

HEALTH • FDA

## After 600 emergency use authorizations for COVID, experts worry the FDA has gone too far

BY KAT ESCHNER

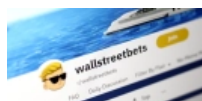
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FORTUNE



COVID-19 is an entirely new disease. When it was first detected in late 2019, there wasn't even a way to test for it, never mind treatments that could help people

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Beginning in late March of 2020, the federal agency began to grant [emergency use authorizations](#) (EUAs) for the use of “medical countermeasures”—tests, drugs, and devices that might be effective in treating the novel coronavirus. Fifteen months later, the measure has shaped the experience of this pandemic and how it might end: [More than half](#) of the total U.S. population has received at least one dose of a COVID-19 vaccine made accessible to them through emergency use.

Over 600 EUAs have been granted in this pandemic to date—many more than all of the other uses of this regulatory pathway combined. As FDA-watchers look back at the successes and failures of this pandemic, they say a precedent has been set. “We have learned that this is a way to handle the medical side of a pandemic,” says Dorit Reiss, a professor at UC Hastings College of the Law who researches law and policy. “Unless the next pandemic is a flu, we will see a use of EUA.”

A [January 2021 report](#) prepared for the FDA suggests as much, laying out a handful of suggestions for how the EUA pathway could be improved in the future, from further streamlining the application process to communicating with the public.

But those aren’t the things that experts are worried about. They are concerned that the broad use of this emergency measure has set a precedent that will make it more difficult for the authority to hold the line against outside influence—and they are hopeful that the FDA is learning how to strike a clearer balance between emergency response and evidence-based approvals.

## How EUAs work

In normal times, the FDA moves slowly—for good reason. Its full approvals process, which establishes both the safety and the efficacy of medical products, is the most substantial thing that stands between the competing interests of for-profit pharmaceutical companies and public health.

The EUA pathway was designed to let it move fast when that speed is necessary. A few things have to happen before the FDA can begin granting EUAs. The secretary of health and human services (HHS) needs to declare a public health emergency and subsequently determine that the emergency has potential to affect the health and security of Americans living at home or abroad. Then the HHS has to grant the FDA [authority](#) to issue EUAs.

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Once that's happened, the FDA has broad authority to make its own determinations when granting EUAs. According to [the statute](#), available scientific evidence must make it “reasonable to believe that the product may be effective,” and the scientists and policymakers of the administration must weigh the potential harms of the product against the material threat posed by the emergency.

The FDA's [industry guidance](#) lays out the pathway: a series of “pre-EUA” interactions with the regulator that aren't publicly available, followed by an application presenting available data. Once those steps are completed, the administration is prepared to issue EUAs within as little as hours “when circumstances warrant and adequate information has been made available for prior review through pre-EUA interactions.”

The emergency authorization is “a very general standard,” says Jesse Goodman, a Georgetown University professor who was chief scientist of the FDA during the 2009 H1N1 pandemic, when several EUAs were granted. It was written to address a variety of scenarios, and it relies on FDA independence from influence to work, he says.

But the standard is still very limited. An EUA only remains in effect as long as the declaration of emergency endures. During that time, pharmaceutical developers are explicitly encouraged to keep working through the trials and other assessments that could lead to full approval of their product when the emergency has ended.

Past regulators [used](#) the EUA pathway to prepare for a possible anthrax attack and to respond to outbreaks of Ebola, Zika, and Middle East respiratory syndrome (MERS). The most extensive use of the pathway prior to COVID-19 occurred during the 2009 swine flu pandemic, when a total of 22 EUAs were issued for PPE, antivirals, and diagnostic tests.

It was only granted for a vaccine once: for specific use of a previously approved anthrax vaccine in the event of an attack. The *New York Times* [recently reported](#) that billions of dollars were spent supplying the Strategic National Stockpile with doses of the vaccine that had been approved under EUA. That purchase, it reported, was a central reason why the stockpile didn't have sufficient PPE at the beginning of the pandemic.

## The issues

The FDA derives its power from a simple fact: If the organization doesn't sanction a medical product, it can't be sold in the United States. It depends on that "proof before profits" power to compel pharmaceutical companies to produce high-quality evidence for the effectiveness as well as the safety of their products, says Christopher Robertson, a Boston University law professor who studies medical regulation.

Producing that evidence in high-quality clinical trials takes substantial time and [millions of dollars](#)—one of the justifications Big Pharma uses for ever-increasing drug prices. And it's in their interest to hasten approvals for another reason: Every day spent ensuring a product meets FDA standards is both a day when that product isn't making money on the market and one day closer to the expiration of that product's [patent or market exclusivity](#).

The industry "might not have the market incentive to do those rigorous studies if FDA didn't require it," says Holly Fernandez Lynch, a lawyer and medical ethicist at the University of Pennsylvania. The FDA's ability to approve or veto means the incentive to do that testing is always there, regardless of market forces. The EUA, like other pathways to market that circumnavigate full FDA approval, "totally reduces the regulatory standard," Fernandez Lynch says.

You can trace these exceptions back to another pandemic: HIV/AIDS. Just as with COVID-19, when it began spreading in the early 1980s, there were no treatments available for the new disease. Even as treatments were developed, there was [no way](#) for tens of thousands of patients who might benefit to all get access, and there was no political will to hasten approvals.

Over the course of the 1980s, activists agitated for a way to gain access to experimental treatments that could help them. They picked up allies in other under-regarded patient groups along the way, most notably those for breast cancer. Finally, in 1987, the FDA [formalized its expanded access program](#) (EAP), giving tens of thousands of people access to drugs that—they hoped—might save or prolong their lives.

The EAP is credited with advancing early antiretrovirals. But it has also caused harm. Jonathan Kimmelman, a McGill University biomedical ethicist who studies drug approval, points to a painful and invasive breast cancer treatment as an example of what can go wrong. Known as high-dose chemotherapy plus autologous bone marrow transplantation, this treatment involved extracting bone marrow from the body of a person with breast cancer, banking that bone marrow, and then exposing the patient to so much chemotherapy that all the remaining marrow in her bones dies before reseeding them with her own banked marrow.

“Over the course of the ’90s this became a standard of care for women with metastatic breast cancer,” he says. Some women sued their insurers to gain access to the expensive treatment on the basis of evidence from a small Phase II trial. More than 41,000 people endured it.

When results from Phase III trials finally came out at the beginning of the new millennium, they revealed something horrifying: The treatment didn’t work and actually made some already compromised patients much sicker.

A complicated and often intersecting network of influence—[patient advocacy groups](#), insurers, courts, the media, oncologists—all lent credence to the idea that this treatment worked. The FDA was part of this network, since it granted expanded access that legitimized the treatment.

Throughout the 1990s, nine out of 10 patients with metastatic breast cancer opted to undergo the treatment, instead of participating in a Phase III clinical trial of the procedure in which they might have received a placebo, researchers [noted](#) in a 2001 review article, substantially slowing trial enrollment and the ultimate finding that the painful, expensive treatment was ineffective.

“You can hurt people by doing something,” says Fernandez Lynch. When access to treatments runs ahead of available evidence—even in emergency circumstances—it creates missed opportunities for research, delays in results, and individual harms, she says.

That’s just as true today. Take the first emergency use authorizations as an example. Publicly endorsed by President Donald Trump, hydroxychloroquine and chloroquine—like many medications—have [serious side effects](#). That means their use for COVID-19 treatment would only be justified if they offered a significant clinical benefit. But the only available evidence when the EUA was granted were a handful of small, anecdotal reports, including one from [a since-disgraced French doctor](#).

Despite mounting evidence of the ineffectiveness of these drugs in treating COVID-19, the EUA remained on the books for nearly three months [before the FDA revoked it](#). In the time since, results from a series of [large-scale randomized trials](#) investigating the medication's effectiveness against COVID-19 have shown no benefit—and possible harms—from its use.

The jury's still out for some other EUAs—like the one for convalescent plasma. This treatment was first granted an EUA last August after nearly 100,000 people [received the treatment](#) through the expanded access pathway that was originally created in the 1980s. Kaiser Health News [reported](#) at the end of May that more than \$646 million in federal contracts was paid to blood centers to collect plasma.

Expanded access allows individual patients with a life-threatening or severe disease to get access to an experimental treatment through their personal doctor under specific criteria. In 2018, Congress passed the [Right to Try Act](#), which offers another pathway for some with a terminal illness.

As with hydroxychloroquine and chloroquine, there was already substantial skepticism from the medical establishment at the time the treatment received its EUA. The administration also supported it: Convalescent plasma was touted by President Trump and [then-FDA commissioner Stephen Hahn](#).

And as with the breast cancer treatment, access ahead of evidence prevented patient enrollment in trials. “We still don’t know if it works,” says Fernandez Lynch. The amount of hype surrounding convalescent plasma, together with the possibility of getting the treatment without having to participate in a study in which you might get a placebo instead, made it almost impossible to enroll patients in trials that would have quickly given a clear picture of the treatment’s effectiveness.

“Maybe we sacrificed some things in the rush to move so quickly,” she says.

In a yearslong pandemic, the fastest response may not be the best use of public health resources—perhaps especially when it’s the most politically expedient. “We’re starting to see that there’s a risk of political pressure leading to unjustified EUAs that can cause harm,” says Reiss.

## The way forward

You can hurt people by doing nothing, too. That’s the bargain at the heart of emergency use.



Experiences during the COVID-19 pandemic have shown that it has pitfalls. But in one essential case—the COVID-19 vaccines—it “seems to have worked out,” says Kimmelman.

We can lay the success partially at the feet of the FDA. To Reiss, the “EUA plus” [requirements](#) that the agency demanded vaccines meet offer a potential way forward. The administration’s [guidance](#) to potential applicants spells out a much stricter set of criteria, including both safety and efficacy data as well as provisions to ensure that study of the vaccine would continue even if it was granted authorization.

“The standards, I think, were reasonable, and they were exceeded,” she says. It helped that the vaccines were far more effective than policymakers had anticipated. But it’s still not clear that the EUA program would have been as useful if the vaccines were less potent—closer to the threshold of 50% efficacy. “Imagine the vaccine data was different,” Reiss says. In that case, the FDA might have had the much harder job of saying no to [Pfizer](#), Moderna, and the other vaccine makers, especially if there was pressure from the sitting politicians who set the FDA’s budget, desperate to offer their constituents a solution.

This emergency is far from over. But experts are concerned about what comes next, both for the FDA’s regulatory standards and for the EUA program.

“The FDA is going to be in this position of having to explain what was unique about the pandemic,” says Fernandez Lynch. She expects to see other patient groups beginning to press for more access to experimental treatments, using the COVID-19 EUAs as precedent.

Kimmelman expects to see pharmaceutical companies moving along a parallel trajectory. “The pharmaceutical industry is very enterprising,” he says, “and I’m sure it will be looking for ways to work [the emergency use authorization precedent] towards its goals.”

Goodman hopes that the FDA will take some time to think about how to use EUA when the next emergency comes. “It’s worth thinking about...whether there should be additional guidance,” he says, noting that will also help the institution shore up against political influence. “You don’t want to be figuring it out when the White House is calling you up.”

Robertson wants to know why the vaccines haven’t yet received full approval, given the fact that they’ve been used in millions of people. Doing so would likely reassure people and result in greater vaccine confidence, he says. “We are accumulating

phenomenal amounts of data, even more data than we normally get from a clinical trial for a new drug,” he says.

The timeline for full approval isn’t clear.

An FDA spokesperson said by email that the administration’s expectation is that any company receiving an EUA for a biologic, such as the Pfizer-BioNTech and Moderna vaccines, would work toward an application for full approval “as soon as possible.” That spokesperson referred *Fortune* to the January 2021 report and related documents online to address other questions about the future of EUA.

Pfizer and Moderna have [both applied for full approval](#) in the past 30 days.

But another wrinkle in the EUA process is the fact that the companies weren’t required to do so on any specific timeline. “There is no ‘clock’ for the submission...to FDA after the issuance of an EUA or completion of clinical trials,” the spokesperson said.

As long as the declaration of a public health emergency [endures](#), the vaccine makers are almost certain to retain market access. Both Fernandez Lynch and Robertson expect they will get full approval at some point. “We know the products work,” Fernandez Lynch says.

There’s currently no mechanism for the American public to figure out when the vaccines that have prevented so much harm are likely to see full approval. That lack of clarity troubles Kimmelman because it says something about EUA’s shortcomings. “Part of what you want in good policy is a transparent mechanism,” he says.

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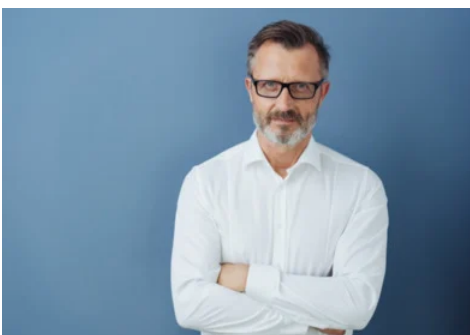
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