain public trust, which is already threatened. To do so, FDA's independence should be protected and the agency must uphold and be transparent about its standards in scientific decision-making. In a recent JAMA article, colleagues and I outline 4 safeguards needed in COVID-19 vaccine development.

First, we need strong evidence of effectiveness. This is best accomplished through large controlled clinical trials, involving thousands of individuals, that compare rates of illness in vaccinated and control individuals. To ensure vaccines work in those who need them most, trials should include diverse populations as well as the elderly and those with chronic conditions. FDA recently published guidance that vaccines should be at least 50% effective, a reasonable starting point. Effectiveness of the vaccines is not a given as it has not been easy to make vaccines against other coronaviruses and natural immunity may wane quickly.

Second, we need strong evidence of safety. Unlike treatments given to the sick, vaccines are given to the healthy and must be extremely safe. COVID-19 is a novel pathogen for which we have no vaccine precedents, and many vaccine candidates are based on novel technologies not yet utilized for approved vaccines. To ensure that benefits outweigh risks, pre-approval safety databases should include at least several thousand vaccinated individuals. In addition, once safety in the general population is documented, studies should move ahead in pregnant women, given the risks they face in their roles in healthcare and other essential work forces.

Third, we need to be very thoughtful about access to vaccines prior to approval. There may be circumstances where use of an unapproved vaccine could be appropriate in a severe outbreak. For example, if a vaccine with documented safety and promising effectiveness were available, but all the data needed not yet submitted, FDA could provide access through an expanded access program or through emergency use authorization (EUA). EUAs are designed to enable flexible responses to public health emergencies and have a lower evidentiary requirement than FDA's normal "safe and effective" standard - that a product "may" be effective and that known and potential benefits outweigh risks. However, experience has shown that the public may interpret an EUA as the same as an approval. If a vaccine used under EUA turns out to be ineffective or to raise safety concerns, and users were unclear that the vaccine was unapproved, a crisis could occur, and confidence in vaccines undermined. Therefore, if a vaccine is used preapproval, we suggest informed consent be part of the process, even under an EUA. In addition, we suggest use be targeted to those at highest risk of infection and complications.

Finally, a fourth safeguard is a robust monitoring system to track safety as vaccines are rolled out. Very rare serious adverse events may not be detected in pre-approval studies. Also, when a vaccine is administered broadly, common medical events will occur coincidentally after vaccination, but it is critical to be sure they are not vaccine related. For the 2009 H1N1 pandemic influenza vaccines, a system, capturing government and private sector data, was stood up and tracked millions of vaccine doses, helping ensure and communicate the vaccines

were safe. We need such a system in place now, with transparency about how safety will be monitored and communicated.

While working to get COVID vaccines quickly, these safeguards can help ensure they will be safe, effective and trusted. Thank you and I look forward to your questions and our discussion.

VIEWPOINT

The Development of COVID-19 Vaccines Safeguards Needed

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Viewpoint

A safe and effective vaccine against coronavirus disease 2019 (COVID-19) is the best way to control and ultimately end the pandemic. Vaccine development is moving at unprecedented speed, with more than 200 candidates, billions of dollars committed, and manufacturing often proceeding before even knowing whether a given vaccine candidate will succeed. To date, the US federal government has rapidly advanced 5 vaccine candidates through Operation Warp Speed.¹ At the same time, a growing movement of skeptics has raised doubt about future COVID-19 vaccines.² A poll of 1056 individuals in the US found that only 49% reported that they currently are planning to receive a COVID-19 vaccine, 31% are uncertain, and 20% are not, with safety a major concern.³

The best response to such concerns is a transparent and rigorous approach to vaccine development and regulation, including for licensure or any preclearance use permitted by the US Food and Drug Administration (FDA). For this effort to be successful, it is critical that the independence of the agency be respected, standards maintained, and politicians kept from pronouncements that create the appearance of interference such as that engendered by the emergency use

[T]hese safeguards must be in place to reach the goal of developing a safe and effective vaccine to end the pandemic...

authorization of antimalarial drugs to treat COVID-19.^{4,5} To help ensure the best possible decision-making and increase public confidence, regulators should be transparent about plans for 4 needed safeguards in COVID-19 vaccine development.

Strong Evidence of Effectiveness, Including in Key Populations

A COVID-19 vaccine should reduce the risk of infection, illness, and resultant complications. Currently, the best way to prove effectiveness is through large clinical trials that compare outcomes of vaccinated with unvaccinated individuals. Such studies, involving thousands of patients, are currently planned to begin over the next 3 months for at least 3 vaccine candidates. If these studies are conducted in communities with ongoing transmission (and, there are still many), it may be possible to determine vaccine effectiveness within months, potentially supporting a pathway to full approval. A critical need is to study effectiveness in racially diverse populations including not only healthy people but also older adults and individuals with chronic illness, populations at high risk of serious illness and death.

The FDA should now begin explaining these studies to the public, along with the standards that will be applied to determine effectiveness. Accelerated approval, which is a pathway based initially on a likely surrogate end point for effectiveness such as antibody levels, rather than clinical end points, is not currently feasible because there is insufficient evidence that specific antibodies predict protection. As a result, it would be premature to assess effectiveness based on antibody status. Should scientific understanding advance, this approach could be revisited.

Strong Evidence of Safety, Including in Key Populations

Mindful of prior vaccine safety challenges, regulators are appropriately cautious about approving vaccines for widespread use. Even during a pandemic, when much of the population is at risk, vaccines, unlike therapeutics, are administered to very large numbers of healthy individuals, and so must be extremely safe.

Phase 3 pivotal vaccine safety and effectiveness trials in the US typically enroll at minimum several thousand vaccinated individuals and control study participants and should detect a major safety signal of an order of magnitude likely to outweigh the benefits of an effective vaccine. The FDA should explain how the agency will require and carefully analyze these trials for safety signals before permitting broader use of a COVID-19 vaccine.

As soon as feasible after vaccine safety is established in trials, studies should also involve pregnant women, including those who risk exposure as health care workers, and young children, who are at risk of developing an infection-related multisystem inflammatory syndrome. In addition, based on animal studies, some vaccines against other coronaviruses have shown the potential to worsen disease among vaccinated individuals who develop breakthrough infections.⁶ Thus, in addition to routine safety analyses, regulators should look for more severe illness in vaccinated individuals who nevertheless develop COVID-19.

Informed Consent for Vaccine Use Prior to Approval

Approval based on safety and effectiveness, supported by well-controlled clinical trials and approved manufacturing processes, facilities, and quality is most desirable, and the "gold standard" for vaccine approval and marketing. However, during a severe ongoing pandemic, the FDA has several options for making a COVID-19 vaccine available to hundreds of thousands or even millions of US residents prior to approval.

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The FDA may make a promising but unproven investigational product available through an expanded access or so-called “compassionate use” program, which can allow access while requiring an informed consent process and adverse event reporting. Additionally, in a declared public health emergency and provided there are no approved alternatives available, the FDA may issue an Emergency Use Authorization (EUA), based on its specific risk-benefit assessment and scientific determination that the evidence supports that a product “may be effective” and that its known and potential benefits are likely to outweigh known and potential risks.⁷

Although an EUA can facilitate wide access and can allow provisions that enhance public health responses, such an approach should only be used cautiously for COVID-19 vaccines because the public may perceive an EUA as the same as approval despite FDA messaging and product labeling to the contrary.⁴ If a vaccine used under EUA were to encounter safety problems, be ineffective, or be perceived as experimentation without consent, the FDA will be challenged about why the agency did not wait for more data before wide vaccine release, and trust in all vaccines may be seriously compromised. Therefore, if an EUA route is used for COVID-19 vaccines, it would be best for the FDA to require informed consent using a process that explains why the product is only available under an EUA, helping ensure all users understand the vaccine is not yet approved.

Whatever pathway or pathways are followed, safety and effectiveness should be monitored to maximize understanding of the vaccines prior to broader use, and to help support eventual approval. In addition, along with informed consent, it would be preferable to focus the initial use of unapproved vaccines for individuals at high risk of infection or severe outcomes (eg, health care workers, other essential workers, nursing home residents, and others in congregate settings, such as older adults and those with chronic medical conditions).

Governments, including regulators and leaders, must clearly and accurately communicate to the public, clinicians and health care organizations, and vaccine recipients. Information should include consistent, comprehensive, and understandable messaging about

whether a vaccine is approved, if not, why not, and what is known and not known about its safety and effectiveness, including adverse effects and their frequency.

Comprehensive Safety Monitoring Systems

Some vaccine-related serious adverse events occur very rarely or may not be detected in prelicensure studies. For example, in 1976, an excess of Guillain-Barre syndrome (GBS) of approximately 1 case per 100 000 recipients was noted only after immunization with the swine influenza vaccine and, as a result, and given the waning of the disease, the program was halted.⁸ To ensure that such rare events, however unexpected, are rapidly detected, reported, and addressed, extensive near real-time monitoring will be critical during the roll out of COVID-19 vaccines. Furthermore, because vaccines will be administered widely in a short time period, events that raise concerns will occur, even coincidentally, after administration. Communication in advance about this possibility and how the FDA will respond can enhance public understanding of the value of monitoring and oversight.

A strong model can be found in the approach to influenza H1N1 vaccines, which were approved rapidly during the 2009 pandemic. At that time, a range of systems, combining federal and private sector databases, was developed to actively monitor the safety of millions of vaccine doses.⁹ An independent assessment group, including nongovernmental experts, reviewed data at least biweekly, helping ensure and communicate that the vaccines used in the US were safe. Since then, more electronic data systems have become available. Standing up these resources, and explaining their use to the public, will help the FDA, the Centers for Disease Control and Prevention, and partners rapidly monitor, analyze, and communicate about the safety of new COVID-19 vaccines.

Conclusions

As the US and other nations race to develop COVID-19 vaccines, these safeguards must be in place to reach the goal of developing a safe and effective vaccine to end the pandemic as quickly and as safely as possible, while earning and keeping public trust and confidence.

ARTICLE INFORMATION

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Disclaimer: The views expressed herein are solely those of the authors, and do not necessarily represent the views of any organizations with which they are affiliated.

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