Regulatory Approval Primer for Vaccine Advocates

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AVAC
25 Years and Counting

Recent media coverage has highlighted concerns over a pre-election "October Surprise" in the United States, in which approval of a COVID-19 vaccine is expedited for political gain before adequate safety and efficacy data are gathered or shared. Approvals of COVID-19 vaccines in China and Russia (in advance of Phase III data) further underscore the risks of placing politics over safety, efficacy and necessary normative review and guidance. These recent events prompted a public pledge from nine pharmaceutical companes that they would not seek government approval without extensive safety and effectiveness data.

The difference between speed and cutting corners can be one of life or death for individuals, and of impact versus impasse for societies. Advancing a vaccine candidate without peer-reviewed research results and thorough regulatory review can also undermine confidence in public institutions and vaccines generally. Global health advocates have an essential role to play as watchdogs of the regulatory systems that have worked well for decades, but may be vulnerable to global pressure for a vaccine and the current politicization of science.

Top-line Messages

- No vaccine should be approved for use until safety and efficacy have been proven in populations at significant risk of COVID-19.
- US FDA review should involve the Vaccines and Related Biologics Product Approval Committee (VRBPAC) to allow unbiased, external experts to evaluate safety and efficacy.
- When results are announced, comprehensive data-sets should be made publicly available for peer review. Publication via press release or political podiums is not scientifically rigorous, promotes mistrust and fuels public concerns around the politicization of science.

The US Food and Drug Administration (FDA) reviews data and issues decisions on a range of medical products, including vaccines. This review is designed to ensure that products offered to the public in the US are safe and effective, that benefits outweigh risks, and that these risks and benefits are clearly labeled for providers and users. The FDA and other agencies worldwide have specific processes for evaluating vaccines and will be called on to assess the data for COVID-19 vaccines. Given the global impacts of the COVID-19 pandemic, there is, understandably, enormous pressure to speed the development and approval of potentially life-saving vaccines. (See also AVAC's Advocates' Guide: the risks and benefits of expedited COVID-19 vaccine research.)

However, if approval appears to have been influenced by politics—or if the process skips essential steps—the implications are significant. First and foremost, there is the risk of a vaccine being administered that is not safe or effective. Further, public faith in regulatory review can be damaged, resulting in decreased uptake of COVID-19 vaccines and other immunizations. This checklist outlines what advocates can watch to ensure that regulatory review of COVID-19 vaccines is unbiased, thorough and swift.

Key factors in evaluating COVID-19 vaccine trials

TRIAL DESIGN: A regulatory opinion is only as sound as the data upon which it is based. To watchdog regulatory processes, advocates need to monitor and engage in trial design.

Enrollment: Enrollment refers to both the number and demographics of volunteers enrolled in a trial. Phase III trials enroll large numbers of people, with some planned large-scale COVID-19 vaccine trials enrolling up to 60,000 volunteers. The FDA has encouraged the inclusion of diverse populations in COVID-19 trials, including older people, people of color, and people with co-morbidities – all of whom are at a higher risk of infection and who experience more severe illness and higher mortality from COVID-19. Without their participation in Phase III trials, there is a real risk of not being able to tell if drugs or vaccines are safe and effective in these populations. In some instances, this may result in the FDA waiting to issue an approval until adequate safety and efficacy data has been obtained; delaying access for the people who need the drugs and vaccines the most.

QUESTIONS TO ASK

- ✓ Were the inclusion and exclusion criteria fully inclusive? What was done to ensure enrollment of populations most at risk of COVID-19?
- ✓ Is there adequate representation of diverse populations in studies, including racial diversity, PLWHIV, pregnant women, older people and people with co-morbiditities for whom safety and efficacy of a vaccine is critical?

Endpoints: A trial "endpoint" is what researchers measure to determine that vaccines are safe and effective (e.g., infections, disease progression, specific biomarkers, etc.). A Phase III vaccine trial is designed to get clear answers about specific endpoints, including the following:

- Infection endpoints: A measure of the reduction in infection with SARS-CoV-2, the virus that causes COVID-19.
- Disease endpoints: A measure of the reduction in the severity of disease and/or symptoms in people who received the vaccine and went on to acquire SARS-CoV-2.
- Safety endpoints: Phase III trials are able to identify both subtle and potentially rare side effects that may not have been identified in earlier, smaller studies. Given the large numbers of people that will likely take an effective COVID-19 vaccine, researchers, regulators, and end-users must be confident of safety profiles and aware of potential side effects.
- Immunologic endpoints: Every vaccine induces an immune response. An effective vaccine induces a "protective" immune response. However, because we don't yet know how the immune system protects against SARS-CoV-2, we don't know how to tell if someone is protected by measuring immune responses using laboratory tests. That means vaccine studies need to provide direct evidence that a vaccine works based on infection and/or disease, rather than laboratory endpoints.

QUESTIONS TO ASK

- ✓ Is the trial measuring infections prevented as well as the reduction in symptoms or severity of disease?
- ✓ What side effects, adverse events and other issues did the trial observe?
- ✓ Is there sufficient data to rule out disease enhancement, that is, the rare occurrence in which the vaccine makes the disease worse once a vaccinated person is naturally infected?
- ✓ What immunologic tests is the trial planning to do? Have product developers agreed to use common platforms and approaches to analyze their samples?

Independent data review and "stopping rules": The study team predetermines 'stopping rules' to decide whether a study should be halted early for efficacy, harm or futility. They also decide on rules for extending the study. For example, if the infection rate is lower than expected, studies may need to run longer or enroll more people to establish efficacy. Vaccine clinical trials are overseen by independent data safety monitoring boards (DSMBs), which are the only groups to review unblinded data. They hold regularly scheduled data review meetings to review safety and the number of COVID-19 cases.

QUESTIONS TO ASK

Based on the data, the DSMB can recommend stopping a study for various reasons, including cases in which the data clearly demonstrate that intervention is working, that it likely will not work, that it causes serious side effects, or causes disease enhancement. Even when a trial is stopped early, study participants will likely be followed for one to two years to gather longer-term safety and efficacy data and evaluate immunological changes.

- ✓ Does the DSMB meet at regularly scheduled intervals, and can they request additional review based on emerging concerns about safety or efficacy?
- ✓ What is the plan for informing trial participants and the public of any decision to stop the study and its rationale? How quickly will this communication happen?

TRIAL DATA: A well-designed trial delivers an answer to the trial's predefined questions. That result can be positive or negative. Here are some things that advocates should look for in trial data and regulatory review.

Efficacy: Every trial result is presented in statistical terms, which establishes the reliability of the findings. An efficacy result (i.e., whether a vaccine effectively protects an individual from infection or severe disease) is reported as both a point estimate and a confidence interval. The point estimate is a number, like 50 percent. A confidence interval is a range of values above and below the point estimate. A 95% confidence interval—standard for scientific analyses—defines the range of values that can be said, with 95 percent certainty, to contain the product's actual efficacy.

QUESTIONS TO ASK

In June, the FDA issued Development and Licensure of Vaccines to Prevent COVID-19: Guidance for Industry, which indicates that for a COVID-19 vaccine to be approved, it must be at least 50 percent effective (i.e., it reduces the risk of infection or severe disease by at least 50 percent compared to people who received a placebo and who were at comparable risk of acquiring SARS-CoV-2). The FDA has said that the lower end of the confidence interval for a COVID-19 vaccine should be greater than 30 percent.

- ✓ Has the vaccine reliably determined efficacy in populations at significant risk for COVID-19?
- ✓ What is the efficacy result point estimate and confidence interval? Does it meet pre-established FDA requirements (i.e., minimum 50%; CI lower bound >30%)
- ✓ First-generation vaccines should not be approved based on surrogate endpoints (e.g., immune response) data alone. In the United States and countries following the US FDA's lead, has the product developer followed FDA guidance and pursued "traditional approval via direct evidence of vaccine efficacy in protecting humans from SARS-CoV-2 infection and/or disease"?

Infections: A minimum number of infections will need to occur in the study population to determine with statistical significance that a product is effective in a way that was planned in advance by vaccine companies and regulators. This will vary between studies based on how effective the vaccine is. For example, it has been estimated that in a 30,000 person trial, one would be able to determine, with statistical significance, if a vaccine were 50 percent effective after ~150 infections. If the vaccine was more effective, that could be determined after fewer infections.

QUESTIONS TO ASK

- ✓ How many infections were there in the vaccine compared to the placebo? How does this compare to the statistical plan outlined in the trial design?
- ✓ Did the trial fully enroll, and continue till completion, or was a pre-specified stopping point reached?

Safety: Vaccine trials can only determine short-term safety events that occur within a few months of receiving the vaccine. However, safety will continue to be monitored and evaluated for one or more years, which may mean after the vaccine is licensed, using a range of surveillance options. A known and unavoidable risk of the urgent need for vaccine development is that long-term safety cannot be established before the deployment of an effective vaccine. This is an important fact in weighing the benefits and the risks: if the benefits are unequivocal, this is likely to be acceptable; if the benefits are equivocal, the risks may outweigh them.

DATA EVALUATION: Data from a well-designed, well-conducted trial must be evaluated in an independent, scientifically-rigorous transparent process, devoid of politics. Here are things to watch for:

Trial Results: Traditionally, the results of scientific studies are peer-reviewed and published in academic journals, or presented at research conferences, following months of preparation and accompanied by a pre-specified statistical analysis, which includes safety, efficacy and validity of the results. Given the devastating impacts of the COVID-19 pandemic, trial results often have immediate and global relevance and are thus being announced to the public ahead of publication. Nevertheless, a minimum set of accompanying data must be made available expeditiously for public analysis and understanding.

WHAT TO WATCH FOR

- ✓ More than 400 experts, have called on the FDA to involve its Vaccines and Related Biologics Product Approval Committee (VRBPAC) in COVID-19 vaccine authorization and approval processes. Such transparency will allow unbiased, external experts to evaluate safety and efficacy, thereby increasing public confidence that the approval process is scientifically valid and has not been politicized. An initial VRBPAC meeting is scheduled for October 2020, not to review a specific application, but to discuss, in general, the development, authorization and/or licensure of COVID-19 vaccines. Advocates can offer both written and oral comment at the meeting.
- ✓ Data provided when results are announced should be publicly available, comprehensive, transparent and should include the study design, participant characteristics, primary findings, safety data such as severe adverse events—organized by study arm and, if available, by sub-populations—and describe any study limitations. Two researchers recently proposed these minimum requirements for announcing clinical trial results during the COVID-19 pandemic.
- ✓ The data released should be fully transparent and published in a peer-reviewed journal. Publication via press release or political podiums is not scientifically rigorous, promotes mistrust and fuels public concerns around the politicization of science.

Emergency Use Authorizations (EUA): During a public health emergency, the FDA can issue an EUA to allow for the use of unapproved medical products, including vaccines. This means that the FDA thinks the product shows promise and is generally safe, but there is insufficient data to prove safety and efficacy using accepted FDA standards for full approval. Given the large numbers of people to protect from COVID-19, as well as growing evidence of the politicization of scientific decision-making, the risks of an unwarranted EUA for a COVID vaccine seem enormous. Even the FDA has said that issuance of a EUA "prior to the completion of large randomized clinical efficacy trials could reduce the ability to demonstrate effectiveness of the investigational vaccine in a clinical disease endpoint efficacy trial to support licensure." As such, **AVAC maintains that both efficacy and safety must be clearly established before a COVID-19 vaccine is authorized for use, in any capacity**.

About AVAC

AVAC is a non-profit organization that uses education, policy analysis, advocacy and a network of global collaborations to accelerate the ethical development and global delivery of new HIV prevention options as part of a comprehensive response to the pandemic.
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