



June 15, 2020

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U.S. Department of Health and Human Services (HHS)
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Dear Dr. Disbrow:

This letter is in response to your request, dated today, that the Food and Drug Administration (FDA) revoke the Emergency Use Authorization (EUA) for emergency use of oral formulations of chloroquine phosphate (CQ) and hydroxychloroquine sulfate (HCQ) to be distributed from the Strategic National Stockpile (SNS) issued on March 28, 2020. Like BARDA's earlier request to FDA to issue the EUA, BARDA's request to revoke the EUA is part of a collaborative, USG-interagency effort to rapidly respond to this continuously evolving public health emergency. Today's request to revoke is based on new information, including clinical trial data results, that have led BARDA to conclude that this drug may not be effective to treat COVID-19 [Coronavirus Disease 2019] and that the drug's potential benefits for such use do not outweigh its known and potential risks.

The authorization of a product for emergency use under section 564 of the Federal Food, Drug, and Cosmetic Act (the Act) (21 U.S.C. 360bbb-3) may, pursuant to section 564(g)(2) of the Act, be revised or revoked when the criteria under section 564(b)(1) of the Act no longer exist, the criteria under section 564(c) of the Act for issuance of such authorization are no longer met, or other circumstances make such revision or revocation appropriate to protect the public health or safety.

FDA has determined that the criteria under section 564(c) of the Act for issuance of the EUA referenced above are no longer met. Under section 564(c)(2) of the Act, an EUA may be issued only if FDA concludes "that, based on the totality of scientific evidence available to the Secretary, including data from adequate and well-controlled clinical trials, if available, it is reasonable to believe that: (A) the product may be effective in diagnosing, treating, or preventing—(i) such disease or condition [...]; and (B) the known and potential benefits of the product, when used to diagnose, prevent, or treat such disease or condition, outweigh the known and potential risks of the product [...]."

As explained in the attached memorandum, based on a review of new information and a reevaluation of information available at the time the EUA was issued, FDA now concludes that these criteria are no longer met. The bases for this decision include the following:

- We now believe that the suggested dosing regimens for CQ and HCQ as detailed in the Fact Sheets are unlikely to produce an antiviral effect.
- Earlier observations of decreased viral shedding with HCQ or CQ treatment have not been consistently replicated and recent data from a randomized controlled trial assessing probability of negative conversion showed no difference between HCQ and standard of care alone.
- Current U.S. treatment guidelines do not recommend the use of CQ or HCQ in hospitalized patients with COVID-19 outside of a clinical trial, and the NIH guidelines now recommend against such use outside of a clinical trial.
- Recent data from a large randomized controlled trial showed no evidence of benefit for mortality or other outcomes such as hospital length of stay or need for mechanical ventilation of HCQ treatment in hospitalized patients with COVID-19.

FDA has concluded that, based on this new information and other information discussed in the attached memorandum, it is no longer reasonable to believe that oral formulations of HCQ and CQ may be effective in treating COVID-19, nor is it reasonable to believe that the known and potential benefits of these products outweigh their known and potential risks. Accordingly, FDA revokes the EUA for emergency use of HCQ and CQ to treat COVID-19, pursuant to section 564(g)(2) of the Act. As of the date of this letter, the oral formulations of HCQ and CQ are no longer authorized by FDA to treat COVID-19.

While HCQ that has been distributed from SNS is no longer authorized under the EUA for the authorized use to treat hospitalized patients for COVID-19, FDA-approved HCQ can be distributed in interstate commerce. The CQ products covered by the EUA are not approved by FDA for any indication and therefore cannot be legally introduced into interstate commerce. In addition, under section 564(f)(2) of the Act, HCQ and CQ that were distributed from the SNS under this EUA remain authorized for emergency use to continue to treat any hospitalized patient to whom the authorized product has already been administered during the COVID-19 public health emergency, to the extent found necessary by such patient's attending physician.

Notice of this revocation will be published in the *Federal Register*, pursuant to section 564(h)(1) of the Act.

Sincerely,

/s/

RADM Denise M. Hinton
Chief Scientist
Food and Drug Administration

Attachment: Memorandum Explaining Basis for Revocation of Emergency Use Authorization
for Emergency Use of Chloroquine Phosphate and Hydroxychloroquine Sulfate



Memorandum Explaining Basis for Revocation of Emergency Use Authorization for Emergency Use of Chloroquine Phosphate and Hydroxychloroquine Sulfate

On March 28, 2020, the Biomedical Advanced Research and Development Authority (BARDA) requested and the U.S. Food and Drug Administration (FDA or The Agency) issued an Emergency Use Authorization (EUA) for emergency use of oral formulations of chloroquine phosphate (CQ) and hydroxychloroquine sulfate (HCQ) for the treatment of 2019 coronavirus disease (COVID-19). Based on information available to FDA at the time, the Agency determined that CQ and HCQ may be effective in treating COVID-19 and that the known and potential benefits of CQ and HCQ outweigh the known and potential risks for this use. The Agency limited the use of the authorized products to adults and adolescents who weigh 50 kg or more and are hospitalized with COVID-19 when participation in a clinical trial is not available, or participation is not feasible.¹

Since that time, emerging data and published literature have raised new questions on whether CQ and HCQ may be effective in treating COVID-19 and whether CQ and HCQ's known and potential benefits outweigh the known and potential risks associated with their authorized use. As part of the Agency's ongoing review of the appropriateness of the EUA, FDA scientific staff conducted reviews of these new data and also conducted new analyses of information known at the time of initial authorization.

A summary of this information includes the following:

- The suggested dosing regimens for CQ and HCQ as detailed in the Fact Sheets are unlikely to produce an antiviral effect.
- Earlier reports of decreased viral shedding with CQ or HCQ treatment have not been consistently replicated and recent data from a randomized controlled trial assessing probability of negative conversion showed no difference between HCQ and standard of care alone.
- Current U.S. treatment guidelines do not recommend the use of CQ or HCQ in hospitalized patients with COVID-19 outside of a clinical trial, and the NIH guidelines now recommend against such use outside of a clinical trial.
- Recent data from a large randomized controlled trial showed no evidence of benefit for mortality or other outcomes such as hospital length of stay or need for mechanical ventilation of HCQ treatment in hospitalized patients with COVID-19.

¹ Letter of Authorization, March 28, 2020. Available at: <https://www.fda.gov/media/136534/download> Accessed June 9, 2020.

Based on the above, the Agency has concluded that it is unlikely that CQ and HCQ may be effective in treating COVID-19. Further, in light of ongoing reports of serious cardiac adverse events and several newly reported cases of methemoglobinemia in COVID-19 patients, the Agency has concluded that the known and potential benefits of CQ and HCQ do not outweigh the known and potential risks for the authorized uses. Therefore, the Agency believes that the criteria² for issuance of an authorization are no longer met and is revoking³ EUA 039.⁴

Authorization of EUA 039

The information available at the time the EUA was issued regarding potential benefit included several components.⁵ First, CQ and HCQ are antimalarial drugs that were reported to have in vitro activity against SARS-CoV-2 at drug concentrations achievable by doses considered safe in humans.^{6,7,8} A brief clinical report on 100 COVID-19 patients in China reported clinical improvement and superior viral clearance with CQ treatment versus an unspecified control.⁹ Additionally, a clinical survey by French researchers involving 20 COVID-19 patients reported that HCQ alone and in combination with azithromycin was associated with viral load reduction over 6 days. In the French report, the viral load changes were statistically significant compared to a nonrandomized control group and were more pronounced in patients who received the combination.¹⁰ Based on experience with other viral illnesses, it was reasonable to believe that reduction in viral load may be predictive of clinical benefit.

At the time, a number of national treatment guidelines had been reported as incorporating recommendations regarding the use of CQ or HCQ in the setting of COVID-19, including guidelines used in China and Korea. Expert assessments associated with a number of U.S. medical institutions also included discussion on the use of these drugs in clinical care. Regarding the known and potential risks, the safety profiles of CQ and HCQ were well established as these are approved and commonly used anti-malarial drugs and, in the case of HCQ, approved for rheumatoid arthritis and systemic lupus erythematosus as well. The suggested dosing for CQ and HCQ under the EUA was within the range of that recommended in the approved labeling for these products. In general, the drugs are well-tolerated for their approved uses, though known

² See Section 564(c) of the Federal Food, Drug & Cosmetic Act (FD&C Act).

³ FDA notes that the Agency has consulted with BARDA on this matter. On June 15, 2020, BARDA requested that FDA revoke this EUA.

⁴ See Section 564(g)(2) of the FD&C Act.

⁵ See FDA Decision Memo for EUA 039, Submitted March 28, 2020.

⁶ Wang M, Cao R, Zhang L, et al. Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro. *Cell Res* 2020; 30: 269-71.

⁷ Liu J, Cao R, Xu M, et al. Hydroxychloroquine, a less toxic derivative of chloroquine, is effective in inhibiting SARS-CoV2 infection in vitro. *Cell Discov* 2020; doi: 10.1038/s41421-020-0156-0. [epub ahead of print]

⁸ Yao X, Ye F, Zhang M, et al. In vitro activity and projection of optimized dosing design of hydroxychloroquine for the treatment of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). *Clin Infect Dis* 2020; doi: 10.1093/cid/ciaa237. [Epub ahead of print]

⁹ Gao J, Tian Z, Yang X. Breakthrough: Chloroquine phosphate has shown apparent efficacy in treatment of COVID-19 associated pneumonia in clinical studies. *Biosci Trends*. 2020. DOI: 10.5582/bst.2020.01047. [Epub ahead of print]

¹⁰ Gautret P, Lagier JC, Parola P, et al. Hydroxychloroquine and azithromycin as a treatment of COVID-19: Results of an open-label non-randomized clinical trial. *Int J Antimicrob Agents*. 2020. doi: 10.1016/j.ijantimicag.2020.105949. [Epub ahead of print]

adverse reactions may include QTc prolongation and ocular, neuropsychiatric, cardiac, and hematologic toxicity.

Hospitalized patients were likely to have greater prospect of benefit (compared to ambulatory patients with mild illness) and could be more closely monitored for potential toxicity, although it was recognized that enrollment in a clinical trial would be the best option when using these drugs so that data on safety and effectiveness could be obtained.

FDA therefore concluded, based on the totality of scientific evidence available to FDA at the time, that it was reasonable to believe that CQ and HCQ may be effective in treating COVID-19, and that, when used under the conditions described in the authorization, the known and potential benefits of CQ and HCQ when used to treat COVID-19 outweigh the known and potential risks of such products. The EUA was authorized at a time when there was widespread use of these drugs by physicians to treat COVID-19 patients, and when such use had presented challenges with ensuring adequate drug availability for patients being treated with these drugs for approved uses as well as adequate drug availability to conduct clinical trials.

Similarity of CQ and HCQ and Rationale for Inclusion of Both Products in EUA 039

CQ and HCQ belong to a class of drugs known as 4-aminoquinolines and both occur as enantiomers (R and S isomers). Desethylchloroquine is an immediate downstream product of CYP-mediated dealkylation of both drugs, whereas desethylhydroxychloroquine is a metabolite of only HCQ. Bisdesethylchloroquine is a downstream metabolite of both drugs.¹¹ HCQ is administered as a sulfate, whereas CQ is administered as a phosphate salt. Both drugs are usually absorbed in the upper intestinal tract. Some studies have reported differences in the pharmacokinetics of CQ and HCQ in humans; however, these differences can be explained by differences in either the analytical methods applied, the sample source used (that is, plasma versus whole blood), or renal clearance of these drugs.¹² Important to the pharmacokinetics, pharmacodynamics, and toxic properties of these drugs is their ability to accumulate in acidic compartments such as lysosomes, as well as inflamed (acidic) tissues. The large volume of distribution and long half-lives of these drugs can explain some of their clinical characteristics, such as their slow onset of action and prolonged effects after drug discontinuation. Both drugs are approved for the treatment of malaria with similar dosing and both have similar adverse

¹¹ Costedoat-Chalumeau, N., Isenberg, D. & Petri, M. Letter in response to the 2019 update of the EULAR recommendations for the management of systemic lupus erythematosus by Fanouriakis et al. *Ann. Rheum. Dis.* <https://doi.org/10.1136/annrheumdis-2019-215573> (2019).

McChesney, E. W. Animal toxicity and pharmacokinetics of hydroxychloroquine sulfate. *Am. J. Med.* **75**, 11–18 (1983).

¹² Tett, S. E. et al. Bioavailability of hydroxychloroquine tablets in healthy volunteers. *Br. J. Clin. Pharmacol.* **27**, 771–779 (1989).

Furst, D. E. Pharmacokinetics of hydroxychloroquine and chloroquine during treatment of rheumatic diseases. *Lupus* **5**, S11–S15 (1996).

Cutler, D. J., MacIntyre, A. C. & Tett, S. E. Pharmacokinetics and cellular uptake of 4-aminoquinoline antimalarials. *Agents Actions Suppl.* **24**, 142–157 (1988).

McChesney, E. W. Animal toxicity and pharmacokinetics of hydroxychloroquine sulfate. *Am. J. Med.* **75**, 11–18 (1983).

effects such as QT prolongation.¹³ While only HCQ has an approved indication for chronic discoid lupus erythematosus and systemic lupus erythematosus in adults and the treatment of acute and chronic rheumatoid arthritis in adults, this is based on NDA submissions to the Agency. Both drugs have been used to treat rheumatologic diseases for many years.¹⁴ Thus, for the purposes of EUA 039 and consideration of data regarding the use of these products for COVID-19, it is reasonable to assume that data regarding one product are applicable to the other.

Review of New Information Relevant to Assessing Whether CQ and HCQ May be Effective in Treating COVID-19

Clinical Pharmacology Assessment Regarding Dosing

Agency clinical pharmacology reviewers have re-assessed the publications relied upon at the time of EUA authorization regarding significantly higher lung concentration relative to the in vitro EC₅₀ value as the rationale to support CQ and HCQ as potentially efficacious against SARS-CoV-2 at the dosage suggested in the EUA. The FDA clinical pharmacology reviewers cite limitations with these studies¹⁵ including that the in vitro antiviral EC₅₀ values reported in the literature were extracellular drug concentrations present in cell culture media and should be compared with in vivo free drug concentration in the plasma (likely to be equal to free extracellular tissue concentration). Under the assumption that in vivo cellular accumulation is similar to that from the in vitro cell-based assays, the calculated free lung concentrations that would result from the EUA suggested dosing regimens are well below the in vitro EC₅₀/EC₉₀ values, making the antiviral effect against SARS-CoV-2 not likely achievable with the dosing regimens recommended in the EUA. The substantial increase in dosing that would be needed to increase the likelihood of an antiviral effect would not be acceptable due to toxicity concerns. The reviewers include the caveat that if these drugs have immunomodulatory effects that could be beneficial in patients with COVID-19, those effects would not be predicated on achieving concentrations that exceed the EC₅₀ value.

Although many published papers predict adequate antiviral effect, the majority of these papers refer to the methods and findings of the publication with the limitations described above. In addition, conclusions in the most recent publication regarding in vitro activity of HCQ and achievable concentrations at the site of action are consistent with the FDA assessment.¹⁶ Results of analyses made available since the EUA was issued lead to the conclusion that it is unlikely that the dosing regimens in the EUA would be able to have an antiviral effect.

¹³ See FDA Decision Memo for EUA 039, Submitted March 28, 2020.

¹⁴ Schrenzenmeir E, Dorner T. Mechanisms of action of hydroxychloroquine and chloroquine: implications for rheumatology. *Nature Reviews Rheumatology* 2020. 16:155-60.

¹⁵ Office of Clinical Pharmacology Consult Review, EUA 039, Submitted May 15, 2020.

¹⁶ Maharaj AR, Wu H, Hornik CP, et al. Simulated Assessment of Pharmacokinetically Guided Dosing for Investigational Treatments of Pediatric Patients With Coronavirus Disease 2019. *JAMA Pediatr.* 2020. doi:10.1001/jamapediatrics.2020.2422.

Published Literature Regarding Viral Shedding

The Agency has reviewed additional published literature becoming available since the EUA was issued regarding the effects of CQ or HCQ on viral RNA shedding (see TABLE 1). The highest quality data are those published by Tang et al. from a randomized open-label trial comparing HCQ with standard of care alone in 150 hospitalized patients with COVID-19. The proportion with conversion of RT-PCR specimens obtained from the upper or lower respiratory tract to negative by day 28 was similar in both groups at multiple timepoints. Other published studies, which include an extremely small randomized trial as well as several observational comparisons, were inconsistent with respect to reporting a difference in viral RNA shedding comparing HCQ- or CQ- treated patients with others who were not treated with either of these medications. These publications are summarized in TABLE 1 below.

TABLE 1: Publications Relevant to Viral Shedding¹⁷

Article (design)	Comparison groups (n)	Viral shedding outcomes
Tang W, et al <i>BMJ</i> (randomized, open-label, stopped early)	HCQ 1200 mg/day x 3 d then 800 mg/day to complete 2-3 weeks plus standard of care (75) SOC alone (75)	53 HCQ and 56 SOC PCR(-) “well before” day 28 endpoint; K-M “probability of negative conversion” by 28 days reported as “similar”; median time to (-) 8 and 7 days respectively; proportion (-) “similar” at multiple time points
Huang M, et al <i>J Mol Cell Biol</i> (randomized, 2 antiviral arms)	CQ 500 mg bid x 10 d (10) Lopinavir/ritonavir (12)	All CQ patients PCR(-) by day 13, 11 of 12 L/r patients PCR(-) by day 14; authors say CQ PCR(-) % “slightly higher” on some days
Chen X, et al medRxiv preprint (retrospective, observational)	Retrospective analysis of multiple interventions (CQ in 25 of 284 on page 7, 28 on page 9; also steroids, L/r, arbidol, oseltamivir)	CQ (and other antivirals) not associated with improvement in viral clearance; median 6 days from admission in 121 on no antivirals, 7 days in 17 patients receiving CQ without other antivirals
Mallat J, et al medRxiv preprint (retrospective, observational)	HCQ 400 mg/day (21) Non-HCQ (13)	Median time to (-) PCR 17 days HCQ, 10 days non-HCQ; 14/23 HCQ, 10/11 controls (-) day 14
Huang M, et al medRxiv preprint (prospective, observational)	CQ Phosphate 500 mg (300 mg base) once or twice daily until (-) (233 but analyzed only 197 who “completed”) Historical controls (192 “collected”; 176 analyzed)	Median time to (-) PCR 3 days CQ, 9 days controls; 91% and 94-96% CQ, 57% and 80% controls (-) at days 10 and 14; 3 CQ patients “re-positive” after discharge

¹⁷ Citations for articles mentioned in table:

Tang W et al. *BMJ*. May 14, 2020;369:m1849. doi:10.1136/bmj.m1849

Huang M et al. *J Mol Cell Biol*. May 18, 2020;12(4):322-325. doi:10.1093/jmcb/mjaa014

Chen X et al. medRxiv 2020.04.09.20058941; doi: <https://doi.org/10.1101/2020.04.09.20058941>

Mallat J et al. medRxiv 2020.04.27.20082180; doi: <https://doi.org/10.1101/2020.04.27.20082180>

Huang M et al. medRxiv 2020.04.26.20081059; doi: <https://doi.org/10.1101/2020.04.26.20081059>

Shabrawishi M et al. medRxiv 2020.05.08.20095679; doi: <https://doi.org/10.1101/2020.05.08.20095679>

Kim M et al. medRxiv 2020.05.13.20094193; doi: <https://doi.org/10.1101/2020.05.13.20094193>

Hraiech S et al. *Ann Intensive Care*. May 24, 2020;10(1):63. doi: <https://doi.org/10.1186/s13613-020-00678-4>

Article (design)	Comparison groups (n)	Viral shedding outcomes
Shabrawishi M, et al medRxiv preprint (retrospective, observational)	HCQ (any dose) ± AZI/other AV (45) Supportive care (48) (excluded those transferred to ICU or isolation facility while still PCR(+))	No significant difference in time to first (-) PCR or proportion (-) by 5 or 12 days (median 3 days from treatment start, 33 by 5 days and 38 by 12 days in each group)
Kim M, et al medRxiv preprint (retrospective, observational)	HCQ 200 mg bid + antibiotics (22) Lopinavir/ritonavir + antibiotics (35) Conservative treatment (40)	Hazard ratio for time to viral clearance 0.49 for HCQ/antibiotics (mean 15.3 days) versus L/r plus antibiotics (mean 19.1 days), 0.44 for HCQ/antibiotics versus conservative treatment (20.7 days)
Hraiech S, et al <i>Ann Intensive Care</i> (retrospective, observational)	HCQ 600 mg/day + AZI (17) Lopinavir/ritonavir (13) No antivirals (15)	At day 6 of treatment, PCR(-) in 3 HCQ/AZI, 5 L/r, 2 no-antivirals

In summary, although there were two positive reports observing an impact on viral shedding available at the time the EUA was issued, this observation has not been consistently replicated. The largest randomized controlled trial assessing probability of negative conversion (Tang et al.) showed no difference: the proportion of patients with detectible shedding of viral RNA was very similar over time in the group that received HCQ when compared to the group that did not. At the time the EUA was issued, it was reasonable to assume that an impact on viral shedding would be associated with a clinical benefit for patients. However, neither a favorable impact of CQ or HCQ on viral shedding nor an established clinical benefit of a decrease in viral shedding has been borne out by data and reports available since the EUA was issued.

U.S. National Treatment Guidelines

At the time EUA 039 was authorized, a number of countries initially impacted by COVID-19 had recommended treatment of patients with COVID-19 with CQ or HCQ in their national treatment guidelines.¹⁸ However, there were no national treatment guidelines available in the U.S. This is no longer the case. On April 11, 2020, The *Infectious Diseases Society of America Guidelines on the Treatment and Management of Patients with COVID-19* published recommendations on CQ and HCQ in the context of a clinical trial among patients admitted to hospital with COVID-19, describing the evidence supporting its use as “very low.”¹⁹ The *NIH COVID-19 Treatment Guidelines*, which were initially published on April 21, 2020, were updated on June 11, 2020,²⁰ to recommend against the use of CQ and HCQ for the treatment of COVID-19, except in a clinical trial. The *Johns Hopkins ABX Guide* updated June 3, 2020, states,²¹ “CQ or HCQ: the overall feeling is that safety is an issue especially in more severely ill patients; however, it remains without high-quality data to argue for or against its use.” In summary, U.S. treatment guidelines are now available and do not recommend the use of HCQ or CQ in hospitalized patients with COVID-19 outside of a clinical trial.

¹⁸ See FDA Decision Memo for EUA 039, Submitted March 28, 2020.

¹⁹ Available at: <https://www.idsociety.org/practice-guideline/covid-19-guideline-treatment-and-management/#toc-1>

²⁰ Available at: <https://www.covid19treatmentguidelines.nih.gov/>

²¹ Available at: https://www.hopkinsguides.com/hopkins/view/Johns_Hopkins_ABX_Guide/540747/all/Coronavirus_COVID_19_SARS_CoV_2

Randomized Evaluation of COVID-19 Therapy RECOVERY Trial (NCT04381936)

The RECOVERY trial is being sponsored by Oxford University in the United Kingdom in collaboration with several foundations and British government agencies. It is designed as an adaptive platform trial in hospitalized patients with COVID-19 to assess the effectiveness of trial treatments in reducing all-cause mortality within 28 days. Treatment arms include: usual care; or usual care combined with corticosteroid therapy, lopinavir/ritonavir, azithromycin, or HCQ. Additional randomizations are included between convalescent plasma and placebo and between tocilizumab and placebo for eligible patients.

Over 11,000 patients have been enrolled so far, of an estimated target enrollment of 12,000. On June 5, 2020, the chief investigators announced closure of the HCQ arm due to lack of benefit.²² With 1542 patients randomized to HCQ and 3132 to the usual care comparator, mortality was reported as 25.7% and 23.5% respectively (hazard ratio 1.11, 95% CI 0.98-1.26, p=0.10).²³ The difference in mortality rates trends in favor of the usual care comparator. No evidence of benefit was reported for other outcomes such as hospital length of stay or need for mechanical ventilation. These were noted as preliminary results with follow-up complete for just over 80% of participants; the investigators announced “These data convincingly rule out any meaningful mortality benefit of hydroxychloroquine in patients hospitalised with COVID-19. Full results will be made available as soon as possible.” While the HCQ findings in the RECOVERY trial were based on a randomized but open label design, the endpoint of mortality is generally less susceptible than other more subjectively assessed endpoints to biases that may be of concern with such a design.

Only randomized controlled trials can answer the question of whether HCQ or CQ is of clinical benefit in hospitalized patients with COVID-19, and the RECOVERY Trial results offer persuasive evidence of a lack of benefit of HCQ in the treatment of hospitalized patients with COVID-19.

There are additional trials ongoing in hospitalized patients.²⁴ It is important to note that the criteria for issuance of an EUA are more stringent than the conditions justifying equipoise to

²² See: <https://www.recoverytrial.net/news/statement-from-the-chief-investigators-of-the-randomised-evaluation-of-covid-19-therapy-recovery-trial-on-hydroxychloroquine-5-june-2020-no-clinical-benefit-from-use-of-hydroxychloroquine-in-hospitalised-patients-with-covid-19>

²³ Preliminary results from the RECOVERY trial were provided to FDA by the chief investigators. See letter from P. Horby and M. Landray, University of Oxford, to J. Woodcock, Director, CDER (June 10, 2020). Archived in the Document Archiving Reporting and Regulatory Tracking System for EUA 039.

²⁴ Some examples of ongoing trials include:

Outcomes Related to COVID-19 Treated with Hydroxychloroquine Among In-Patients with Symptomatic Disease (ORCHID) Study (NCT04332991): This trial is being conducted by the Prevention and Early Treatment of Acute Lung Injury (PETAL) Clinical Trials Network of the National Heart, Lung, and Blood Institute (NHLBI), part of the National Institutes of Health. ORCHID is a multicenter, blinded, placebo-controlled, randomized clinical trial evaluating HCQ for the treatment of adults hospitalized with COVID-19. The primary aim is to compare the effect of HCQ versus placebo on clinical outcomes, measured using the COVID Ordinal Outcomes Scale at Day 15. The current planned sample size is 510. Over 400 participants have been enrolled to date. The trial has undergone recent DMC review and the DMC recommended continuation of the trial.

continue a clinical trial. In addition to trials in hospitalized patients, numerous clinical trials have been in progress studying treatment of outpatients with COVID-19 or use of HCQ or CQ for pre- or post-exposure prophylaxis. One such trial conducted under U.S. IND recently published results showing no significant difference in development of symptomatic illness compatible with COVID-19 between HCQ and placebo recipients for post-exposure prophylaxis, though with limitations that outcomes were largely self-reported with little opportunity for laboratory confirmation.²⁵

Review of New Information on Known and Potential Risks of the Products

Office of Surveillance and Epidemiology Review of Adverse Events Associated with CQ or HCQ Use for COVID-19²⁶

The FAERS database and literature were searched for adverse events associated with CQ or HCQ use for COVID-19, as well as the American Association of Poison Control Centers (AAPCC) National Poison Data System (NPDS) for calls associated with CQ OR HCQ exposure.

As of May 6, 2020, key findings were as follows: A total of 347 HCQ and 38 CQ cases were identified. The majority of the cases (69%) involved males with a median age in the early 60s. Five cases reported HCQ use through the EUA. Of all serious adverse events (cardiac and non-cardiac), QT prolongation was the most commonly reported adverse event for both HCQ and CQ.

There were 109 cases with serious cardiac AEs, some reporting one or more of the following: 80 (73%) reported QT prolongation, 4 (4%) reported Torsades de Pointes, 14 (13%) reported ventricular arrhythmia, ventricular tachycardia or ventricular fibrillation, and 25 (23%) had a fatal outcome. Among the 109 cases, 92 (84%) reported concomitant use of at least one other medication that prolongs the QT interval and 75 (69%) reported concomitant use of azithromycin.

There were 113 cases with serious non-cardiac AEs. Hepatitis/increased liver enzymes/hyperbilirubinemia were the most commonly reported adverse event (59%). These are

Solidarity Clinical Trial for COVID-19 Treatments: This is a collaborative trial facilitated by the World Health Organization enrolling adults with COVID-19 admitted to hospital. Patients are randomized to local standard of care or local standard of care plus one of remdesivir, hydroxychloroquine, lopinavir with ritonavir, or lopinavir with ritonavir plus interferon beta-1a. National arms of this trial, such as those from Canada (NCT04330690) and Norway (NCT04321616), may be listed separately in ClinicalTrials.gov. The primary endpoint is in-hospital mortality. As of 3 June 2020, more than 3500 patients have been recruited in 35 countries, with over 400 hospitals actively recruiting patients.

²⁵ Boulware DR, Pullen MF, Bangdiwala AS, et al. A Randomized Trial of Hydroxychloroquine as Postexposure Prophylaxis for Covid-19 [published online ahead of print, 2020 Jun 3]. *N Engl J Med.* 2020;10.1056/NEJMoa2016638. doi:10.1056/NEJMoa2016638;

Cohen MS. Hydroxychloroquine for the Prevention of Covid-19 - Searching for Evidence [published online ahead of print, 2020 Jun 3]. *N Engl J Med.* 2020;10.1056/NEJMe2020388. doi:10.1056/NEJMe2020388

²⁶ Office of Surveillance and Epidemiology Pharmacovigilance Memorandum, EUA 039, Submitted May 19, 2020.

labeled events for HCQ and CQ. The most commonly reported unlabeled adverse event was acute kidney injury/renal failure (5%). Of note, acute kidney injury has been associated with COVID-19. Methemoglobinemia was reported in 4 cases (4%); two of these cases were fatal (methemoglobinemia is currently not in the labels for HCQ or CQ).

The reviewers were unable to assess the rates of these AEs using FAERS data, NPDS data, and literature alone because the total number of persons exposed to either product is unknown. The cardiac adverse events identified are serious risks associated with death in some patients. On April 24, 2020, FDA issued a Drug Safety Communication cautioning against the use of HCQ and CQ for COVID-19 outside of the hospital setting or a clinical trial due to risk of heart rhythm problems.²⁷ The EUA 039 Health Care Provider Fact Sheets recommend use with caution in patients at increased risk for ventricular arrhythmia, performing a baseline electrocardiogram, and monitoring the electrocardiogram during treatment. While this monitoring can reduce the risk of harm, the risk of cardiac adverse events under the EUA 039 authorized use remains. Methemoglobinemia is an adverse event which was not included in labeling for either products and is now reported in the setting of COVID-19. A recent case series described 3 cases of methemoglobinemia occurring in critically ill COVID-19 patients from a single institution.²⁸

Additional Information Reviewed

Outcome Data Reported to BARDA

The Health Care Provider Fact Sheets for EUA 39 state that the prescribing health care provider and/or the provider's designee are/is responsible for submitting patient outcomes via an on-line reporting form.²⁹ However, few reports have been submitted to date. As of May 22, 2020, the Strategic National Stockpile reports dispensing approximately 2.4 million HCQ 7-day treatment courses to State and local health authorities. The approximate number of treatment courses dispensed to hospitals by State and local health authorities is not available at this time. As of May 26, 2020, outcome data for 1763 patients receiving HCQ (1762) or CQ (1) through the EUA have been reported to BARDA (see TABLE 2).

TABLE 2: Outcome Data Reported to BARDA for 1762 Patients as of May 26, 2020

Baseline Characteristics

- The mean (SD) age was 62.6 (15.50) years
- Sex: 35% male, 23.3% female, 41.7% missing
- Baseline severity of illness: 5% mild, 33% moderate, 45% severe, 17% critical
- Comorbidities: 6% had cardiovascular disease, 23% had HTN, and 20% had DM

²⁷ Available at: <https://www.fda.gov/drugs/drug-safety-and-availability/fda-cautions-against-use-hydroxychloroquine-or-chloroquine-covid-19-outside-hospital-setting-or>

²⁸ Naymagon L, Berwick S, Kessler A, Lancman G, Gidwani U, Troy K. The emergence of methemoglobinemia amidst the COVID-19 pandemic. American Journal of Hematology epub ahead of print 15 May 2020. <https://doi.org/10.1002/ajh.25868>

²⁹ See: Mandatory Patient Outcome Reporting Survey - EUA for Chloroquine Phosphate and Hydroxychloroquine Sulfate. Available at: <https://euachloroquine-hydroxychloroquine-outcome.ppd.com/>.

Clinical Characteristics

- The mean (SD) number of days patients received a dose was 4.1 (2.24), maximum number of days was 23
- The mean (SD) number of days hospitalized was 9.7 (12.12)
- 68.3% of patients were discharged and 31.7% of patients were deceased
- Ventricular arrhythmias were reported in 6 (0.34%) subjects
- Other cardiac AEs were reported in 30 (1.70%) subjects

Treatment Outcomes and Characteristics

- The mean number of days of dosing was the same in the discharged and deceased groups
- The rate of ventricular arrhythmia was similar in the discharged and deceased groups
- Other cardiac AEs were reported in 17 (1.41%) of discharged patients and 12 (2.33%) of deceased patients

Data interpretation is limited due to the low number of patients with a reported outcome and the absence of a comparison group.

Office of Surveillance and Epidemiology Memorandum – Literature Review on CQ and HCQ Use in the COVID-19 Population³⁰

The CDC Stephen B. Thacker Library of COVID-19 research articles was searched for articles that contain “hydroxychloroquine” or “chloroquine” in the title or abstract and at a minimum had the following design features: conducted in a population with confirmed COVID-19 infection, reported quantitative estimates of treatment effectiveness or safety associated with HCQ or CQ use, and included a reference group that was not treated with HCQ or CQ. The search identified 317 articles. After excluding non-observational studies (e.g., RCTs) and studies not designed to evaluate HCQ or CQ treatment outcomes in the COVID-19 population, there were 10 observational studies eligible for review and one additional study that had been shared with FDA in manuscript proof format. All 11 studies were cohort studies conducted in hospitalized COVID-19 populations. All 11 studies reported findings on HCQ or CQ treatment effectiveness.

FDA reviewers concluded that the findings on the effectiveness endpoints were inconsistent across all reviewed studies. Most of the point estimates reported were imprecise, with confidence intervals that crossed the null.

Only one study evaluated cardiac safety associated with HCQ treatment (Rosenberg et al³¹). This study was a retrospective multicenter cohort study of patients with laboratory-confirmed COVID-19 admitted to one of 25 participating New York metropolitan region hospitals. The primary effectiveness outcome was in-hospital mortality. After adjustment for demographic characteristics, hospital, preexisting conditions and illness severity, no significant differences in mortality were found between patients receiving HCQ + azithromycin, HCQ alone or azithromycin alone compared with neither drug. The secondary cardiac safety outcomes were cardiac arrest and abnormal ECG findings (based on chart review). Compared to patients who received neither HCQ nor azithromycin, risks of cardiac arrest were higher among patients

³⁰ Office of Surveillance and Epidemiology Memorandum - Literature review on hydroxychloroquine or chloroquine use in COVID-19 population, EUA 039, Submitted May 28, 2020.

³¹ Rosenberg ES, Dufort EM, Udo T, et al. Association of Treatment with Hydroxychloroquine or Azithromycin With In-Hospital Mortality in Patients With COVID-19 in New York State [published online ahead of print, 2020 May 11]. *JAMA*. 2020;e208630. doi:10.1001/jama.2020.8630

receiving HCQ + azithromycin, and those receiving HCQ alone, although the risk estimates were not statistically significant for the monotherapy group. FDA reviewers concluded that this study is limited by potential for residual confounding and bias due to outcome misclassification, and overall, the available observational data are of insufficient quality to inform the effectiveness or safety of HCQ or CQ use in the COVID-19 population.

In an Addendum included in the Memorandum, reviewers additionally evaluated a large observational study of HCQ and CQ with or without a macrolide for the treatment of patients hospitalized with COVID-19, based on data from a multinational registry (Mehra et al³²). This publication was subsequently withdrawn by the authors³³ and will not be included in this Memorandum.

Conclusion

Since FDA initially authorized CQ and HCQ for emergency use on March 28, 2020, new scientific and clinical data, as well as published literature, have raised questions regarding whether CQ and HCQ may be effective in treating COVID-19 and whether CQ and HCQ's known and potential benefits outweigh the known and potential risks associated with their authorized use. FDA has reviewed this information and data as part of its ongoing assessment of whether an EUA remains appropriate.

Based on its review, the Agency has determined the following:

- The suggested dosing regimens for CQ and HCQ as detailed in the Fact Sheets are unlikely to produce an antiviral effect.
- Earlier reports of decreased viral shedding with HCQ or CQ treatment have not been consistently replicated and recent data from a randomized controlled trial assessing probability of negative conversion showed no difference between HCQ and standard of care alone.
- Current U.S. treatment guidelines do not recommend the use of HCQ or CQ in hospitalized patients with COVID-19 outside of a clinical trial, and the NIH guidelines now recommend against such use outside of a clinical trial.
- Recent data from a large randomized controlled trial showed no evidence of benefit for mortality or other outcomes such as hospital length of stay or need for mechanical ventilation of HCQ treatment in hospitalized patients with COVID-19.

Therefore, based on the totality of scientific evidence available, it is no longer reasonable to believe that CQ and HCQ may be effective in treating COVID-19 for the authorized uses detailed in EUA 039. Further, in considering the known safety profile for both CQ and HCQ and

³² Mehra MR, Desai SS, Ruschitzka F, Patel AN. Hydroxychloroquine or chloroquine with or without a macrolide for treatment of COVID-19: a multinational registry analysis [published online ahead of print, 2020 May 22] 6

³³ Mandeep R Mehra, Frank Ruschitzka, Amit N Patel. Retraction—Hydroxychloroquine or chloroquine with or without a macrolide for treatment of COVID-19: a multinational registry analysis

The Lancet Published: June 5, 2020 Available at: [https://www.thelancet.com/journals/lancet/article/PIIS0140-6736\(20\)31324-6/fulltext](https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(20)31324-6/fulltext)

the ongoing reports of serious cardiac adverse events, in addition to several new reports of methemoglobinemia in COVID-19 patients, it is no longer reasonable to believe that the known and potential benefits of CQ and HCQ outweigh the known and potential risks associated with the authorized use.

BARDA has received few reports from healthcare providers and/or provider designees detailing outcome data as requested in the EUA. Interpretation of these data is limited due to the low number of patients with a reported outcome and the absence of a comparison group. A review of recent published literature describing observational studies does not provide informative findings given residual confounding and other methodological issues.

Based on the above, FDA concludes that the criteria for Emergency Use Authorization as outlined in Section 564(c)(2) of the FD&C Act are no longer met and is revoking EUA 039 for CQ and HCQ for the treatment of COVID-19.