

# Drug and Vaccine Development and Access

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**SUMMARY.** This chapter explains how COVID-19 drugs and vaccines reach the market in the United States. As is always true, drug and vaccine manufacturers may seek U.S. Food and Drug Administration (FDA) approval of their products via traditional mechanisms, and pre-approval access may be granted under the expanded access or right to try pathways. In a public health emergency like COVID-19, an additional mechanism is also available: Emergency Use Authorizations (EUAs). This Chapter (1) assesses how FDA has used its EUA authorities for COVID-19 drugs and vaccines thus far, (2) considers how FDA has balanced the need for robust evidence of safety and effectiveness for COVID-19 products against the urgent need to speed patients' access amid the clinical and political realities of the pandemic, and (3) highlights additional considerations specific to vaccines. The Chapter concludes with recommendations for policymakers and regulators at the federal and state levels, intended to improve public understanding of the regulatory process for COVID-19 drugs and vaccines, protect scientific decision making from undue political pressure, and ensure that manufacturers develop robust evidence of safety and effectiveness – and ultimately safe and effective COVID-19 countermeasures.

## Introduction

This section briefly explains the typical regulatory processes for FDA approval of drugs and vaccines and for non-trial pre-approval access for seriously ill patients. It then explains the additional EUA mechanism that is available during public health emergencies, such as the COVID-19 pandemic. Although FDA is the primary gatekeeper for drugs and vaccines, this section highlights that states also play a role through their authority to regulate medical practice. Further discussion of FDA and state regulatory processes and roles is provided in *Volume I*.

## FDA Approval and Pre-approval Access

Before a new drug or vaccine may be distributed in U.S. interstate commerce, FDA must approve the product as safe and effective for its intended use. To make the necessary showing of safety and effectiveness, manufacturers typically generate significant information about their products through pre-clinical testing and three phases of clinical trials in humans. Although this process can take substantial time, it is critical for public health because it helps protect people from unsafe or ineffective products and ensure that necessary information about drugs' and vaccines' effects is generated, which, in turn, incentivizes the development of products that actually work (Eisenberg, 2007).

There are, however, ways that patients can access products for uses that FDA has not approved, or products that are not FDA-approved for any use. Once FDA has approved a product for one use, health care professionals are often free to prescribe and dispense it for any use, including unapproved uses (known as "off-label" uses). Additionally, in certain circumstances manufacturers may provide patients wholly unapproved, experimental products outside of clinical trials for treatment purposes. One such form of non-trial pre-approval access is "expanded access," which requires FDA authorization among other things, and another is the Right to Try Pathway, created by Congress in 2018, which does not require FDA authorization.

These processes for drugs and vaccines remain available during public health emergencies. Manufacturers may seek FDA approval for drugs or vaccines for COVID-19. For example, in October 2020 FDA approved Gilead Sciences' drug, remdesivir, to treat COVID-19 patients requiring hospitalization (this approval followed use of the drug under an EUA). Likewise, manufacturers may provide COVID-19 patients non-trial pre-approval access to experimental products through the Right to Try Pathway or expanded access – which is how many patients received convalescent plasma, and President Trump received an antibody drug when hospitalized with COVID-19, before FDA issued EUAs for those products. Health care

professionals also generally may prescribe and dispense already-approved products for COVID-19. For instance, a long-approved corticosteroid, dexamethasone, has been used off-label based on research suggesting it can reduce mortality in certain COVID-19 patients.

### FDA's Power to Issue EUAs During Public Health Emergencies

In addition to the above-outlined mechanisms, in 2004 Congress created the EUA pathway by adding Section 564 to the Federal Food, Drug, and Cosmetic Act (FDCA) (21 U.S.C. § 360bbb-3). This provision allows FDA to issue EUAs authorizing the distribution of unapproved medical products, or unapproved uses of already-approved products, when the Secretary of the Department of Health and Human Services (HHS) determines there is a “public health emergency, or a significant potential for a public health emergency.” Although patients generally can access already-approved products for off-label uses without an EUA, the federal government could not distribute products for off-label uses through the Strategic National Stockpile, and liability protections for manufacturers and health care professionals under the Public Readiness and Emergency Preparedness Act may not be available.

For FDA to issue an EUA, whether for an unapproved product or an off-label use of an approved product, various criteria must be met. These include that the manufacturer show “it is reasonable to believe” “the product may be effective” for the relevant condition — a bar that is decidedly lower than the “substantial evidence” of effectiveness required for FDA approval. FDA may impose restrictions on products through EUAs, including requiring information collection through patient registries or restricting who may administer the product and to what categories of patients. EUAs are time-limited—they only remain in effect during the public health emergency. Additionally, the FDCA requires FDA to “periodically” review existing EUAs and authorizes FDA to revoke or revise EUAs at any time if appropriate to protect public health or safety. FDA, thus, has broad power to shape how products distributed under EUAs are used, and can change conditions or revoke permission to distribute more easily than it can for approved products.

FDA typically decides whether a product meets approval or authorization standards and determines any conditions on authorization. Given the political nature of responses to public health emergencies, however, it is important to understand that FDA is an agency within HHS, and federal law expressly authorizes the Secretary of HHS — and not FDA — to make these decisions. The secretary delegates that decision-making authority to FDA and rarely has overridden FDA decisions about product authorization. But in 2020, the Trump administration exerted significant pressure on FDA to rush the authorization of COVID-19 drugs and vaccines, leading to renewed calls to protect FDA independence (Califf et al, 2020).

### The States' Role

States also play various roles in determining product access and helping patients and health care professionals understand what is known about product safety and effectiveness. For example, in

March 2020, there were concerns about shortages of chloroquine and hydroxychloroquine — drugs approved for malaria, lupus, and rheumatoid arthritis, but that were being hyped at the time for COVID-19 and hoarded by physicians, despite a lack of reliable evidence demonstrating their effectiveness. In response, some states (and the District of Columbia) used their authority to regulate medical practice to limit off-label prescribing or dispensing of the drugs for COVID-19 and communicated the lack of evidence demonstrating their effectiveness for COVID-19.

States might also try to use their authority over medical practice to permit access to products that lack any FDA authorization or to completely prohibit use of FDA-authorized COVID-19 products. Indeed, in fall 2020 several states, including New York, established independent review committees for COVID-19 vaccines due to concerns about political interference with FDA's process. As of February 2021, however, no state has attempted to prohibit any FDA-authorized COVID-19 vaccines. Any such efforts would raise questions about preemption, while state laws or regulations more permissive than federal ones may be without practical effect, as states cannot eliminate applicable federal requirements (Zettler, 2017).

Importantly, states also have a role in vaccine allocation, distribution, and administration. Due to limited vaccine supply, the Centers for Disease Control and Prevention (CDC) issued non-binding guidance on priority-access categories, and many states re-worked the priority access hierarchy. Moreover, each state has determined which hospitals, clinics, providers, and pharmacies have access to vaccines, and how many doses will be allocated to each. Particularly because FDA does not consider equity when determining the scope of an EUA, states, local governments, and these private institutions are largely responsible for ensuring equitable allocation (Persad, 2021). Additionally, no state has issued a COVID-19 vaccine mandate, and several experts (including one of the authors) have noted that such mandates, for products under EUAs, would be illegal and unethical (Parasidis & Kesselheim, 2021).

### Assessing the Regulatory Approach during the COVID-19 Pandemic

In a global public health emergency, like the COVID-19 pandemic, FDA is faced with an undeniably difficult task. On one hand, developing rigorous evidence of products' safety and effectiveness is no less important — rather it is equally, if not more, important (London & Kimmelman, 2020). Generating this evidence will take time. Non-trial pre-approval access, including via EUAs, has the potential to interfere with this necessary evidence generation by making it difficult to enroll participants in clinical trials. On the other hand, there is an urgent need to move quickly. The addition of the EUA mechanism to the FDCA arguably reflects a societal decision that FDA ought to have flexibility to lower standards of safety and effectiveness during public health emergencies to speed access to promising, but unproven, products. FDA is likely to face tremendous political pressure — whether from the White House, HHS, Congress, industry, patients, or other stakeholders — to use that flexibility, and may lose public trust if the agency is viewed as either unresponsive to patients' concerns or as moving too quickly to authorize access to countermeasures based on insufficient data.

This Section examines how FDA has balanced these sometimes-competing societal interests and operated amid these political realities during the COVID-19 pandemic thus far.

### Balancing Evidence and Access

The federal government, including FDA, has taken some beneficial steps to exercise flexibility and proactively speed the development of promising COVID-19 drugs and vaccines. For example, “Operation Warp Speed,” a public-private partnership of industry and government representatives working together on product development, is credited with helping to make possible the remarkably efficient development of COVID-19 vaccines. FDA also has issued dozens of guidance documents on drugs and biological products for COVID-19, to help clarify what is needed to bring a product to market. Additionally, FDA has made use of the flexibility that the EUA mechanism offers by issuing, revising, and revoking EUAs. As of February 14, 2021, the agency has issued seven EUAs for drugs to treat COVID-19 and two EUAs for COVID-19 vaccines. It revoked two of the drug EUAs, for hydroxychloroquine and chloroquine, on June 15, 2020, and has revised numerous EUAs. As a final example, FDA has taken steps to improve transparency as the pandemic has evolved, committing in November 2020 to proactively make public its reviews of data and information supporting decisions to issue, revise, or revoke drug and biological product EUAs. Such transparency can help the public understand the agency’s reasoning and what is known about the safety and effectiveness of COVID-19 countermeasures, as well as encourage public trust in agency decision-making.

At the same time, there is room for improvement, particularly with respect to public understanding of EUAs, implementation of FDA’s EUA authorities, and providing equitable access to COVID-19 countermeasures. Although FDA generally distinguishes between EUAs and approvals in its communications, some media reports continue to equate EUAs with FDA approval. Even for those EUAs based on more robust evidence, such as the December 2020 vaccine EUAs based on evidence that the products reduce symptomatic cases, it remains critical to understand that EUAs are a form of pre-approval access, and products issued EUAs are not necessarily safe or effective COVID-19 countermeasures. Misunderstandings about what an EUA signifies could drive inappropriate policy decisions or undermine public trust in FDA decisions when products issued EUAs prove ineffective or unsafe.

Another major concern is that FDA, perhaps driven by political pressure, may too freely issue EUAs for COVID-19 countermeasures, even judged against the relatively low statutory standard for issuing EUAs. The now-revoked EUAs for hydroxychloroquine and chloroquine provide apt examples. That the EUAs were ultimately revoked is not in and of itself troubling. Because the EUA mechanism permits FDA to authorize products with less evidence than is required for approvals, we should expect that FDA will authorize products that, once on the market, no longer meet the criteria for an EUA (or ultimately prove unsafe or ineffective). FDA should revoke EUAs when evidence warrants it — a revocation reflects the uncertainty surrounding safety and effectiveness of countermeasures that receive an EUA, along with

the iterative nature of EUA issuance and oversight. In the case of hydroxychloroquine and chloroquine, however, FDA’s original decision to issue the authorizations rested on a particularly shaky foundation: limited data of effectiveness from one randomized pilot study of 30 subjects that found little to no effect of the drugs in COVID-19, and an open-label, non-randomized study in 26 subjects that was later discredited, balanced against several known serious risks of the drugs, which were already approved for other uses. FDA issued the EUAs only nine days after the president publicly touted the drugs as COVID-19 countermeasures and, according to a whistleblower complaint from the former director of the Biomedical Advanced Research and Development Authority, at the Secretary of HHS’s direction — raising significant concerns about inappropriate political interference. Similar concerns were raised about FDA’s August 2020 decision to issue an EUA for convalescent plasma as well as about agency officials dramatically overstating the evidence supporting that product’s effectiveness (Sachs, 2020). In February 2021, FDA revised the EUA for convalescent plasma to restrict its use to a subset of hospitalized patients, based on the agency’s ongoing evaluation of the evidence supporting the product’s use for COVID-19.

Yet another major concern is how to provide equitable access to COVID-19 countermeasures once they are issued an EUA or approved. For example, the CDC’s Advisory Committee on Immunization Practices and an ad hoc committee of the National Academies of Sciences, Engineering, and Medicine and the National Academy of Medicine have offered recommendations for equitable vaccine distribution. Many aspects of product access, such as ensuring the affordability of countermeasures and developing logistical arrangements for fair distribution, generally fall outside FDA’s purview and likely require intragovernmental and cross-sector coordination. But, there are steps that FDA might take to use the authorities that it does have to further the goal of equitable access. For instance, Sarpatwari and colleagues argued that FDA could have required a registry for remdesivir that collects information on patient demographics (among other things) when that drug was under an EUA, to enable better tracking of access disparities (Sarpatwari et al., 2020).

### Special Considerations for Vaccines


COVID-19 vaccine EUAs pose many of the same issues as those posed by drug EUAs, as well as additional issues specific to vaccines. A drug that is issued an EUA is typically administered to a sick person with no other treatment options, whereas a vaccine is administered to a healthy person. This difference in health status alters the ethical and clinical risk-benefit calculus. A COVID-19 vaccine also may be used widely across the population in individuals of varying ages and co-morbidities. Moreover, COVID-19 vaccines are used against the background of existing vaccine hesitancy, making creating and maintaining public trust in FDA’s decision-making more difficult (Parasidis, 2016).

Vaccine research and development, like drug research and development, generally takes time. Most vaccines take a decade or longer to develop. Before the COVID-19 vaccines, the quickest vaccine to come to market was the mumps vaccine, which took four

years from the time virus samples were collected to FDA approval. Death or serious side effects from a COVID-19 vaccine could cause panic among the public and drive people away from vaccination — particularly if the vaccine were not supported by robust evidence demonstrating its safety and effectiveness. Although not perfectly analogous, one worthwhile example to consider is the 1976 swine flu vaccination program. The swine flu vaccine was rushed to market to address a public health emergency. Although an outbreak of swine flu did not materialize, the vaccine itself caused dozens of deaths and thousands of vaccine-induced injuries, including paralysis (Parasidis, 2017).

For all of these reasons, developing rigorous evidence of safety and effectiveness, developing such evidence across all sub-populations for which a vaccine is intended, and being transparent about the basis for agency decisions is particularly critical before distributing a COVID-19 vaccine. Consistent with this idea, FDA has taken steps to assure that vaccine EUAs are supported by robust evidence and to reassure the public about the agency's scientific standards, notwithstanding numerous instances of inappropriate political pressure during the Trump administration, including threats to fire the FDA Commissioner (Califf et al., 2020). In summer and fall 2020, FDA issued guidance documents on COVID-19 vaccines that emphasize the importance of large, randomized clinical trials. Before issuing any COVID-19 vaccine EUAs, FDA also held advisory committee meetings in October and December 2020, on COVID-19 vaccine development generally as well as on each specific vaccine candidate for which the agency had received requests for EUAs. These meetings, which were public, as required by law, provided FDA an opportunity to obtain outside experts' input and to make transparent more information about the scientific evidence supporting COVID-19 vaccines before making any decisions on particular EUAs. In December 2020, FDA ultimately issued EUAs for Pfizer/BioNTech and Moderna's COVID-19 vaccines, both of

which were supported by evidence of safety and effectiveness. But there also were significant gaps in the data. Neither vaccine was examined for preventing asymptomatic infection and transmission, which is important because at least 40% of COVID-19 cases are asymptomatic and transmission from asymptomatic individuals constitutes more than 50% of COVID-19 transmissions. Vaccine safety was tracked for only two months, a period that is far shorter than for any other vaccine. Indeed, days after authorization, serious adverse events caused a warning to be issued to advise against vaccination for individuals with severe allergies. Moreover, it is not yet clear whether FDA included conditions in the EUAs adequate to ensure that vaccine access under EUAs does not thwart continued research on the authorized vaccines, as well as on other vaccine candidates in development.

Although as of February 2021 the demand for the authorized vaccines appears to outstrip current supply, in our view, it is critical that vaccinations with products under EUAs be entirely voluntary. As discussed above, the FDCA precludes government mandates for vaccines distributed under EUAs (Parasidis & Kesselheim, 2021). Even if, as some have suggested, the FDCA does not preclude employer and other private mandates for EUA vaccines, such mandates would be unethical and counterproductive to public health strategies encouraging vaccination (Rothstein et al, 2021). Moreover, should a COVID-19 vaccine ultimately receive full approval, this alone should not be viewed as sufficient to trigger mandates. Rather, mandates should be viewed as a last resort and used only if several other measures are first exhausted and appropriate risk mitigation procedures have been implemented, including but not limited to an adequate system of compensation for vaccine-related injuries (Halabi et al., 2020; Mello et al., 2020). 



# Recommendations for Action

## Federal government:

- FDA should clearly communicate and reiterate that EUAs are not approvals and that the legal standard for issuing an EUA does not include a determination that the product has been shown to be safe or effective for its intended purpose.
- For all decisions that FDA makes about COVID-19 countermeasures, the agency should be as proactively transparent as the law permits it to be, consistent with its November 2020 commitment.
- Congress and FDA should consider creating specific processes to protect decision-making during pandemics, such as requiring FDA to proactively release detailed information about the bases for its EUA decisions immediately after they are made. Additionally, Congress should consider whether FDA should be a stand-alone agency, outside HHS.
- FDA should issue EUAs judiciously. The FDCA permits, but does not require, FDA to issue an EUA when the specified criteria are met. The agency retains flexibility to determine that an EUA is not appropriate for the public health even when all statutory criteria are met.
- FDA should consider routinely requiring patient registries for products that are issued EUAs to help gather information both about patient outcomes and about any disparities in access to such products (Sarpawari et al., 2020).
- FDA should pay particular attention to the risk that an EUA for a drug or vaccine will delay further research with that product as well as potential competitor products, and design the scope of and conditions on EUAs to prevent such outcomes to the extent possible.
- Consistent with its obligations under Section 564 of the FDCA (21 U.S.C. §360bbb-3), FDA should actively and carefully review EUAs, revoking or revising them when needed. The rationale for the timing of such post-market reviews should be data-driven and publicly disclosed. The results of FDA's reviews, coupled with a summary analysis of data, also should be made public as soon as they are completed.
- Unless COVID-19 vaccine EUAs are (1) supported by safety and effectiveness data sufficient to allow approval of a biologics license application (BLA) and (2) necessary as a stopgap to allow time to prepare, review, and approve a BLA, FDA should decline to authorize such EUAs. Particular attention should be paid to whether an EUA for a vaccine that can be used across the entire population may create unnecessary risks to healthy individuals and may delay or prevent clinical trials.
- Congress should consider whether establishing the same statutory standard for EUAs for drugs, intended to treat seriously ill patients without other options, and for vaccines, intended for widespread use in healthy people, is appropriate and whether revisions to Section 564 of the FDCA (21 U.S.C. § 360bbb-3) are needed.

## State governments:

- State officials and agencies, including boards of medicine and pharmacy and public health departments, should clearly communicate to health care institutions, health care professionals, and the public the difference between EUAs and FDA approvals, and what is known, and not known, regarding the safety and effectiveness of products available under EUAs.
- State boards of medicine and pharmacy should discourage off-label use of existing products unless strong evidence supports use for COVID-19.
- States should not issue COVID-19 EUA vaccine mandates.
- Particularly given FDA's efforts to improve the transparency of its COVID-19 drug and vaccine reviews, any states with plans for independent vaccine review committees should reconsider such efforts.



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## References

- Califf, R. M., Hamburg, M., Gottlieb, S., Henney, J., Kessler, D., McClellan, M., & von Eschenbach, A. (2020). Opinion | 7 former FDA commissioners: The Trump administration is undermining the credibility of the FDA. *The Washington Post*.
- Eisenberg, R. S. (2007). The Role of the FDA in Innovation Policy. *Michigan Telecommunications and Technology Law Review*, 13(2), 345–388.
- Halabi, S., Heinrich, A., & Omer, S. B. (2020). No-Fault Compensation for Vaccine Injury—The Other Side of Equitable Access to COVID-19 Vaccines. *New England Journal of Medicine*, 383(23), e125. <https://doi.org/10.1056/NEJMp2030600>
- London, A. J., & Kimmelman, J. (2020). Against pandemic research exceptionalism. *Science*, 368(6490), 476–477. <https://doi.org/10.1126/science.abc1731>
- Mello, M. M., Silverman, R. D., & Omer, S. B. (2020). Ensuring Uptake of Vaccines against SARS-CoV-2. *New England Journal of Medicine*. <https://doi.org/10.1056/NEJMp2020926>
- Parasidis, E. (2016). Public Health Law and Institutional Vaccine Skepticism. *Journal of Health Politics, Policy and Law*, 41(6), 1137–1149. <https://doi.org/10.1215/03616878-3666204>
- Parasidis, E. (2017). Recalibrating Vaccination Laws. *Boston University Law Review*, 97(6), 2153–2241.
- Parasidis, E., Kesselheim, A. (2021). Assessing the Legality of Mandates for Vaccines Authorized Via an EUA. *Health Affairs Blog* (forthcoming).
- Persad, G. (2021). Allocating Medicine Fairly in an Unfair Pandemic. *University of Illinois Law Review* (forthcoming).
- Rothstein, M. A., Parmet, W. E., Rubinstein Reiss, D. (2021). Employer-Mandated Vaccination for COVID-19. *American Journal of Public Health*. <https://doi.org/10.2105/AJPH.2020.306166>.
- Sachs, R. (2020). Understanding The FDA's Controversial Convalescent Plasma Authorization. *Health Affairs Blog*.
- Sarpawari, A., Kaltenboeck, A., & Kesselheim, A. S. (2020). Missed Opportunities on Emergency Remdesivir Use. *JAMA* 324(4), 331–332. <https://doi.org/10.1001/jama.2020.11932>
- Zettler, P. J. (2017). Pharmaceutical Federalism. *Indiana Law Journal*, 92, 845–900.