Memorandum Explaining Basis for Declining Request for Emergency Use Authorization for Emergency Use of Hydroxychloroquine Sulfate

On July 6, 2020, the United States Food and Drug Administration (FDA) received a submission from Dr. William W. O'Neill, co-signed by Dr. John E. McKinnon[1], Dr. Dee Dee Wang, and Dr. Marcus J. Zervos requesting, among other things, emergency use authorization (EUA) of hydroxychloroquine sulfate (HCQ) for prevention (pre- and post-exposure prophylaxis) and treatment of "early COVID-19 infections". We interpret the term "early COVID-19 infections" to mean individuals with 2019 coronavirus disease (COVID-19) who are asymptomatic or pre-symptomatic or have mild illness.[2]

The statutory criteria for issuing an EUA are set forth in Section 564(c) of the Federal Food, Drug and Cosmetic Act (FD&C Act). Specifically, the FDA must determine, among other things, that "based on the totality of scientific information available to [FDA], including data from adequate and well-controlled clinical trials, if available," it is reasonable to believe that the product may be effective in diagnosing, treating, or preventing a serious or life-threatening disease or condition caused by the chemical, biological, radiological, or nuclear agent; that the known and potential benefits, when used to diagnose, treat, or prevent such disease or condition, outweigh the known and potential risks of the product; and that there are no adequate, approved, and available alternatives.

FDA scientific review staff have reviewed available information derived from clinical trials and observational studies investigating the use of HCQ in the prevention or the treatment of COVID-19. FDA scientific review staff have also assessed the dosing regimens for HCQ as proposed in the current EUA request. A summary of the review includes the following:

- Results from 6 randomized, controlled trials[3] have consistently failed to demonstrate that HCQ may be effective as a therapeutic for either treatment or prevention across the spectrum of COVID-19 infections. Four of these randomized, controlled trials of HCQ evaluated the prevention and the treatment of outpatients with COVID-19, and 2 additional randomized, controlled trials evaluated the treatment of hospitalized patients with COVID-19.

- Numerous observational studies on the use of HCQ for the prevention or the treatment of COVID-19 have also been reported with mixed results regarding the effectiveness of

[1] On July 9, 2020, Dr. McKinnon agreed to be considered the sponsor of EUA 077 and facilitated providing additional information requested by FDA.
[2] *See:* https://www.covid19treatmentguidelines.nih.gov/ for recognized criteria for these severity of illness categories.
[3] As described more fully below, randomized and controlled clinical trials are, by design, the most robust mechanism for assessing the safety and effectiveness of a drug for its proposed use.

HCQ in different COVID-19 populations. FDA scientific review staff determined that these studies are of insufficient quality to provide evidence regarding the proposed authorized use. The majority of the observational studies referenced to support the EUA request did not fulfill minimum study design elements needed to evaluate the effectiveness of HCQ use for prevention or treatment. For example, they did not include a comparison group of patients not treated with HCQ, or they did not study HCQ. Among the studies that could be fully reviewed, FDA scientific review staff identified other significant limitations that preclude their use to support a determination of HCQ effectiveness for prevention or for treatment of COVID-19. The primary concerns include residual confounding, capture of drug exposure, capture of outcomes, choice of index time, and statistical methods. These are described in detail below. These issues limited the interpretation of study findings and likely result in biased study findings, leading to an inaccurate estimation of the benefit.

- Detailed pharmacological assessment by FDA scientific review staff using in vitro data and modeling indicates that the drug levels achieved with the dosing regimens proposed are unlikely to be effective. Any possible antiviral effect against SARS-CoV-2 is not likely achievable with a safe dosing regimen.

Based on the above, FDA has concluded that it is unlikely that HCQ may be effective in the prevention or the treatment of COVID-19.

Further, in light of ongoing reports of serious cardiac adverse events and other adverse drug effects, FDA has concluded that the known and potential benefits of HCQ in the prevention or the treatment of COVID-19 do not outweigh the known and potential risks for these proposed uses.

Therefore, FDA has determined that the criteria for issuance of an EUA are not met and is declining to issue an EUA covering HCQ for the prevention or the treatment of COVID-19 at this time.

Approved Uses of HCQ

HCQ is FDA-approved for the treatment of malaria, lupus, and rheumatoid arthritis. FDA has determined that the drug is safe and effective for these uses when used in accordance with its FDA-approved labeling, and patients prescribed the drug for the approved uses should continue to take their medication as directed by their healthcare providers. There is no new information that impacts FDA's conclusions about the safety and efficacy of HCQ for the currently approved uses.

Review of Information Relevant to Assessing Whether HCQ May be Effective in the Prevention or Treatment of COVID-19

Randomized Controlled Trials (RCTs) Evaluating HCQ for the Prevention or Treatment of COVID-19.

There is a scientific consensus that, when available, RCTs are the best way to determine the effectiveness of drugs. Control groups allow discrimination of patient outcomes caused by the test treatment 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 providing a sound basis for statistical inference. Although the statute does not require "substantial evidence" to support potential effectiveness for a proposed authorization for emergency use, the Agency has a longstanding history of evaluating available evidence against the characteristics of clinical studies that are recognized by the scientific community as adequate to draw conclusions regarding effectiveness (see 21 CFR 314.126). When such RCTs are available, they will generally be given more weight in assessing potential effectiveness than other types of less rigorous evidence.

To date, there are 4 completed RCTs of HCQ use for the prevention or outpatient treatment of COVID-19 and 2 RCTs in patients hospitalized with COVID-19 for which published results are available. FDA's scientific review staff reviewed these RCTs[4] and the findings are summarized below. There are two additional RCTs conducted in hospitalized patients with COVID-19 in which the entire trial or the HCQ arm was discontinued due to lack of evidence of benefit based upon interim analyses. These studies have not yet been published, and are not included in this review.

<u>RCTs of HCQ for Prevention of COVID-19:</u>
The University of Minnesota conducted a double-blind placebo-controlled trial in 821 asymptomatic healthcare workers and household contacts with a significant COVID-19 exposure assessing the rate of new COVID-19 cases as the primary endpoint. In this RCT, HCQ was not associated with a statistically significant reduction in the rate of new COVID-19 cases (49/414, 11.8% and 58/407, 14.3% in the HCQ and placebo arms, respectively, P=0.35).[5] Due to the virtual nature of this trial (limited direct contact with study participants) and limited availability of PCR testing at the time this trial was conducted, the majority (91/107) of the patients met the primary endpoint based on symptoms without PCR-confirmed infection. Participants could be defined as a new COVID-19 case based on symptoms alone. The lack of PCR-confirmation of infection is a limitation of this trial, although the proportions of patients with confirmed and unconfirmed COVID-19 cases were similar in each arm.

Another prevention RCT conducted by Mitjà et al. involved the identification of clusters of asymptomatic adults who had close contact with a PCR-confirmed COVID-19 case in the proceeding 7 days. There were 672 index cases and 2,314 contacts identified. Clusters were randomized so that each contact participant received either HCQ or "usual care." The study

[4] Division of Antivirals, Clinical Review, EUA 077, Submitted July 29, 2020.
[5] Boulware DR, Pullen MF, Bangdiwala AS, et al. A randomized trial of hydroxychloroquine as postexposure prophylaxis for COVID-19. N Engl J Med. Published online June 3, 2020.

found that the rate of PCR-confirmed, symptomatic COVID-19 was similar in both arms (6.2% and 5.7% in the control and intervention arms, respectively; risk ratio 0.89 [95% confidence interval 0.54-1.46]).[6] FDA notes that the results from this Mitjà et al. trial come from a preprint publication and have not been peer-reviewed.

RCTs of HCQ for Outpatient Treatment of Patients with Mild COVID-19:
The University of Minnesota also conducted a randomized placebo-controlled trial of HCQ among outpatients with laboratory-confirmed COVID-19 or symptoms compatible with COVID-19 and a recent COVID-19 exposure, with 423 participants contributing to the primary outcome analysis. This trial showed no difference in mean change in symptom severity (using a 10-point analog scale) from baseline to day 14 (2.55 and 2.29-point reduction in the HCQ and placebo arms, respectively (absolute difference -0.27 [95% CI, -0.61 to 0.07] P=0.117).[7] This trial was limited by a lack of available PCR testing and unconfirmed SARS-CoV-2 infection in a large portion of participants.

An open-label randomized controlled trial conducted in 293 symptomatic outpatients with COVID-19 in Spain showed that compared to those who received "usual care", those who received HCQ showed no difference in the mean change in SARS CoV-2 viral load from baseline to Day 3 (-1.41 and -1.41 $\log_{10}$ copies/mL in the control and intervention arm, respectively [95% CI –0.28; 0.29]) or Day 7 (–3.37 and –3.44 $\log_{10}$ copies/mL in the control and intervention arm, respectively [95% CI –0.44; 0.29]). The rate of hospitalization was numerically similar in both groups (7.1% and 5.9% in the control and intervention arms, respectively). The trial was not powered for rate of hospitalization, and statistical testing was not performed. No subjects required mechanical ventilation and there were no deaths. The median time from randomization to the resolution of symptoms was not statistically significantly different between the two arms (12.0 days and 10.0 days, in the control and intervention arms, respectively) (p = 0.38).[8]

RCTs of HCQ for Treatment of Hospitalized Patients with Moderate-Severe COVID-19:
There have been 4 large randomized controlled trials conducted in patients hospitalized with COVID-19: RECOVERY,[9] ORCHID,[10] SOLIDARITY,[11] and a trial published by Cavalcanti, et al.[12] At this time, the HCQ arm of the RECOVERY and SOLIDARITY trials and the entire ORCHID study have been stopped for lack of evidence of benefit. Of these trials, full results

[6] Mitjà O, Ubals M, Corbacho-Monné M, et al. A cluster-randomized trial of hydroxychloroquine as prevention of COVID-19 transmission and disease. medRxiv. https://doi.org/10.1101/2020.07.20.20157651.
[7] Skipper CP, Pastick KA, Engen NW. et al. Hydroxychloroquine in nonhospitalized adults with early COVID-19: A randomized trial. Ann Intern Med. Published July 16, 2020.
[8] Mitjà O, Corbacho-Monné M, Ubals M. et al. Hydroxychloroquine for early treatment of adults with mild covid-19: A randomized-controlled trial. Clin Infect Dis. Published online July 16, 2020.
[9] *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
[10] *See:* https://www.nih.gov/news-events/news-releases/nih-halts-clinical-trial-hydroxychloroquine
[11] *See*: https://www.who.int/news-room/detail/04-07-2020-who-discontinues-hydroxychloroquine-and-lopinavir-ritonavir-treatment-arms-for-covid-19
[12] Cavalcanti AB, Zampieri FG, Rosa RG, et al. Hydroxychloroquine with or without azithromycin in mild-to-moderate COVID-19. N Engl J Med. Published online July 23, 2020.

have been published only for the RECOVERY trial (which was published as a non-peer reviewed preprint)[13] and the Cavalcanti et al. trial.

The randomized controlled trial published by Cavalcanti, et al. enrolled a lower proportion of hospitalized patients with severe disease than the RECOVERY trial. Participants were randomized 1:1:1 to receive standard care, standard care plus HCQ, or standard care plus HCQ plus azithromycin. Among 504 participants with PCR-confirmed COVID-19, there were no significant between-group differences in the proportional odds of having a higher score on an ordinal scale at day 15 (HCQ plus azithromycin vs. control: odds ratio, 0.99; 95% confidence interval [CI], 0.57 to 1.73; P=1.00; HCQ alone vs. control: odds ratio, 1.21; 95% CI, 0.69 to 2.11; P=1.00; and HCQ plus azithromycin vs. HCQ alone: odds ratio, 0.82; 95% CI, 0.47 to 1.43; P=1.00). Further, there were no significant differences in any of the secondary efficacy analyses (e.g., clinical status at Day 7, duration of hospital stay, in-hospital death, number of days alive and free from respiratory support up through day 15). [12]

In the RECOVERY Trial, among a total of 1561 patients randomized to HCQ plus the usual standard of care and 3155 patients randomized to usual standard of care alone, there was no significant difference in the primary endpoint of 28-day mortality (26.8% HCQ vs. 25.0% usual care; rate ratio 1.09 [95% confidence interval 0.96 - 1.23]; p=0.18). Analysis of the secondary efficacy endpoints revealed that the probability of discharge alive by day 28 was greater for the standard of care arm (60.3% and 62.8% in HCQ and standard of care arms, respectively [rate ratio 0.92, 95% CI 0.85 to 0.99]) and that the rate of progression to a composite endpoint of mechanical ventilation or death among subjects not requiring mechanical ventilation at baseline was higher in the HCQ arm (29.8% and 26.5% in HCQ and standard of care arms, respectively [risk ratio 1.12, 95% CI 1.01 to 1.25]).[13]

RCT Conclusions:
In conclusion, across 4 published randomized controlled trials evaluating HCQ for prevention of COVID-19 or treatment of outpatients with mild COVID-19, HCQ was not found to be significantly different than placebo or standard care on any clinical or virologic endpoints. Randomized controlled trials are considered the gold standard for evaluating the effectiveness of a given intervention. Despite limitations, these trials represent the highest quality data available at this time and they consistently fail to provide evidence that HCQ may be effective for the prevention or treatment of early COVID-19. Although less directly related to the current EUA request, published data from 2 large RCTs of inpatient treatment have not shown beneficial effects.

Observational Studies on the Prevention or Treatment of COVID-19.

FDA's scientific review staff also reviewed the information presented in the observational studies cited in the EUA request.[14] Observational studies that assessed the benefit of HCQ

[13] Horby P, Mafham M, Linsell L, et al. Effect of hydroxychloroquine in hospitalized patients with COVID-19: Preliminary results from a multi-centre, randomized, controlled trial. MedRxiv. https://doi.org/10.1101/2020.07.15.20151852.
[14] Division of Epidemiology II Consult Review, EUA 077, Submitted July 22, 2020.

treatment for COVID-19 were identified in the following three sections of the HCQ EUA request:

- Pre- or post-exposure prophylaxis with HCQ (3 studies)[15,16,17]
- Outpatient HCQ intervention (1 study)[18]
- Early hospitalization HCQ intervention (4 studies and 1 meta-analysis)[19,20,21,22,23]

In addition, several observational studies or analyses were described without references in the EUA request. The requester provided these references (n=6) in their response to an information request.[24,25,26,27,28,29]

The quality of evidence was evaluated based on the design and methods of the original observational studies or analyses that generated the findings. The following criteria were considered necessary to conduct an in-depth effectiveness review of the observational studies:

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[15] Bhattacharya R, Chowdhury S, Mukherjee R, et al. Pre exposure Hydroxychloroquine use is associated with reduced COVID19 risk in healthcare workers - a Retrospective cohort. medRxiv. 2020:2020.2006.2009.20116806.
[16] Chatterjee P, Anand T, Singh KJ, et al. Healthcare workers & SARS-CoV-2 infection in India: A case-control investigation in the time of COVID-19. Indian J Med Res. 2020;151(5):459-467.
[17] Ferreira A, Oliveira-e-Silva A, Bettencourt P. Chronic treatment with hydroxychloroquine and SARS-CoV-2 infection. medRxiv. 2020:2020.2006.2026.20056507.
[18] Barbosa Esper R, Souza da Silva R, Costa Oikawa FT, et al. Empirical treatment with hydroxychloroquine and azithromycin for suspected cases of COVID-19 followed-up by telemedicine. https://jornalggn.com.br/sites/default/files/2020/04/paper-preventsenior.pdf
[19] 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. 2020:105949
[20] Million M, Lagier JC, Gautret P, et al. Early treatment of COVID-19 patients with hydroxychloroquine and azithromycin: A retrospective analysis of 1061 cases in Marseille, France. Travel Med Infect Dis. 2020;35:101738.
[21] Malek AE, Granwehr BP, Kontoyiannis DP. Doxycycline as a potential partner of COVID-19 therapies. IDCases. 2020;21:e00864.
[22] Arshad S, Kilgore P, Chaudhry ZS, et al. Treatment with Hydroxychloroquine, Azithromycin, and Combination in Patients Hospitalized with COVID-19. Int J Infect Dis. 2020.
[23]Million M, Gautret P, Colson P, et al. Clinical Efficacy of Chloroquine derivatives in COVID-19 Infection: Comparative metaanalysis between the Big data and the real world. New Microbes and New Infections. 2020:100709.
[24] Lee SH, Son H, Peck KR. Can post-exposure prophylaxis for COVID-19 be considered as an outbreak response strategy in longterm care hospitals? Int J Antimicrob Agents. 2020;55(6):105988.
[25] Conforti C, Giuffrida R, Zalaudek I, Di Meo N. Doxycycline, a widely used antibiotic in dermatology with a possible anti-inflammatory action against IL-6 in COVID-19 outbreak. Dermatol Ther. 2020:e13437
[26] Bonzano C, Borroni D, Lancia A, Bonzano E. Doxycycline: From Ocular Rosacea to COVID-19 Anosmia. New Insight Into the Coronavirus Outbreak. Front Med (Lausanne). 2020;7:200.
[27] Lagier JC, Million M, Gautret P, et al. Outcomes of 3,737 COVID-19 patients treated with hydroxychloroquine/azithromycin and other regimens in Marseille, France: A retrospective analysis. Travel Med Infect Dis. 2020:101791.
[28] Scholz MD, R.; Zelenko, V. COVID-19 Outpatients – Early Risk-Stratified Treatment with Zinc Plus Low Dose Hydroxychloroquine and Azithromycin: A Retrospective Case Series Study. Preprints 2020, 2020070025 (doi: 10.20944/preprints202007.0025.v1).
[29] Ahmad I, Alam M, Saadi R, Mahmud S, Saadi E. Doxycycline and Hydroxychloroquine as Treatment for High-Risk COVID-19 Patients: Experience from Case Series of 54 Patients in Long-Term Care Facilities. medRxiv. https://doi.org/10.1101/2020.05.18.20066902.

1) Conducted in a population with COVID-19 infection confirmed by virological test for studies evaluating HCQ as COVID-19 treatment, or required virological test results to define COVID-19 infection for studies evaluating prophylactic HCQ use for COVID-19
2) Reported quantitative estimates of treatment effectiveness associated with HCQ use
3) Included a reference group that was not treated with HCQ

Five observational studies (four studies provided by the requester[17,17,19,22] and one component observational study[30] of the meta-analysis[23]) were reviewed in depth. Less than half of the 15 observational studies referenced by the requestor provided sufficient detail on study methods for evaluation or met the minimum design criteria above to inform HCQ treatment effectiveness. Of the studies not meeting the minimum criteria, one of the studies did not report quantitative assessments of treatment effectiveness, five did not include a reference group that was not treated with HCQ, one was conducted in patients who were suspected to have COVID-19 based on symptoms without laboratory confirmation, and three did not study HCQ but studied another drug.

FDA scientific review staff concluded that the observational studies cited in this EUA request are of insufficient quality to provide evidence to support the requested use. Among the studies that met minimum criteria, the reviewers identified significant limitations that preclude their use to support a determination of HCQ effectiveness for prevention or for treatment. The issues identified limited the interpretation of study findings and likely result in biased study findings, leading to an inaccurate estimation of the benefit. The primary concerns are summarized below.

For the studies evaluating HCQ in the prevention of COVID-19 infection, the following issues limited the interpretation of the study results used to support HCQ to prevent COVID-19 infection:

- Residual confounding- The patients receiving HCQ may be different than the group who did not receive HCQ in a way that could impact the risk of contracting COVID-19 as not all important factors were measured or could be accounted for. These include frequency of hand washing, hand sanitizer use, practice of social distancing, etc.
- Capture of exposure- Information on exposure was collected through self-report, or pharmacy dispensing records from 2019, instead of during a time period relevant to preventing COVID-19 infection, such as in early 2020.

For the studies evaluating the use of HCQ as treatment, the following issues were identified that may lead to an inaccurate estimation of the benefit:

- Residual confounding- The studies did not sufficiently capture or account for disease severity at baseline, different care standards between centers or over time, and use of other medications such as dexamethasone.
- Capture of outcomes- Issues related to measuring the outcome such as loss to follow-up of patients who die or transfer to the intensive care unit, inconsistencies of testing frequency between comparison groups.

[30] Ashraf AA, Shokouhi N, Shirali E, et al. COVID-19 in Iran, a comprehensive investigation from exposure to treatment outcomes. medRxiv. https://doi.org/10.1101/2020.04.20.20072421.

- Choice of index time- Setting the index time as hospital admission rather than the start of medication could underestimate mortality risk due to immortal time bias[31]. Additionally, it may lead to the inability to capture the differences in disease severity between patients who received HCQ and those who did not.
- Statistical methods- Identified issues include lack of a prespecified protocol in the majority of studies, and failing to account for post-baseline variables in some studies.

The only observational study provided to support the use of HCQ as an outpatient intervention for COVID-19 was not conducted in patients with a confirmed diagnosis of COVID-19. The studies cited to support HCQ as early inpatient treatment, including the component studies that were included in the referenced meta-analysis, had significant limitations including residual confounding and inappropriate index time choice (described above). FDA scientific review staff evaluated[32] the meta-analysis.[23] Similarly, FDA scientific review staff noted that the metanalysis has numerous statistical limitations (for example, no study protocol, evaluating only a subgroup in at least one study, and testing multiple comparisons without control that could lead to a chance finding).

On July 22, 2020 the EUA requestors submitted two additional publications in support of the EUA request (a Letter to the Editor[33] addressing comments published in response to the Arshad et al. observational study publication[22] and a preprint report of an observational study[34]). FDA scientific review staff evaluated these additional publications. They concluded that the new observational study met the criteria for an in-depth review, but that the additional information provided in the Letter to the Editor did not address the previously identified significant limitations. Additionally, the Letter to the Editor cited an additional observational study[35] which also met the criteria for an in-depth review.

In an addendum,[36] FDA scientific review staff concluded that the two new observational studies provided insufficient quality of data due to possible residual confounding, confounding by disease severity, potential immortal time bias, and the appropriateness of the statistical approaches or the conduct of the statistical analyses (described above). The evidence provided in the two additional observational studies does not change the assessment of the quality of evidence from observational studies that were cited in the EUA request. The Agency has

[31] Because time was indexed to admission rather than the start of HCQ, patients receiving HCQ had to survive long enough to receive the drug and had a period of time when they could not experience the outcome and are "immortal". This may underestimate mortality in the HCQ treated group.
[32] Division of Biometrics VII Consult Review, EUA 077, Submitted July 23, 2020.
[33] Zervos M, Arshad S, Kilgore P, et al. Letter to Editor [Regarding: Treatment with Hydroxychloroquine in Patients Hospitalized with COVID-19, by Arshad et al.]. Int J Infect Dis. Submitted July 21, 2020.
[34] Bernaola N, Mena R, Bernaola A et al. Observational Study of the Efficiency of Treatments in Patients Hospitalized with COVID-19 in Madrid. medRxiv. doi: https://doi.org/10.1101/2020.07.17.20155960
[35] Mikami T, Miyashita H, Yamada T et al. Risk Factors for Mortality in Patients with COVID-19 in New York City. J. Gen Intern Med. DOI: 10.1007/s11606-020-05983-z
[36] Division of Epidemiology II and Division of Biometrics VII Consult Review Addendum, EUA 077, Submitted July 28, 2020.

previously conducted a literature review and assessment of observational studies in COVID-19 populations treated with HCQ or chloroquine and reached the same conclusion.[37]

Clinical Pharmacology Assessment Regarding Dosing

FDA scientific review staff reviewed the HCQ dose regimen proposed in this EUA request for the prevention and early treatment of COVID-19.[38] FDA scientific review staff conducted a thorough literature review and evaluation of reported mechanism of action, in vitro antiviral pharmacology experiments, known clinical pharmacology information, modeling and simulation, and nonclinical prophylaxis models to evaluate the proposed HCQ dosing regimens for pre-/post-exposure prophylaxis and treatment of COVID-19. In response to this consult, FDA scientific review staff integrated in vitro antiviral activity of HCQ and simulated exposures achieved with the HCQ dosing regimens approximately equal to or higher than those proposed in this EUA request to predict antiviral activity at relevant sites of infection. Based on these assessments, under the assumption that in vivo cellular accumulation is similar to that from the in vitro studies, the calculated free concentrations in lung or other relevant tissues that would result from the proposed dosing regimens (400 mg BID on Day 1, followed by 200 mg BID on Days 2-5; 400 mg weekly; and 400 mg once, then 200 mg daily) and doses up to 600 mg daily, are predicted to be below the in vitro EC_{50} values. It is important to note that even if exposures exceeded the in vitro EC_{50} value, it is not known if this would translate to clinical effectiveness. Given potential dose-related safety concerns, significant increases in the dose of HCQ are not feasible, making any possible antiviral effect against SARS-CoV-2 not likely achievable with a safe oral dosing regimen.

Animal Models

FDA scientific review staff reviewed three recent publications describing nonclinical studies that included evaluations of the treatment and/or prophylactic activity of HCQ (combined with azithromycin in two of the studies) in animal models of SARS-CoV-2 infection.[39,40,41] No evidence of antiviral activity was demonstrated in any of these 3 studies utilizing hamster, ferret, and macaque models. FDA scientific review staff concluded that these publications do not provide support for the potential efficacy of HCQ in humans as treatment or prophylaxis for SARS-CoV-2 infection and/or the development of COVID-19.[42]

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[37] *See:* FDA Letter of Revocation of the Emergency Use Authorization for emergency use of oral formulations of chloroquine phosphate and hydroxychloroquine sulfate to be distributed from the Strategic National Stockpile issued on March 29, 2020. June 15, 2020. *Available at: https://www.fda.gov/media/138945/download*

[38] Office of Clinical Pharmacology Consult Review, EUA 077, Submitted July 22, 2020.

[39] Kaptein SJF, Jacobs S, Langendries L, et al. Antiviral treatment of SARS-CoV-2-infected hamsters reveals a weak effect of favipiravir and a complete lack of effect for hydroxychloroquine. bioRxiv 2020; https://doi.org/10.1101/2020.06.19.159053. [preprint]

[40] Park SJ, Yu KM, Kim YI, et al. Antiviral efficacies of FDA-approved drugs against SARS-CoV-2 infection in ferrets. mBio 2020; DOI: 10.1128/mBio.01114-20. [epub ahead of print]

[41] Maisonnasse P, Guedj J, Contreras V, et al. Hydroxychloroquine in the treatment and prophylaxis of SARS-CoV-2 infection in non-human primates. ResearchSquare 2020; https://doi.org/10.21203/rs.3.rs-27223/v1. [preprint]

[42] Division of Antivirals, Clinical Virology Consult Review, EUA 077, Submitted July 23, 2020.

Review of Information on Known and Potential Risks of the Products

As described above, FDA has determined that is not reasonable to believe that HCQ may be effective for the prevention or early treatment of COVID-19. There are potential risks associated with the use of HCQ for the treatment or prevention of COVID-19. Of particular concern are cardiac events related to the known QT interval prolonging potential of HCQ.

The Agency has previously conducted a safety assessment which included a search of the FAERS database, published literature, and National Poison Data System[43]. The safety assessment found that serious cardiac adverse events (QT prolongation, n = 80; ventricular arrhythmias, n = 14; and torsades de pointes, n=4) have been reported in association with the use of HCQ or the closely related drug chloroquine for COVID-19, including 25 cardiac serious adverse events with 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.

The most commonly reported non-cardiac serious adverse events were hepatic events. Notably, the labeling for HCQ associated with its approved uses includes information on QT prolongation and resultant ventricular arrhythmias and the label recommends that HCQ be used with caution in persons with hepatic disease. Non-labeled adverse events reported in association with HCQ use for COVID-19 included acute kidney injury/renal failure and methemoglobinemia. Of 4 reported methemoglobinemia cases, 2 were fatal.

While the degree of risk of cardiac adverse events in association with HCQ use in outpatients with mild COVID-19 or persons at risk for COVID-19 is unclear, this risk in outpatients is less readily mitigated than it would be in a hospital setting with close cardiac and laboratory monitoring. Further, in the absence of benefit, the risk is not acceptable. Therefore, the risk/benefit balance is unfavorable. FDA has determined that the known and potential benefits do not outweigh the known and potential risks of HCQ for the proposed use.

Conclusion

Based on the data reviewed from RCTs and observational studies and the clinical pharmacology and virology assessment, it is not reasonable to believe that HCQ may be effective in preventing or treating COVID-19. Based on the absence of evidence that HCQ may be effective in preventing or treating COVID-19 and the known risks of cardiac and other adverse drug effects, it is not reasonable to believe that the known and potential benefits outweigh the known and potential risks of HCQ for the proposed use. FDA has determined that the criteria for issuance of an EUA are not met and is declining to issue an EUA covering HCQ for the prevention or treatment of COVID-19 at this time.

[43] *See:* FDA Letter of Revocation of the Emergency Use Authorization for emergency use of oral formulations of chloroquine phosphate and hydroxychloroquine sulfate to be distributed from the Strategic National Stockpile issued on March 29, 2020. June 15, 2020. *Available at: https://www.fda.gov/media/138945/download*

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