VIEWPOINT

Emergency Use Authorizations During the COVID-19 Pandemic
Lessons From Hydroxychloroquine for Vaccine Authorization and Approval

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In response to the novel coronavirus disease 2019 (COVID-19) crisis, the Food and Drug Administration (FDA), via its Emergency Use Authorization (EUA) authority, initially provided, and then revoked, authorization for use of hydroxychloroquine for treating patients with COVID-19. This process was politically and scientifically contentious and illustrates central problems that can arise with emergency drug authorizations during crises. These problems include the authorization of potentially ineffective or unsafe therapeutics, the appearance of nonexpert political advocacy generating public pressure for product authorizations with questionable safety and efficacy, and the imposition of significant costs on the health of the public and on the credibility and influence of regulatory agencies such as the FDA.

Because COVID-19 vaccines are being developed at an unprecedented pace, and because their review will also occur during a pandemic and in a presidential election year, lessons from the hydroxychloroquine authorization may apply to the regulation of these vaccines. In this environment, questions are being raised about the rigor and speed with which the FDA will assess the safety and efficacy of vaccines before granting marketing authorizations via EUAs or licensure. Because FDA Commissioner Stephen Hahn, MD, has stated that the FDA would "consider using an emergency use authorization if we felt that the risks associated with the vaccine were much lower than the risks of not having a vaccine,"[1] and as COVID-19 vaccines undergo standard review in parallel, the EUA granted for hydroxychloroquine offers important insights and suggests key improvements that the FDA and medical community can pursue before, during, and after emergency authorizations.[1,2] Ultimately, such improvements could increase the likelihood of safe, effective, and durable vaccine market authorizations as well as bolster public confidence in and adoption of COVID-19 vaccines.

The Hydroxychloroquine EUA

Public health crises are inevitable, but their timing and form vary. As such, health regulatory bodies like the FDA have emergency authorities for providing swift and flexible crisis responses. Chief among these is the FDA's EUA authority. Under section 564 of the Federal Food, Drug, and Cosmetic Act (FD&C Act), the secretary of the Department of Health and Human Services may declare that circumstances exist justifying the authorization of products for emergency use when there is a public health emergency or significant potential for one. Following the declaration of an emergency by the secretary, the FDA may grant an EUA for the marketing and use of unapproved products or unapproved indications for otherwise approved products when evidence suggests it is "reasonable to believe" that the product in question "may be effective" in treating the disease or condition identified in the emergency declaration.[3] This standard is lower than the "substantial effectiveness" required for regular drug approvals and is evaluated on a case-by-case basis.[4]

An EUA remains effective until the emergency declaration under section 564 of the FD&C Act is terminated, but it may also be revised or revoked prior to the termination of an emergency declaration when new information shows that the authorization criteria are no longer met or when other circumstances make revocation appropriate to protect public safety. Ideally, such emergency authorization procedures maintain rigorous expert direction, their use is not subject to politicization, and the decisions they yield avoid negatively affecting the credibility and influence of an agency.

Prior to the hydroxychloroquine EUA, interest in hydroxychloroquine as a COVID-19 treatment emerged in mid-March following the release of a controversial open-label nonrandomized French study that included 36 patients.[5] Soon after, the Trump administration, followed by media outlets and segments of the US public, began championing hydroxychloroquine.

On March 28, 2020, the FDA issued a letter granting an EUA "for emergency use of oral formulations of chloroquine phosphate and hydroxychloroquine sulfate for the treatment of" COVID-19.[6] The letter did not describe the evidence underlying the decision. The FDA stated that the authorization was supported by recommendations "for treatment of hospitalized COVID-19 patients in several countries, and a number of national guidelines" based on "limited in-vitro and anecdotal clinical data in case series," presumably the French study and Chinese and Korean guidelines.[6]

By early June, virtually every published study reported that hydroxychloroquine was not effective in reducing either mortality or morbidity. On June 15, the FDA revoked the hydroxychloroquine EUA.

Problems Illustrated by the Hydroxychloroquine Authorization and Revocation

The swift authorization of hydroxychloroquine raises a number of issues. First, such a process raises concerns regarding the authorization of an ineffective or unsafe therapeutic. Identifying positive treatment effects and adverse effects often requires large studies with adequate sample sizes, long time horizons, and well-powered subsamples of key demographic groups.

Second, nonexpert political advocacy groups appeared to have generated public pressure on the FDA for authorization. This pressure can yield suboptimal policies and public support for regulatory errors. Health

crises, which increase unelected regulators' sensitivities to public pressures, exacerbate these concerns. In contrast, standard models of administrative government describe a virtuous cycle of "policy feedback" in which politically insulated experts usually make good policies that the public experiences as positive, and the resulting public support sustains good policies.

Third, even if regulators reverse erroneous authorizations, the process imposes costs on the public's health and regulators' influence. Public health costs include ineffective or harmful therapeutic use, reduced attention to other potentially beneficial therapeutics, and strained or rationed access to a therapy already used for other conditions. Following revocation of these erroneous authorizations, public demands for problematic off-label prescribing may persist. The cost for regulators such as the FDA is the potential negative effect on their reputation.[7] This reduced regulatory credibility can exacerbate public skepticism and decrease confidence in later drug approvals.

Improving Drug Authorizations During Crises

The hydroxychloroquine EUA and revocation suggest a number of improvements the FDA could make in the EUA process, some of which the agency has already incorporated in its review of COVID-19 vaccines. Other changes may require regulatory processes that would delay their implementation but should be considered both in the near term and moving forward in preparation for future pandemics and public health emergencies.

First, the FDA has committed to discuss COVID-19 vaccine candidates at the Vaccines and Related Biological Products Advisory Committee prior to issuing an EUA or granting a license. Advisory committees, while imperfect, merge expert guidance with accountability by providing a venue for including external experts, patient representatives, and interested parties. To enhance transparency in the process, committees could consider livestreaming proceedings, and the agency could create other forms of public input. The FDA should also consider incorporating advisory committee views prior to issuing future EUAs, particularly for therapeutics that have the potential for widespread use. All such measures could serve to enhance scientific expertise, transparency, and accountability.

Second, the FDA has acknowledged the need for robust postmarketing surveillance,[2] which should be a priority if an EUA is granted after a phase 3 trial that is shorter than what is typical for vaccine licensure. In addition to proactively establishing extensive adverse event reporting systems, the FDA should provide resources and arrange for large and rigorous phase 4 trials, and deliberately incorporate the successful National Vaccine Injury Compensation Program whether a vaccine is licensed or granted an EUA, all of which could help reduce concerns regarding safety and efficacy when COVID-19 vaccines come on the market.

Third, while the FDA has increased communication regarding the potential for a COVID-19 vaccine EUA,[2,8] the agency and medical community could more vigorously and deliberately inform the public of the meanings of and underlying evidence for regulatory decisions. Particularly when nonexpert claims shape public discussions during a crisis, involvement of experts is essential. Enhanced public-facing communication tools can assist this process. The FDA could more robustly communicate to the public by launching public education campaigns, issuing model informed consent forms, adopting informational tools like drug facts boxes, or adapting existing practices like black box warnings to clearly communicate potential risks to patients and health care professionals and organizations, all to ensure that consumers receive high-quality information. As others have suggested, the FDA should also regularly review adverse event information and communicate it to the public as it becomes available.[9]

Moving forward, the hydroxychloroquine EUA suggests that the FDA should clarify evidentiary standards for EUAs. This could increase consistency, the likelihood of sound EUA decisions, and public confidence, as well as decrease the risk of political intervention. The FDA could further create differentiated standards, higher standards for therapeutic products than diagnostic tests, and higher standards for widely used therapeutics like vaccines than for products that may be used only by select subpopulations. New guidance could clarify that evidence underlying authorization and revocation will be made public. The FDA could also issue public health emergency–specific process and standards guidance for EUAs, as it has for the development and licensure of COVID-19 vaccines.[10]

Regulators should do whatever they can to ensure that lifesaving therapeutics and vaccines reach the public as soon as possible. But they must likewise ensure that these efforts do not come at the expense of public safety or trust in regulatory institutions.

ARTICLE INFORMATION

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Disclaimer: The views, thoughts, and opinions expressed in this article are solely those of the authors and do not necessarily reflect the authors' employers.

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