Emergency Use Authorizations (EUAs) Versus FDA Approval: Implications for COVID-19 and Public Health

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See also Morabia, p. 982, and the Vaccines: Building Long-Term Confidence section, pp. 1049–1080.

In response to the COVID-19 pandemic, the Food and Drug Administration (FDA) rushed hundreds of medical products for testing, prevention, and treatment onto the market through Emergency Use Authorizations (EUAs), rather than FDA approval. This policy began on February 4, 2020, when Health and Human Services Secretary Azar announced that the pandemic justified the authorization of emergency use of in vitro diagnostics for detection or diagnosis of the virus.[1] As the virus spread rapidly, and health care personnel and morgues became overwhelmed, the FDA responded by specifying policies and standards for a wide range of essential medical products, including diagnostic tests, treatments, masks, and vaccines. To what extent did reliance on EUA lower standards—in some cases with no review by the FDA at all—benefit public health or put it at unnecessary risk in 2020 or in the future? Answering this question requires an understanding of EUA standards compared with FDA approval standards, how and why EUA standards changed during 2020, and the quality of EUA products used by millions of Americans.

FDA APPROVAL VS EMERGENCY USE AUTHORIZATION

The FDA was created in 1906, but the EUA provision was not added until 2004, to respond to chemical, biological, nuclear, or radiation threats. The track record of early EUAs has implications for how COVID-19 EUAs affect access to urgently needed medical products and information about their risks and benefits.

The FDA's first EUA was in 2005, for anthrax prevention for military personnel,[2] and the FDA later approved a reformulation. Two other EUAs, issued in 2008 and 2016 for doxycycline products for postanthrax exposure, are still active; the FDA never approved those drugs for that purpose, although doxycycline is approved for other infections.

The FDA's first EUAs for civilians were in 2009, during the H1N1 (swine flu) pandemic, authorizing two previously approved flu medications—Tamiflu and Relenza—and a new drug, Rapivab. The EUAs expired in 2010.[3] In 2014, Rapivab was approved for the treatment of acute, uncomplicated cases of influenza types A and B, including H1N1; but not for hospitalized patients.

In 2013 and 2014, the FDA authorized two diagnostic tests for a coronavirus called Middle East Respiratory Syndrome (MERS). Both EUAs are still active; neither test has received FDA approval. From 2014 to 2018, the FDA issued 11 EUAs for Ebola diagnostic tests; one was subsequently cleared for market, whereas the other 10 are still active EUAs. From 2016 to 2017, the FDA issued 20 EUAs for diagnostic tests for Zika; only four of those tests were subsequently allowed on the market permanently, one was withdrawn, one was discontinued, and 14 EUAs remain active.

These examples indicate that (1) EUA products were not previously widely used in the United States and (2) most EUA products were not subsequently approved. Since medical products authorized through EUAs are not typically covered by Medicare or health insurance, and since the FDA can withdraw EUAs at any time, companies have financial incentives to gather additional data to transition from EUA to FDA approval. If approval never happens, is that a red flag? Perhaps subsequent evidence indicates that the products are not proven safe or effective, or possibly companies determine that the cost of conducting additional research needed for approval outweighs the incentive of selling more products. Either way, unanswered questions about safety and

efficacy remain. Since the stakes are much higher during the current pandemic than for previous EUAs, public health would benefit if the FDA improved incentives for COVID-19 EUAs to transition to approval on the basis of additional research needed to more definitively prove risks and benefits.

Standards for FDA approval vary for different types of medical products; devices rarely require clinical trials, whereas drugs and biologics usually require randomized clinical trials proving safety and efficacy. EUA policies typically require data supporting—not proving—safety and effectiveness, with lower standards and faster reviews than FDA approval. Although consistently less stringent than approval standards, EUA standards for COVID-19 products varied considerably, in some cases not requiring any FDA review of safety or efficacy.

COVID-19 VACCINES

The FDA issues Guidance documents to provide companies with research guidelines for specific types of applications. In a June 2020 Guidance, the FDA specified standards for approval of COVID-19 vaccines, recommending that thousands of adults diverse in race, ethnicity, and age be studied in Phase 3 randomized double-blind clinical trials to determine benefits and risks. Clinical trials "should continue as long as feasible, ideally at least one to two years."[4] In contrast, the FDA's EUA Guidance for COVID-19 vaccines, published in October, specified that data from double-blind randomized "Phase 3 studies should include a median follow-up duration of at least two months," which the FDA described as the minimum needed "to achieve some confidence that any protection . . . is likely to be more than short-lived."[5]

EUA vaccine applications met that minimum follow-up and were quickly authorized. Pfizer-BioNTech submitted its EUA on November 20, 2020, FDA's Advisory Committee reviewed it at a public meeting on December 10, and the FDA authorized it for adults aged 16 years and older the following day.[6] Moderna submitted its EUA on November 30; the FDA's Advisory Committee[7] reviewed it on December 17, and the FDA authorized it for adults aged 18 years and older the following day.

Safety data were based on thousands of adults in each study, and serious (potentially life-threatening) adverse events were rare. Systemic adverse events such as fatigue, fever, chills, and headache were common, but fewer than 18% of Moderna's vaccinated patients reported that "at least one" of these adverse events interfered with daily life.[7] Pfizer did not calculate how many participants reported "at least one" adverse event that interfered with daily life.[6]

COVID-19 cases were defined as a positive diagnostic test and at least one symptom after the second dose. Pfizer's 95% efficacy was based on only 162 placebo cases and eight vaccinated cases, and Moderna's 94% efficacy was based on 185 placebo cases and 11 vaccinated cases.

Janssen's COVID-19 vaccine was authorized on February 27, the day after their data were reviewed by the FDA's Advisory Committee. The study was similar in design, sample size, and seven-week median follow-up, but because their data were collected during the surge in cases in December and January, the data included 464 cases in the vaccinated and placebo groups, including the South Africa variant.[8]

The FDA's decisions to authorize COVID vaccines were carefully worded to reflect uncertainties: "it is reasonable to believe" that the vaccine "may be effective."[8] Although the efficacy data for all three vaccines were more impressive than the 50% efficacy EUA guidelines required, the FDA acknowledged that lack of data on asymptomatic patients and short follow-up meant that it was not possible to determine if the vaccines prevent asymptomatic COVID-19, or how long immunity lasted. It stated that two-month median follow-up was insufficient to answer key public health questions: how long these vaccines prevent moderate and severe COVID for which patients, and if and when booster shots are needed. Although FDA advisors urged longer follow-up, the vaccine companies did not agree. Pfizer announced on their vaccine Web site that study participants have the option of being unblinded and vaccinated in March 2021; Janssen and Moderna made similar public statements.

COVID-19 DIAGNOSTIC TESTS AND ANTIBODY TESTS

Prior to COVID-19, diagnostic tests for other coronaviruses could not be marketed until approved by the FDA based on proven accuracy. In February 2020, with no tests available because of problems with the Centers for Disease Control and Prevention's COVID-19 diagnostic test, the FDA temporarily lifted the agency's requirement that COVID-19 diagnostic tests be validated before they are marketed. That policy was modified in May with the announcement that companies could sell their COVID-19 diagnostic tests for only 15 business days prior to submitting EUA applications. However, sales continued for months before the FDA completed reviewing each application.[9]

The first authorized diagnostic tests were polymerase chain reaction (PCR)

tests, requiring nasopharyngeal swabs. In April, the FDA authorized the first saliva-based test. As of January 7, 2021, 203 COVID-19 PCR or saliva tests were authorized.[10]

Antibody tests were intended to evaluate previous exposure to the novel coronavirus. In March 2020, those tests could be sold without submitting EUAs, but after the FDA noted "that a concerning number of commercial serology tests" were "performing poorly based on an independent evaluation by the NIH [National Institutes of Health]," the FDA revised its policy to require commercial entities to submit an EUA within 10 days, but allowed certified laboratories to market antibody tests without an EUA.[11] With hundreds of different tests submitted for EUAs, there were lengthy delays as the FDA reviewed the data.

By May 2020, the FDA had temporarily authorized diagnostic and antibody tests for 84 different labs and companies; more than 400 additional applications were awaiting FDA review.[12] Neither the 84 that were authorized nor the other 400 had proven accuracy that was independently verified by the FDA or another entity. Doctors were reporting many false negatives and false positives, and a review of published studies of various diagnostic tests found that the "probability of a false-negative result in an infected person decreases from 100% on day 1 to 67% on day 4."[13] On the day of symptom onset, the median false negative rate was still 38%.

By February 1, 2021, the FDA had rejected 225 antibody tests and placed 88 firms on alert for violations.[14] To date, many COVID-19 tests are still not independently validated on patients to ensure accuracy, and the reported range of accuracy varies considerably.

In medicine, many screening tests have substantial false positives and false negatives; however, there are no biopsies to provide definitive confirmation for COVID-19 results as there are for cancer screening tests, for example. Retesting with PCRs is an option, but with results often delayed, infected people who tested negative do not self-quarantine and are likely to spread the virus. Similarly, because the media had reported that people previously infected with the virus were probably immune, those whose antibody test results indicated that they were previously infected were likely to assume they could therefore be less careful about avoiding future exposures.

TREATMENTS

Early in the pandemic, with vaccines months away, there was tremendous political and medical pressure to find effective treatments as quickly as possible. Hydroxychloroquine was an FDA-approved drug for malaria, lupus, and rheumatoid arthritis; the FDA authorized it for COVID-19 in March 2020. That EUA was based primarily on anecdotal clinical reports from France and pressure from the White House, despite known risks of heart failure and potentially fatal heart arrhythmia.[15] Although preliminary data from randomized trials soon suggested the risks outweighed the benefits, the FDA did not withdraw that EUA until June 15, 2020.

Remdesivir was authorized on May 1, 2020, and approved in October 2020 for hospitalized COVID patients. Approval remains controversial because the World Health Organization recommended against its use, stating that clinical trials failed to prove clinically meaningful benefits.[16]

In August, the Trump administration pressured the FDA to issue an EUA for convalescent plasma, which is antibody-laden plasma from someone who survived COVID-19. Despite a published study finding no benefit for hospitalized patients,[17] the FDA issued a broad EUA, undermining efforts to conduct randomized clinical trials. In February 2021, a smaller study found a benefit for older hospitalized patients only if it was given within 72 hours of mild symptoms.[18]

In August, the FDA authorized investigational monoclonal antibodies for hospitalized patients, despite lacking data. In November, the FDA authorized the monoclonal antibody bamlanivimab for mild to moderate COVID-19 in high-risk adults and children, based on interim results from a Phase 2 randomized dosing trial.[19] That EUA was revoked in April, but a February 2021 EUA is still in effect for bamlanivimab in combination with the monoclonal antibody etesevimab for the same indication, based on a double-blind randomized trial of over 1000 adults.

Overall, research standards have improved for treatment EUAs, but we will never know if research could have determined effective treatments sooner had EUAs not made unproven treatments widely available.

PERSONAL PROTECTIVE EQUIPMENT

The FDA has the authority to regulate face masks used "for medical purposes," defined as providing protection from infection anywhere, not only in medical settings. The FDA had required companies to submit evidence proving the safety and effectiveness of these products, or their substantial equivalence to other products on the market. However, in response to dangerous shortages of

personal protective equipment (PPE) in April 2020, the FDA announced it would not enforce its usual requirement that companies submit applications with scientific evidence before marketing face masks, surgical masks, and respirators.[20] The FDA later issued EUAs requiring safety data for respirators and surgical masks, which are made from nonwoven plastic material, but not for cloth face masks.

CONCLUSIONS

The FDA justified authorizing hundreds of different COVID-19 tests, treatments, and vaccines to show its commitment to "expediting the development and availability of potential COVID-19 treatments and providing sick patients timely access to new therapies where appropriate, while at the same time supporting research to further evaluate whether they are safe and effective."[21] To address urgent shortages, PPE that was not evaluated by the FDA became widely available, apparently assuming that even poorly designed PPE was better than nothing.

Balancing urgent needs and unproven benefits is challenging. EUAs are available as short-term emergency solutions, but most are renewed for years without data to warrant FDA approval. "Gaiter" masks are a simple example of a product that is still sold despite evidence that it is less effective than other masks. Similarly, hundreds of different COVID-19 diagnostic tests are being sold, although some are proven to be much less accurate than others. Vaccines rushed to market give hope and protection to many, but FDA scientists stated that vaccine efficacy has not yet been proven to last, and specified that FDA approval would require longer-term data than a median of two months.[8] I agree with the FDA staff and advisors who expressed concerns that we might never get the longer-term data that would determine which vaccines last longest or are most effective against specific variants if participants drop out of clinical trials as EUA vaccines become widely available.

The failure to replace EUAs with more stringent FDA approval is less problematic when products are no longer urgently needed. Indefinitely renewing EUAs for Zika, Ebola, and anthrax has not attracted concerns because few Americans are exposed, but this track record raises important questions about the hundreds of unproven COVID-19 tests, PPE, and treatments currently on the market. EUA treatment standards have generally improved over the past year, but standards for tests remain inconsistent, and standards for many types of PPE are not enforced. Vaccines' data are very encouraging, but primarily based on two-month data on small numbers of COVID patients.

The tragic death toll from the pandemic has resulted in greater flexibility and faster FDA decisions, and has also resulted in hundreds of EUA products subsequently found not to benefit patients, consumers, or public health. We will never know if the pandemic's toll would have been lower if EUA standards had been higher, but it is essential to ensure that COVID-19 EUAs supplement and not replace the gold standard of FDA approval, and not be extended longer than is absolutely necessary, whether during the height or waning of the COVID-19 public health emergency. AJPH

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CONFLICTS OF INTEREST

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