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ANALYSIS

An Overview Of Vaccine Development, Approval, And Regulation, With Implications For COVID-19

ABSTRACT The Food and Drug Administration generally approves vaccines when their benefits outweigh their risks for their intended use. In this paper, we review current and potential approaches to this critical role of the FDA. The FDA has established pathways to accelerate vaccine availability prior to approval, such as emergency use authorization, and to channel resources to high-priority products and allow more flexibility in the evidence required for approval, including accelerated approval based on surrogate markers of effectiveness. Among the 35 new vaccines approved in the US from 2006–2020, about two-thirds of their pivotal trials used the surrogate outcome of immune system response, and just one-third evaluated actual disease incidence. Post-approval safety surveillance of new vaccines—particularly vaccines receiving expedited approval—is crucial. Currently this is accomplished through such mechanisms as the Centers for Disease Control and Prevention/FDA Vaccine Adverse Event Reporting System, the CDC Vaccine Safety Datalink, and the CDC Clinical Immunization Safety Assessment Project. Adverse events detected in this way may lead to changes in a vaccine's recommended use or its withdrawal from the market. Regulatory oversight of new vaccines will have to balance speed with rigor and decisiveness to effectively address the coronavirus disease 2019 (COVID-19) pandemic. [*Editor's Note: This Fast Track Ahead Of Print article is the accepted version of the peer-reviewed manuscript. The final edited version will appear in an upcoming issue of* Health Affairs.]

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As complex biological products administered to millions of generally healthy people, vaccines have been among the most carefully evaluated medical products. Historically, it has taken years to move a vaccine from initial discovery to US Food and Drug Administration (FDA) approval.[1] But the unprecedented impact of the coronavirus disease 2019 (COVID-19) pandemic has brought attention to the process of vaccine development and evaluation and whether it can be expedited. Vaccine regulatory assessment demands a balance of efficacy, safety, and speed. In this paper, we review current and potential approaches to this critical role of the FDA.

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Vaccine Clinical Testing And Approval

Vaccine approval comes under FDA authority through the Federal Food, Drug, and Cosmetic Act (FDCA), and is also governed by the Public Health Service Act, which regulates biological products. The process and requirements for vaccine approval and regulation therefore follow a pattern similar to those for other medical products, including preclinical testing, human testing, and post-approval safety monitoring. Within the FDA, the Center for Biologics Evaluation and Research is responsible for vaccine approval and regulation.

Once in-vitro testing and animal studies help identify the appropriate dosage and provide pharmacokinetic and toxicology data,[2] a manufacturer submits an Investigational New Drug (IND) application to the FDA. An IND contains preclinical data, a description of the proposed manufacturing process and quality control procedures, and a description of planned human trials.[3] After the manufacturer submits a valid IND, such trials can proceed. If preliminary data from these trials raise safety or efficacy concerns, the FDA may request additional studies or halt the trials.

Consistent with FDA regulations, Phase 1 clinical studies assess vaccine safety, dosage, and capacity to induce an immune response in a small number of healthy subjects. Phase 2 trials evaluate initial safety and efficacy in a larger population, perhaps a few hundred. Phase 3 trials provide more definitive evidence of a vaccine's efficacy. They are usually large, randomized, blinded, and controlled, and involve hundreds to thousands of subjects. Because vaccines are administered to healthy people, there is a low tolerance for adverse events, even rare ones.[4] This requires a larger sample size than would be needed, for example, for a study of a new antibiotic to treat an acute infection. As a result, the Phase 3 trials that comprise the pivotal data supporting FDA approval are often much larger for vaccines than for other drugs.[5] If additional safety or—less commonly—efficacy questions remain, the manufacturer may commit to one or more Phase 4 studies to be conducted after approval.

The FDA can rely on several programs to expedite development and regulatory review of new vaccines by channeling agency resources to high-priority products, and accepting greater uncertainty by allowing more flexibility in the evidence required for approval.[6] Three programs expedite FDA approval: fast track, breakthrough therapy, and accelerated approval.

For fast-track evaluation, for products designed to prevent a life-threatening disease or condition and have the potential to address an unmet need, manufacturers receive the benefit of heightened internal prioritization by FDA during clinical development and can submit portions of the licensing application on a rolling basis. With so-called breakthrough therapy designation, intended for products that may offer a substantial benefit over existing options, manufacturers receive fast-track benefits plus more formalized FDA response-time commitments. Under accelerated approval, permission to market a product may be based on surrogate measures, such as antibody levels, that may not be well-established but are seen as reasonably likely to predict clinical benefit. In June 2020, the FDA indicated that no acceptable surrogates yet existed for a COVID-19 vaccine, and that unless agreement is reached with the FDA on the use of an appropriate surrogate, primary endpoints should be limited to severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection confirmed serologically or virologically.[7] But the agency left open the possibility that future insights into COVID-19 immunology might lead to definition of an acceptable surrogate of this sort.

Other programs authorize special access to a vaccine before FDA approval: expanded access and emergency use authorization.[8] Expanded access allows patients with serious or life-threatening conditions to request experimental products from the manufacturer prior to FDA approval. For example, in 2014 the FDA allowed expanded access to a meningococcal group B vaccine (Bexsero) during an outbreak at Princeton University more than a year before the vaccine was approved.[9] In a declared public health emergency the FDA Commissioner can issue an Emergency Use Authorization, allowing more widespread use of a vaccine prior to meeting the substantial evidence criteria for FDA approval, so long as the FDA determines that the product's potential benefits outweigh its potential risks.[10] On February 4, 2020, the Secretary of Health and Human Services declared that COVID-19 posed such a threat, and in March the FDA issued an umbrella Emergency Use Authorization covering certain ventilators and other products. There has been substantial debate, however, over whether and how Emergency Use Authorization would apply to COVID-19 vaccines and what defines "potential" benefits and risks.[11]

In the non-emergency authorization pathway, once a vaccine successfully moves through Phase 3 trials, the manufacturer submits a biologics license application (BLA). The FDA may solicit input from the Vaccines and Related Products Advisory Committee, an outside group of experts, for advice on the approval decision. The

FDA usually follows the recommendations of the committee but is not legally required to do so.[12]

The FDA has generally refrained from setting minimum efficacy thresholds (other than zero) for vaccines. However, a 2007 FDA guidance document indicated that accelerated approval of a vaccine for a pandemic influenza virus could potentially be supported by evidence showing that the lower bound of the 95% confidence interval for the percent of subjects achieving seroconversion (the production of detectable antibodies) was at least 30%.[13] Similarly, recent FDA guidance on COVID-19 vaccine evaluation indicated that the product should reduce disease incidence or severity in at least 50% of subjects, with a lower bound of the 95% confidence interval of more than 30%.[14] FDA guidance documents, however, are generally not binding.

Some other vaccines achieve levels of efficacy of 80% or higher in clinical trials,[9] whereas annual influenza vaccines may achieve more modest levels, similar to the efficacy threshold FDA has proposed for COVID-19 vaccines. Pfizer and BioNTech recently issued a press release describing preliminary results of Phase 3 study data showing that their mRNA-based vaccine candidate may be over 90% effective in preventing COVID-19 in participants without known SARS-CoV-2 infection.[15] However, vaccine efficacy as measured in clinical trials may imperfectly predict effectiveness in routine care owing to differences in real-world patient characteristics and practice patterns (such as whether a person receives both doses of a two-administration vaccine).

Even with modest efficacy, however, a vaccine can reduce disease incidence, hospitalization, mortality, and disability,[16] either directly or through herd immunity. Between 2008 and 2018 the annual flu vaccine varied in efficacy between 19% and 60%, with a mean of 45%, in part due to the difficulty of predicting which strain of flu will become widespread in any given year.[17,18]

Safety Studies

For any vaccine, efficacy must be weighed in light of the risk of disease occurrence and the incidence and severity of vaccine side effects. Not all adverse reactions can be detected during pre-approval clinical trials. Rare but serious adverse reactions are a particularly salient concern for a pandemic vaccine intended to be administered to healthy members of nearly the entire population in a short period of time. Even moderately large trials may not be sufficiently powered to define important safety risks. Study participants also may not be fully representative of the population to be vaccinated in terms of their age, race, frailty, co-morbidities, genetics, or pregnancy status. It is therefore necessary to conduct post-market safety surveillance to understand how the vaccine performs in a real-world setting. This is particularly important for vaccines developed under an expedited timeline, or those that use molecular approaches never before deployed in any marketed product, both of which are characteristics of some COVID-19 vaccines in development.

The contemporary post-approval surveillance and safety system for vaccines involves Phase 4 post-approval studies and other post-approval oversight and analysis arising from the FDA and the Centers for Disease Control and Surveillance (CDC): the CDC/FDA Vaccine Adverse Event Reporting System (VAERS); the CDC Vaccine Safety Datalink (VSD), and the CDC Clinical Immunization Safety Assessment (CISA) Project.

Phase 4 studies to obtain additional efficacy and safety data may be conducted at the discretion of the manufacturer, or sought by the FDA at the time of vaccine licensure.[19] Case-control or cohort studies designed to study a particular adverse event are common Phase 4 study designs.[20] Analyses of required Phase 4 studies across all drugs and biologics have found that they are frequently not completed on time, if at all.[21]

VAERS,[22] established in 1990, is a spontaneous reporting system in which clinicians, manufacturers, and the public can voluntarily report adverse events following vaccination. It allows the CDC and FDA to monitor new, unusual, or rare adverse events and to determine if further studies are warranted.[23] At the Uppsala Monitoring Center, the World Health Organization assesses the output of this system in light of findings from similar approaches around the world. One limitation of VAERS is under-reporting, with reporting sensitivities to VAERS varying widely across vaccines and types of adverse events.[24] This problem is also well-documented for the FDA's analogous drug adverse event reporting system. Because spontaneous reports lack denominator data and reflect voluntary, unsystematic reporting, VAERS is most relevant as a tool for generating hypotheses for other studies and generally cannot be used alone in determining causality.[25]

To more systematically study potential safety problems, the CDC established the Vaccine Safety Datalink in 1990, which contains data from eight health care systems around the country, representing about 10 million patients.[26] Each site contributes electronic health data that can be used to monitor vaccine safety and conduct studies about rare and serious adverse events.[27]

The CISA Project,[28] using the statistical signals

reported by the Vaccine Safety Datalink, enables vaccine safety experts to conduct detailed clinical reviews of patients who had an adverse event possibly caused by a vaccine, and to identify possible risk factors.[29] These studies are particularly important for understanding adverse events in certain populations, such as pregnant women and immunocompromised patients, who are typically excluded from pre-licensure clinical trials.

One approach used by the Vaccine Safety Datalink is Rapid Cycle Analysis, in which weekly data feeds are analyzed using sequential statistical methods. When a pre-specified threshold is exceeded, this indicates a potential problem requiring evaluation. For example, the year after the measles-mumps-rubella-varicella (MMRV) was introduced in 2006, after the administration of about 43,000 doses,[30] the Vaccine Safety Datalink detected the possibility of one additional febrile seizure per 2,000 children vaccinated with MMRV. This led to a change in national recommendations, which removed the preference for the MMRV vaccine over separate MMR and varicella vaccines.[31]

Many vaccine-related adverse events may be unexpected. Using ICD-10 codes, a novel tree-based statistical scanning approach makes it possible to evaluate thousands of different potential adverse reactions, which would otherwise generate hundreds of false positives based on chance alone.[32] W. Katherine Yih and colleagues used this approach to evaluate the quadrivalent human papillomavirus vaccine, and found only mild adverse reactions such as injection site rashes.[33] To complement the CDC post-market safety surveillance, the FDA uses data from the Centers for Medicare and Medicaid Services (CMS) and the FDA's Sentinel Post-Licensure Rapid Immunization Safety Monitoring (PRISM) system that was inaugurated during the 2009 H1N1 pandemic.[34] FDA is also setting up a new system based on commercial insurance claims data to replace or complement the FDA Sentinel PRISM system.

If any of these surveillance approaches reveal a mild or very rare adverse reaction, it may lead to an additional cautionary statement on the product labeling. Labeling changes for safety problems following new vaccine approval have been less common than those for new drugs.

For more serious problems, the Advisory Committee on Immunization Practices may revise its recommendation, recommending either a different vaccine or no vaccination at all. Even the unconfirmed possibility of a serious problem can lead to voluntarily market withdrawal. This occurred with LYMErix, a vaccine developed to prevent Lyme disease. After 1.4 million doses were administered, 59 cases of arthritis were reported to VAERS. Although the rate was similar to that seen in unvaccinated individuals, and a post-licensure study by the manufacturer did not find a higher rate of adverse reactions among vaccine recipients, the manufacturer withdrew the vaccine from market, citing poor sales that were likely a result of press coverage and the risks of ongoing litigation.[35]

The FDA can also initiate vaccine removal from the market if it determines that statutory benefit-risk requirements are no longer satisfied. This is rare, but occurred in 1999, after about 1.2 million doses of the Rotashield vaccine against rotavirus infection were administered. During pre-licensure trials, the number of cases of intussusception—in which part of the intestine telescopes into itself and causes bowel obstruction—was statistically indistinguishable from the background rate. But 15 cases were reported to VAERS within a year of the vaccine's introduction. A more systematic study using the Vaccine Safety Datalink found that the Rotashield vaccine was associated with an increased risk of intussusception in infants. Although the rotavirus vaccine was still considered useful in countries where many infants die from diarrheal disease, the Advisory Committee on Immunization Practices determined that the risks of intussusception did not outweigh the benefits of the prevention of diarrheal disease in the US, where such disease is more manageable. Two subsequent rotavirus vaccines were introduced in 2006 and 2008, and were thoroughly evaluated using VAERS spontaneous reports,[36] the Vaccine Safety Datalink near-real time weekly monitoring system,[37] and the FDA Sentinel PRISM system[38] and found to be sufficiently safe.

A safety challenge particular to vaccines is the risk of immune enhancement, in which vaccinated subjects may develop more severe disease when exposed to the target pathogen than those who were not vaccinated. While unusual, such a finding in the Philippines was the cause for the suspension of the Dengvaxia vaccine against dengue fever. Such rare reactions further increase the importance of effective and vigorous pharmacovigilance programs.

Past safety evaluations have sometimes used a comparator vaccine, well-care visits, historical population-based incidence rates, or self-controls in which a risk window soon after vaccination is compared to a comparator window from the same patient before or further away from vaccination. These programs can also provide information on the comparative effectiveness and safety of different vaccines directed against the same condition. For COVID-19, both the Vaccine Safety Datalink and FDA and CMS surveillance systems could be used to conduct near-real

time rapid cycle analyses to quickly detect any potential safety problem and unsuspected adverse reactions.

Current Landscape Of Vaccine Approvals And Post-Market Studies

To provide context for the assessment of proposed vaccines related to COVID-19, we assessed the characteristics of pivotal trials of all new vaccines approved in the last fifteen years, and reviewed required post-market studies. The methods and full results of this analysis are provided in an online appendix.[39] We identified 35 novel vaccines approved in the US between 2006 and July 2020, including 6 that were the first vaccine approved for that disease ("first-in-disease" products), including Gardasil for human papillomavirus and Trumenba for meningococcal group B infections. More than half of new vaccines were for adults ($N = 20$, 57%) and the number approved each year was stable throughout the time period (appendix exhibit 1).[39]

There were 61 pivotal trials conducted for these novel vaccines. All were randomized, and most were double-blinded. About half ($N = 28$, 46%) used active controls, in which an already approved vaccine product is compared to the experimental vaccine. The remainder were either placebo-controlled ($N = 23$, 38%) or self-controlled (in which comparisons of antibody levels or other outcomes are made within individuals before vs. after vaccination; $N = 10$, 16%). About two-thirds of trials used the surrogate outcome of immunogenicity, measuring a change in antibody levels or a similar biomarker; only about one-third evaluated whether the vaccine actually reduced the incidence of the targeted disease (appendix exhibit 2).[39] A similar division was seen even for first-in-disease vaccines ($N = 15$), in which nearly half of trials relied on a surrogate measure of efficacy. Subunit-based vaccines were considerably more common than whole-pathogen vaccines, and were far more likely to rely on laboratory tests to determine efficacy rather than actual clinical endpoints (76% vs. 38%, respectively).

The pivotal trials enrolled a median of 2,415 patients (interquartile range [IQR]: 884–4,605), with a median of 1,713 (IQR: 466–3,084) in the intervention group, and lasted for a median of 18 months (IQR: 8.7–27.2) (appendix exhibit 3).[39]

Of the 35 vaccines, 32 (91%) had commitments or requirements for post-approval studies. Twenty vaccines had statutorily-mandated post-market study requirements, including 19 under the Pediatric Research Equity Act for testing in children, 6 under the accelerated approval pathway for confirmatory testing of products based on a non-well-established surrogate measures, and 2 under the FDA Amendments Act Section 505(o)(3) authorities for products with potentially serious safety questions.

Vaccine Injury Compensation

The National Childhood Vaccine Injury Act in 1986 established the National Vaccine Program to direct vaccine research and development, and ensure the production, procurement, and distribution of safe and effective vaccines. The Act also established the National Vaccine Injury Compensation Program, which compensates those with certain injuries caused by certain vaccines, using a "no fault" system as an alternative to litigation.[40] The program is funded by a small ($0.75) tax levied on each dose of CDC-recommended children's vaccines.

Not all vaccines are covered under the VICP. The Public Readiness and Emergency Preparedness Act (PREP Act) of 2005 authorized the Secretary of HHS to establish the Countermeasures Injury Compensation Program, which has been administered by the Health Resources and Services Administration since 2010. This program is designed to compensate individuals injured by countermeasures, including vaccines, administered during public health emergencies like pandemic influenza and COVID-19.[41] The standards for compensation are similar to those of the VICP: the requester has the burden of proving he or she sustained a certain injury covered by the program within an allowable time period following receipt of the countermeasure. As in the Vaccine Injury Compensation Program, manufacturers are granted immunity from liability except in cases of willful misconduct.

Discussion

Our review of novel vaccine trials from the last 15 years showed consistency in some of the characteristics of the trials, including randomization and blinding. About half used active controls as comparators. Most pivotal trials enrolled large numbers of patients and required 1–2 years or longer to complete. We also found that most vaccine trials used surrogate measures of efficacy, predominantly immunogenicity, rather than demonstration of differences in the rate of disease incidence.

When immunogenicity is used as a surrogate measure to support vaccine approval, it is important for that surrogate to be well-validated for predicting clinical protection. It then falls to post-approval phase 4 studies or other oversight activities from the manufacturer or FDA to con-

firm the expected benefit in typical "real-world" populations. Nearly all new vaccine approvals came with post-approval commitments or requirements.

For pandemic vaccines, the approach to an approval decision must be calibrated to the fact that the new product will be administered to very large numbers of healthy people in a short period of time, shaping the pre-approval benefit-risk determination. Because of the clinical and ethical implications of precipitating rare severe side effects, initial evaluation requires large randomized trials of considerably greater size than are needed for approval of a new drug, as well as meticulous post-approval safety surveillance. The time required to accrue adequate person-time experience in a trial is also greater for a new vaccine compared to a new drug; unlike a trial for a medication to treat an acute condition, a vaccine trial must go on for many months before a statistically significant difference can be seen in the incidence of a condition that may not occur in most patients without a vaccine. This is particularly true when clinical events (such as disease incidence) are studied, rather than a surrogate marker such as antibody levels. If a vaccine candidate is expected to be only partially effective (for instance, reducing disease occurrence or severity in only 50% of people receiving it), the requirements on sample size are even more demanding. Simple measures of immunogenicity may be acceptable if the immune response is already well understood and the vaccine has a mechanism of action similar to existing vaccines, but may be less justifiable if the pathogen is a new one, its immunology is incompletely understood, if the vaccine embodies a new technology not employed previously, or some combination of these considerations.

After approval, it is imperative that systems be in place to detect signals of adverse events once a vaccine is in widespread use. As with medications, approaches that require voluntary spontaneous reports are likely to be less useful than those that use routine surveillance of clinical events in millions of patients in typical care systems. Approaches such as the CDC Vaccine Safety DataLink are in place to make this possible. Following a massive, perhaps nation-wide immunization program against SARS-CoV-2, provision will also have to be made for compensating people who develop complications following vaccination, perhaps based on programs addressing this need for prior vaccines.

Conclusion

Over the past several decades, health care systems throughout the world have accumulated substantial evidence, experience, and insights about vaccine development, use, and surveillance. While the COVID-19 pandemic is unprecedented in the past century, insights from past vaccine development programs can provide valuable understanding about vaccines for this new clinical, public health, and policy challenge. ■

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