EDITORIAL

The FDA and the Importance of Trust

Lindsey R. Baden, M.D., Caren G. Solomon, M.D., M.P.H., Michael F. Greene, M.D., Ralph B. D'Agostino, Ph.D., and David Harrington, Ph.D.

As SARS-CoV-2 emerged, the global scientific community first studied the virus at the bench, then took what was learned to the bedside in the hope of helping patients, and later returned to the bench with observations from the bedside.[1] Such a process has led to progress in the treatment and prevention of every important disease we have faced, including AIDS, cancer, and diabetes. In the case of SARS-CoV-2, the information we have gathered has increased our understanding of the biology of the virus, the diagnosis of the infection, the nature of the injury it causes, and potential therapies to treat it, but much is still unknown. In Covid-19, clinicians at the bedside continue to face an imperfectly understood disease that leads to tragic consequences for too many patients. Under enormous pressure to help patients while doing no harm, clinicians rely on the transparency of the scientific process and on the careful judgment of regulators who base their decisions on the best available scientific understanding of the disease.

Adequately sized and well-conducted randomized clinical trials are the foundation of evidence-based medicine, but they take time. As clinicians wait for trial data to emerge, they must often try available treatments without proof of their efficacy. This clinical urgency should not, however, be confused with knowledge of which treatment works and which has little value or may be harmful. Unbiased, transparent decisions by regulators are essential in times of uncertainty. Regulators ensure the essential steps of analyzing information from scientists and providing thoughtful guidance to clinicians and patients.

In the United States, the Food and Drug Administration (FDA) has the critical role of assessing emerging evidence to determine whether new therapies are safe and effective. Some of us serve or have served on FDA advisory committees and have first-hand knowledge of the FDA's exhaustive, unbiased, highly informative review process. To minimize the possibility of bias, members of advisory committees and FDA panels must be free of relevant intellectual and financial conflicts of interest, and the FDA has historically operated with complete independence from other parts of the government, including the executive branch, from which it derives its authority.

The challenges posed by Covid-19 have required our federal agencies to move with greater speed than ever before to provide guidance on which treatments should be used, perhaps selectively, in the care of patients. Emergency Use Authorization (EUA) allows the FDA to approve the use of an emerging potential therapy when there is reason to believe that the new therapy is likely to be safe and that it may work. Although the EUA that was issued for remdesivir required fewer data than standard FDA approval, it relied on results from at least one high-quality randomized, placebo-controlled trial.[2] But the EUAs granted for hydroxychloroquine and chloroquine and, more recently, for convalescent plasma have raised the troubling concern that political pressure rather than a data-driven process influenced the FDA's decision making. In fact, the EUA for hydroxychloroquine and chloroquine, issued on March 28, 2020, was withdrawn on June 15, as data from randomized, controlled trials consistently showed no benefit and potential risks.[3]

Observational and physiological data suggest that convalescent plasma may be helpful in patients with Covid-19, as it is considered to be in

some other infectious diseases. But many therapies that have been associated with improved outcomes in observational studies have failed to confer anticipated benefits or have resulted in unanticipated harm in randomized, controlled trials (the use of postmenopausal hormone therapy and antioxidants for the prevention of coronary heart disease are just two examples). The EUA approval memo that was issued on August 23 states that convalescent plasma may be effective in the treatment of Covid-19 and that the potential benefits outweigh the known or potential risks.[4] But no randomized trial has established efficacy or addressed potential toxicity, and the data underlying the FDA's recommendation are opaque and unclear. Many questions remain: Does convalescent plasma work? Are all units of convalescent plasma equal (i.e., is the immune response generated by one person generalizable to all recovered persons)? Do the active antibodies generated in Covid-19 persist in potential donors, allowing proper harvesting? Will antibody activity be equivalent in all patients and at every stage of illness? And are there adverse effects? Given these fundamental gaps in our knowledge, the National Institutes of Health (NIH) Treatment Guideline Panel affirmed in September that "There are insufficient data to recommend either for or against the use of convalescent plasma for the treatment of COVID-19. . . . Convalescent plasma should not be considered standard of care for the treatment of patients with COVID-19. Prospective, well-controlled, adequately powered randomized trials are needed to determine whether convalescent plasma is effective and safe for the treatment of COVID-19. Members of the public and health care providers are encouraged to participate in these prospective clinical trials."[5]

Both the FDA and the NIH currently encourage properly conducted studies to determine whether convalescent plasma has any efficacy in Covid-19 and in which settings. But what are the consequences to ongoing and future research when equipoise has been shifted by the EUA?

Without a clear, transparent, and scientifically sound decision-making process, the trust the FDA has built and maintained over the past century is eroding. As potential therapies for Covid-19 come before the FDA for consideration, only an open, rigorous scientific process that relies on high-quality data can assure clinicians and patients that the new approaches are safe and effective. Such a process will be particularly important as the FDA considers emerging candidate SARS-CoV-2 vaccines.

Determining the safety and efficacy of the therapies clinicians use and patients receive is at the heart of the medical system. The FDA has been the envy of the world, setting standards for the studies it requires and then following the resulting science and data in its regulatory decisions. Today more than ever, as science is being manipulated and disregarded, it is critical that the FDA uphold its standards and its objectivity. Truth may be difficult to know, but the scientific process is our best path to knowing it. Treatments for patients should evolve as new data accumulate. But physicians and patients must be confident that any approval from the FDA is based on a careful evaluation of all the available data and that the agency's decisions are well reasoned and objective. There should be no political interference in the FDA process. The FDA and the executive branch should not squander the trust that the agency has carefully built over many decades of hard work.

Disclosure forms provided by the authors are available with the full text of this editorial at NEJM.org.

From the Department of Obstetrics and Gynecology, Massachusetts General Hospital (M.F.G.), Boston University (R.B.D.), and the Department of Biostatistics, Harvard T.H. Chan School of Public Health, and the Department of Biostatistics and Computational Biology, Dana–Farber Cancer Institute (D.H.) — all in Boston.

This editorial was published on September 30, 2020, at NEJM.org.

1. Zhu N, Zhang D, Wang W, et al. A novel coronavirus from patients with pneumonia in China, 2019. N Engl J Med 2020;382:727-33.
2. Beigel JH, Tomashek KM, Dodd LE, et al. Remdesivir for the treatment of Covid-19 — preliminary report. N Engl J Med. DOI: 10.1056/NEJMoa2007764.
3. Food and Drug Administration. Letter revoking the Emergency Use Authorization (EUA) for chloroquine phosphate and hydroxychloroquine sulfate issued on March 28, 2020. June 15, 2020 (https://www.fda.gov/media/138945/download).
4. FDA issues Emergency Use Authorization for convalescent plasma as potential promising COVID-19 treatment, another achievement in administration's fight against pandemic. Press release of the Food and Drug Administration, August 23, 2020 (https://www.fda.gov/news-events/press-announcements/fda-issues-emergency-use-authorization-convalescent-plasma-potential-promising-covid-19-treatment).
5. National Institutes of Health. The COVID-19 Treatment Guidelines Panel's statement on the Emergency Use Authorization of convalescent plasma for the treatment of COVID-19. September 1, 2020 (https://www.covid19treatmentguidelines.nih.gov/statement-on-convalescent-plasma-eua/).

DOI: 10.1056/NEJMe2030687