

October 6, 2020

The Honorable Ron Johnson
United States Senate
Washington, D.C. 20510-2402

Dear Senator Johnson:

Thank you for your letter of August 18, 2020, cosigned by two of your colleagues, regarding the Food and Drug Administration (FDA or the Agency) decision to issue and then subsequently revoke the Emergency Use Authorization (EUA) that permitted the use of hydroxychloroquine sulfate (HCQ) and chloroquine phosphate (CQ) to treat certain hospitalized COVID-19 patients, and FDA's August 10, 2020, declination of an EUA request for outpatient use of HCQ by Henry Ford Health System physicians.

Below, we have restated your questions in bold followed by the Agency's response.

- 1. Please provide any studies and data that informed FDA's apparent determination that giving HCQ or CQ to COVID-19 infected outpatients within seven days from onset of symptoms, under a doctor's supervision, will have no clinical effect and may be harmful to the patient.**

Please see response to Questions 1 and 2 below.

- 2. Please provide any scientific studies, medical papers and data involving COVID-19 outpatients that have started HCQ or CQ under a doctor's supervision and begin in the ambulatory care outpatient setting. This includes post-exposure outpatient treatment and/or pre-exposure prophylaxis. This should not include late stage studies involving patients started on HCQ while in hospital.**

During the COVID-19 pandemic, as with previous public health emergencies, FDA is balancing the urgent need for safe and effective therapies while providing oversight that ensures patients can depend on the products being deployed. The Agency has been utilizing the full breadth of its available resources and authorities, including its emergency authorities, to expedite its review of clinical trial protocols and development programs, evaluate emerging scientific information on potential therapeutics for the prevention or treatment of COVID-19, and make available medical products as soon as scientifically supportable in the current public health emergency.

Under section 564 of the Federal Food, Drug & Cosmetic Act (FD&C Act), FDA may, pursuant to a determination and declaration by the Secretary of the Department of Health and Human Services (HHS), authorize an unapproved product or unapproved uses of an approved product for emergency use. In issuing an EUA, FDA must determine, among other things, that the product may be effective in diagnosing, treating, or preventing a serious or life-

threatening disease or condition caused by a chemical, biological, radiological, or nuclear (CBRN) agent; that the known and potential benefits outweigh the known and potential risks for the product; and that there are no adequate, approved, and available alternatives. An EUA is not the same as an FDA approval or licensure. Final Agency determinations on the safety and efficacy of a drug for a proposed use are made in the context of the Agency's review of a formal marketing submission (e.g., a New Drug Application).

There are various methods for obtaining information on use of a potential therapeutic product. The scientific consensus is that among those methods, randomized, controlled trials, when available, are the best way to determine the effectiveness of drugs. Control groups allow patient outcomes caused by the test treatment to be distinguished from outcomes caused by other factors. Randomization ensures reasonable similarity of the test and control groups and protects against various imbalances and biases that could lead to erroneous conclusions, as well as provides a sound basis for statistical inference. Furthermore, the statutory criteria for issuance of an EUA require that the Agency's conclusions be based on the "totality of scientific evidence available to the Secretary, including data from adequate and well-controlled trials, if available". See section 564(c)(2) of the FD&C Act. For these reasons, when data from randomized, controlled trials are available regarding a potential therapeutic product for which an EUA has been requested, they will be evaluated by the Agency and generally be given more weight in assessing potential effectiveness than other types of less rigorous evidence.

In the context of HCQ and CQ, there are several relevant publications detailing randomized, controlled trials concerning the prevention or the treatment of mild COVID-19 disease. Results from these randomized, controlled trials have consistently failed to meet their study objectives in determining whether HCQ may be effective as a therapeutic for either prevention or treatment of mild COVID-19 disease. These clinical trials were consistent with other randomized, controlled trials that enrolled participants with more severe disease, which also failed to meet their study objectives regarding HCQ. See Table 1 below.

FDA acknowledges that data from observational studies can also be informative, but notes that the findings from such studies can be challenging to interpret. A number of publications of observational studies have also been reviewed by FDA and are listed in Table 2 below. However, most of the observational studies reviewed did not provide sufficient detail on study methods for evaluation, or did not fulfill minimum study design elements needed to evaluate the effectiveness of HCQ use for prevention or treatment of COVID-19.

Table 1: Randomized, Controlled Trials of Hydroxychloroquine

Study Type	Journal	Author	Title
Prevention	New England Journal of Medicine	Boulware, et al.	A Randomized Trial of Hydroxychloroquine as Postexposure Prophylaxis for Covid-19 ¹
	Preprint	Mitja, et al.	A Cluster-Randomized Trial of Hydroxychloroquine as Prevention of Covid-19 Transmission and Disease ²
Treatment: <i>Mild Disease Severity</i>	Annals of Internal Medicine	Skipper, et al.	Hydroxychloroquine in Nonhospitalized Adults with Early COVID-19: A Randomized Trial ³
	Clinical Infectious Diseases	Mitja, et al.	Hydroxychloroquine for Early Treatment of Adults with Mild Covid-19: A Randomized-Controlled Trial ⁴
Treatment: <i>Moderate - Severe Disease Severity</i>	Preprint	Horby, et al. (RECOVERY)	Effect of Hydroxychloroquine in Hospitalized Patients with COVID-19: Preliminary results from a multi-centre, randomized, controlled trial ⁵
	N/A	N/A (NIH trial)	Outcomes Related to COVID-19 treated with hydroxychloroquine among In-patients with symptomatic Disease study (ORCHID) ⁶
	N/A	N/A (WHO trial)	SOLIDARITY trial ⁷
	New England Journal of Medicine	Cavalcanti, et al.	Hydroxychloroquine with or without Azithromycin in Mild-to-Moderate Covid-19 ⁸

¹ <https://www.nejm.org/doi/full/10.1056/NEJMoa2016638>

² <https://www.medrxiv.org/content/10.1101/2020.07.20.20157651v1>

³ <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7384270/>

⁴ <https://academic.oup.com/cid/advance-article/doi/10.1093/cid/ciaa1009/5872589>

⁵ <https://www.medrxiv.org/content/10.1101/2020.07.15.20151852v1.full.pdf+html>

⁶ <https://www.nih.gov/news-events/news-releases/nih-halts-clinical-trial-hydroxychloroquine>

⁷ <https://www.who.int/emergencies/diseases/novel-coronavirus-2019/global-research-on-novel-coronavirus-2019-ncov/solidarity-clinical-trial-for-covid-19-treatments>

⁸ <https://www.nejm.org/doi/full/10.1056/NEJMoa2019014>

Table 2: Observational Studies of Hydroxychloroquine

Study Type	Journal	Author	Title
Prevention	Preprint	Bhattarchaya, et al.	Pre exposure Hydroxychloroquine use is associated with reduced COVID19 risk in healthcare workers ⁹
	Indian Journal of Medical Research	Chatterjee, et al.	Healthcare workers & SARS-CoV-2 infection in India: A case-control investigation in the time of COVID-19 ¹⁰
	Journal of Medical Virology	Ferreira, et al.	Chronic treatment with hydroxychloroquine and SARS-CoV-2 infection ¹¹
	International Journal of Antimicrobial Agents	Lee, et al.	Can post-exposure prophylaxis for COVID-19 be considered as an outbreak response strategy in long-term care hospitals? ¹²
Treatment: <i>Mild Disease Severity</i>	Preprint	Barbosa Esper, et al.	Empirical treatment with hydroxychloroquine and azithromycin for suspected cases of COVID-19 followed-up by telemedicine ¹³
Treatment: <i>Moderate -Severe Disease Severity</i>	International Journal of Antimicrobial Agents	Gautret, et al.	Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial ¹⁴
	International Journal of Infectious Diseases	Arshad, et al.	Treatment with Hydroxychloroquine, Azithromycin, and Combination in Patients Hospitalized with COVID-19 ¹⁵
	Travel Medicine and Infectious Disease	Million, et al.	Early treatment of COVID-19 patients with hydroxychloroquine and azithromycin: A retrospective analysis of 1061 cases in Marseille, France ¹⁶

⁹ <https://www.medrxiv.org/content/10.1101/2020.06.09.20116806v2>

¹⁰ <https://pubmed.ncbi.nlm.nih.gov/32611916/>

¹¹ <https://www.medrxiv.org/content/10.1101/2020.06.26.20056507v1>

¹² <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7162746/>

¹³ <https://pgibertie.files.wordpress.com/2020/04/2020.04.15-journal-manuscript-final.pdf>

¹⁴ <https://pubmed.ncbi.nlm.nih.gov/32205204/>

¹⁵ <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7330574/>

¹⁶ <https://pubmed.ncbi.nlm.nih.gov/32387409/>

Study Type	Journal	Author	Title
	Travel Medicine and Infectious Disease	Lagier, et al.	Outcomes of 3,737 COVID-19 patients treated with hydroxychloroquine/azithromycin and other regimens in Marseille, France: A retrospective analysis ¹⁷
	Preprint	Scholz, et al.	COVID-19 outpatients – early risk-stratified treatment with zinc plus low dose hydroxychloroquine and azithromycin: a retrospective case series study ¹⁸
	Preprint	Ahmad, et al.	Doxycycline and Hydroxychloroquine as Treatment for High-Risk COVID-19 Patients: Experience from Case Series of 54 Patients in Long-Term Care Facilities ¹⁹
	Preprint	Bernaola, et al.	Observational Study of the Efficiency of Treatments in Patients Hospitalized with Covid-19 in Madrid ²⁰
	Journal of General Internal Medicine	Mikami, et al.	Risk Factors for Mortality in Patients with COVID-19 in New York City ²¹
	New Microbes and New Infections	Million, et al.	Clinical Efficacy of Chloroquine derivatives in COVID-19 Infection: Comparative metaanalysis between the Big data and the real world ²² <i>Metanalysis and 8 of the analyzed studies are included below</i> <ul style="list-style-type: none"> • Ashraf et al.²³ • Geleris et al.²⁴ • Huang et al.²⁵ • Magagnoli et al.²⁶ • Mahevas et al.²⁷ • Rosenberg et al.²⁸ • Shabrawishi et al.²⁹

¹⁷ <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7315163/>

¹⁸ <https://www.preprints.org/manuscript/202007.0025/v1>

¹⁹ <https://www.medrxiv.org/content/10.1101/2020.05.18.20066902v1>

²⁰ <https://www.medrxiv.org/content/10.1101/2020.07.17.20155960v1>

²¹ <https://link.springer.com/article/10.1007/s11606-020-05983-z>

²² <https://www.sciencedirect.com/science/article/pii/S2052297520300615>

²³ <https://www.medrxiv.org/content/10.1101/2020.04.20.20072421v1>

²⁴ <https://www.nejm.org/doi/full/10.1056/nejmoa2012410>

²⁵ <https://academic.oup.com/nsr/article/7/9/1428/5848167>

²⁶ <https://www.medrxiv.org/content/10.1101/2020.04.16.20065920v2>

²⁷ <https://www.medrxiv.org/content/10.1101/2020.04.10.20060699v1>

²⁸ <https://jamanetwork.com/journals/jama/fullarticle/2766117>

²⁹ <https://www.medrxiv.org/content/10.1101/2020.05.08.20095679v1>

Study Type	Journal	Author	Title
			<ul style="list-style-type: none"> <li data-bbox="857 268 1036 302">• <i>Yu et al.</i>³⁰

3. Please provide any public statements or records that FDA has issued to clarify that the FDA does not regulate the practice of medicine and that state governments may not regulate the sale or prohibit the sale of prescription drugs:

The license to practice medicine is granted by the state and each state has laws and regulations that govern medical practice. Local medical boards typically issue medical licenses and regulate the practice of medicine through enforcement of those state-specific laws and regulations. In addition, states also license and regulate the practice of pharmacy through state boards of pharmacy. State medical and pharmacy boards are independent actors that make independent decisions regarding the practice of medicine and pharmacy in their respective states. Such boards may review relevant scientific data and treatment guidelines to inform the scope of practice and recommendations for these disciplines, including prescribing practices. FDA refers you to these state and local boards of medicine and pharmacy regarding their legal and regulatory practices.

4. Please provide any potential treatments for COVID-19 that have been utilized internationally whether those treatments are authorized or approved by the FDA, and what steps the FDA has taken to ensure that these treatments are available in the U.S.

FDA does not surveil other countries to see what products are being used there to treat COVID-19 and then, on that basis, try to authorize or approve those products for use in the United States. Instead, pursuant to the statutory framework established by Congress, we work with individual companies that submit applications for FDA review. We also work with other stakeholder groups, including the National Institutes of Health (NIH), to advance drug development programs. We approach these tasks with the strongest sense of urgency.

While there are currently no drugs or biological products approved or licensed for the treatment of COVID-19 in the United States, FDA is committed to working with drug developers through its Coronavirus Treatment Acceleration Program (CTAP) to move new treatments to patients as quickly as possible, while finding out whether they are helpful or harmful. To promote transparency and accountability for results, we have posted a dashboard tracking key metrics at <https://www.fda.gov/drugs/coronavirus-covid-19-drugs/coronavirus-treatment-acceleration-program-ctap>. As of August 31, 2020, there are over 590 therapeutic development programs in the planning stages and FDA has reviewed over 310 studies for COVID-19 therapeutics.

³⁰ <https://www.medrxiv.org/content/10.1101/2020.04.27.20073379v1>

Under section 564 of the FD&C Act, FDA can issue an EUA if the statutory criteria are met. Currently two products, remdesivir and convalescent plasma, are authorized for emergency use for the treatment of hospitalized patients with COVID-19. On August 28, 2020, based on the totality of scientific information available, including data from randomized, controlled clinical trials that have become available since the May 1 original issuance of the EUA, FDA revised the EUA for remdesivir to broaden the scope of its authorized uses. In addition, FDA has issued three EUAs for drugs for the treatment of secondary conditions caused by COVID-19, as part of its efforts to mitigate drug shortages that impact the care of patients with COVID-19.

FDA is aware of clinical guidelines, which frequently rely on emerging scientific information, for the treatment of COVID-19 in the United States provided by NIH,³¹ and The Infectious Disease Society of America.³² Internationally, the World Health Organization has also published interim guidance on the clinical management of COVID-19.³³

Thank you for your interest in FDA's important work in response to the COVID-19 pandemic. The same response has been sent to your cosigners.

Sincerely,

Andrew Tantillo
Acting Associate Commissioner
for Legislative Affairs

³¹ <https://www.who.int/publications/i/item/clinical-management-of-covid-19>

³² <https://www.idsociety.org/practice-guideline/covid-19-guideline-treatment-and-management/>

³³ <https://www.who.int/publications/i/item/clinical-management-of-covid-19>