PRODUCTION OF DOCUMENTS PURSUANT TO SCHEDULE “I” OF THE SUBPOENA
DATED SEPTEMBER 23, 2021, SERVED UPON DR. STEVEN J. HATFILL, ADJUNCT
ASSISTANT PROFESSOR OF MICROBIOLOGY, IMMUNOLOGY, AND TROPICAL
MEDICINE, GEORGE WASHINGTON UNIVERSITY
Thursday, October 7, 2021
11:07 am Eastern Standard Time

Steven Hatfill
@protonmail.com>
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Thursday, October 7, 2021
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Stored with zero-access encryption
Sent July 6th, 2020
Star message
To: Navarro, Peter K. EOP/WHO
Show details
Has 2 attachments
Mark as unread
Move to trash
More options
Custom filter
Move to Label as
Reply
Reply all
Forward

Good Morning:
You asked me to prepare a combined EUA critique and EUA Request
I don’t trust the FDA to do the right thing unless there is fear.
Not sure if I should leave in the last paragraph outlined in red, just before my signature, but I
think this RADM may be the cause of all the trouble and would relish a fight.
Please change anything you deem necessary to obtain a superior product.
I think I have taken out all the words like "idiot" and "dumbass"
I’m just going to grab a bit of sleep and I’ll be in at 10:30

REQUEST FOR FDA EMERGENCY USE AUTHORIZATION
Hydroxychloroquine Sulfate with and without Zinc or antibiotic additions

Executive Summary

1. The FDA has failed to keep informed on the current literature and the basic 2-phase pathogenesis of
COVID-19. It has either ignored or failed to make the proper conclusions in the large amount of data that
has now accumulated indicating the positive early use of hydroxychloroquine in COVID-19 infection.
Instead it has apparently relied on information from non-peer reviewed publications as well as several
retracted papers and unsubstantiated statements in the mainstream media and following cancellation of
the faulty UK/Oxford RECOVERY Trial. This was restarted on 30 June 2020 by the UK Health Regulatory
agencies, hopefully with a better trial design.

2. Since mid-April, it has been apparent in the scientific literature and from discussions with Intensive Care
physicians, that the major role for hydroxychloroquine was in the early management of COVID patients
before they were severe enough to be hospitalized. Consequently, an April Memo to the COVID-19 Task
Force outlined this requirement for Early-Treatment with hydroxychloroquine. By following Dr. A. Fauci
from the NIH/NIAID and insisting that hydroxychloroquine be administered to only hospitalized patients,
the FDA effectively blocked any maximum effect of this drug because of its narrow window for treatment
in early COVID-19 patients.
3. The FDA’s inaccurate black box warning on cardiac side-effects cannot be substantiated. Real world data shows no deleterious cardiac effects when given to COVID patients early and within the dose and time frame recommended. The media storm surrounding false, poorly-reviewed papers and the FDA’s failure to accurately review this data before making national decisions, has had a documented negative effect that has essentially halted new patient recruitment for urgent early-use hydroxychloroquine trials.

4. These trials would have been characterized by the outpatient use of hydroxychloroquine where the presenting patient was still ambulatory, did not require supplemental O₂ to maintain their blood oxygen saturation, with lesions in 3 or less lobes of the pulmonary system. The study goals were to prove weeks ago, that hydroxychloroquine has a statistically significant ability to keep patients out of the ICU wards and reduce the associated horrendous mortality rate associated with invasive ventilation in severe COVID-19 disease management.

5. In the last week of July, 2 major U.S. studies by major medical systems (Ford in Detroit and Mt. Sinai in NYC), have provided evidence for a 51% and 50% reduction in COVID mortality for patients given hydroxychloroquine in the very early phase of the infection. The French have released their study of 3,737 early treatment cases, and Zelenko has released his retrospective case series study. These true early use studies show dramatic results without any serious cardiac events.

The NIH strategy for COVID-19 management promoted by A. Fauci and backed by the ongoing FDA regulations is no longer tenable.

Based on the totality of scientific evidence, including data from adequate and well-controlled clinical trials, it is unreasonable to believe that the current HHS/NIH doctrine of individual case isolation until a patient requires hospitalization, and then the initiation of hospital-based antiviral drug treatment in the LATE stages of infection, may have any practical effect in halting the epidemiological spread and significantly reducing the mortality rate associated with COVID-19, a viral disease caused by the SARS-CoV-2 Virus.

This doctrine is in a complete contradiction to the United States National Pandemic Influenza Plan which was to have served as the general guidance for management of an emerging pandemic respiratory RNA virus. The decision by HHS and the NIH to recommend lockdown and quarantine while waiting for COVID victims to develop shortness of breath and the onset of the more severe second phase of COVID-19 disease pathogenesis is not supported by the progressively accumulating early-treatment data that began on 15 February 2020. (Table One).

The early use of hydroxychloroquine is not simply anecdotal data as claimed by Dr. Anthony Fauci of the NIH, who has openly opposed hydroxychloroquine use in spite of it already being an approved FDA drug with millions of doses already safely prescribed for patients with connective tissue disorders over the last 50-years. The recent FDA withdraw of its EUA based on the multiple points of its unsupported reasoning and its refusal to allow physicians to prescribe hydroxychloroquine as they deem necessary, appears to have added a possible 50% greater overall mortality to the U.S. COVID pandemic.
The last hope for some degree of COVID-19 control now lies with the initiation of physician-directed hydroxychloroquine outpatient drug therapy, given within the first 7-days of patient symptoms, as well as the pre-exposure prophylactic use of hydroxychloroquine in asymptomatic, uninfected, high-risk Health Care Workers (HCW) and individuals with a high number of inter-personal contacts during their normal daily activities. (Figure 1, 3). These COVID countermeasures are now being proven in India, as well as in Brazil which in some locations has been able to drastically limit its COVID hospital admissions.

Despite the money spent on Remdesivir, this drug was never suitable for outpatient use, and outside of hydroxychloroquine, there is only the future development of a vaccine for control and thousands more Americans are going to lose their lives during this “immunization gap” with further catastrophic economic damage to the Nation.

REQUEST FOR EMERGENCY USE AUTHORIZATION

On behalf of Dr, Steven Hatfill an Emergency Use Authorization is requested for hydroxychloroquine in limited circumstances to treat EARLY COVID-19 infections pursuant to Section 564 of the Federal Food, Drug and Cosmetic Act (the Act) (21 U.S.C. 360bbb-3).

Background

On February 4, 2020, pursuant to Section 564(b)(1)(C) of the Act, the Secretary of the Department of Health and Human Services (HHS) determined that there is a public health emergency that has significant potential to affect national security or the health and security of United States citizens living abroad, and that involves the virus that causes COVID-19. On the basis of such determination, the Secretary of HHS on March 27, 2020, declared that circumstances exist justifying the authorization of emergency use of drugs and biologics during the COVID-19 outbreak, pursuant to section 564 of the Act, subject to terms of any authorization issued under that section.

According to the requirements set out in Section 564(c) of the Act, namely;

(1) that COVID-19 can cause a serious or life threatening condition as reported by the Secretary in his public health emergency,

(2) that, based on the totality of scientific evidence available to the Secretary, including data from adequate and well-controlled clinical trials, it is unreasonable to believe that the current HHS/NIH doctrine of individual case isolation until a patient requires hospitalization, and then the initiation of hospital-based anti-viral drug treatment in the LATE stages of infection, may have any practical effect in halting the epidemiological spread and significantly reducing the mortality rate associated with COVID-19, a viral disease caused by the SARS-CoV-2 Virus. This applies to the use of remdesivir, favipiravir lopinavir/ritonavir, hydroxychloroquine with and without Zinc and an added antibiotic, and arbidol.
(3) that there is no adequate, approved, and available alternative to the product for diagnosing, preventing, or treating such disease or condition with the exception being the correctly timed use of systemic steroids in hospitalized patients with lower respiratory tract disease involvement. No other criteria of issuance have been prescribed by regulation under Section 564(c)(4) of the Act.

Early outpatient illness is very different than later hospitalized florid disease and as numerous clinical trials have demonstrated, the treatments grossly differ. This has been apparent since mid-April in the scientific literature and in discussions with Intensive Care physicians.

In 2005, a National Pandemic Influenza Plan was announced and painstakingly developed by HHS as the prototype response for a large serious respiratory RNA virus infectious disease outbreak. The strategy of the plan was to develop anti-viral medications that could be rapidly sent to communities for outpatient use wherever possible. The States were to develop their own plans for rapid drug distribution to communities, although DHHS did make helpful suggestions. The goal of isolation and treatment at home was to avoid overwhelming surges in the demand for ICU beds and ventilator support during the period of the “Vaccine Gap”, that is the time needed to test, manufacture and distribute a vaccine for the respiratory pathogen to the population of the United States.

As the COVID-19 pandemic reached the U.S., a search was made for a suitable orally available drug to cover the “Vaccine Gap” and previous studies suggested Chloroquine, an inexpensive and safe anti-malarial drug that showed in-vitro promise as an anti-viral agent in 2005 with the original SARS Coronavirus. Early data from China indicated a related drug, hydroxychloroquine was an even a more effective and safer anti-viral agent for use against COVID-19.

The drug started to be used widely by physicians’ off-label and scientific/medical papers began to appear describing the efficacy of both chloroquine and hydroxychloroquine in the management of COVID-19.

On March 30, 2020, the FDA issued an Emergency Use Authorization (EUA) allowing the use of hydroxychloroquine and chloroquine products donated to the Strategic National Stockpile (SNS) to be distributed and used for adolescent and adult patients with COVID-19 who are hospitalized and who cannot be part of a clinical trial.

At the same time the National Institutes of Allergy and Infectious Diseases under the National Institutes of Health, established a COVID-19 Treatment Panel. It also recommended that the pandemic strategy should be for patients to isolate at home until they were sick enough to come into hospital to receive treatment. At the same time under the leadership of Dr. Anthony Fauci, the NICHId began to place a directed hope into a drug called Remdesivir, a drug that must be given IV and not suitable for outpatient use. The only role for such a drug in the National Pandemic Plan, would be for the sickest patients.

As the clinical course and pathophysiology of COVID-19 became better defined, it became clear that around day 7 to 8 after first symptom onset, there was a fundamental change in the pathophysiology
of the COVID disease. As a result, COVID-19 now appeared to be a sequential basic two-stage pathological process typified by an EARLY STAGE of infection up to roughly day 7 after first symptom onset, with either the resolution or progression to a more dynamic, systemic, severe and evolving LATE PHASE of infection after day 7.

This understanding of the pathogenesis of COVID-19 had been developed by mid-March and it became further established by early April 2020 when it was obvious by clinical and laboratory determinations that a Systemic Inflammatory Syndrome and a Cytokine Release Syndrome ("Cytokine Storm") could clearly be a part of COVID-19 infection.

Data continued to appear which suggested that this very severe, second phase of the disease might be minimized if hydroxychloroquine was given very EARLY (i.e. within the first 7 days of symptoms.) The dose selected by the US national authorities was associated with only minimal side effects if used for only a short course of treatment.

Consequently, an official Early-Use Memo from OTMB was drafted and sent to the COVID-19 Task Force in April 2020. This Memo stated that the available evidence at that time suggested that there appeared to be a narrow treatment window for the early administration of clinically safe doses of HCQ for it to have a maximum effect. The Memo Recommendations were to mandate an early use HCQ treatment via a drug label that should be attached to the hydroxychloroquine EUA.

However, during this time, two non-peer reviewed research papers appeared on the internet.

- 16 April 2020 MedRxiv: Chloroquine diphosphate in two different dosages as adjunctive therapy of hospitalized patients with severe respiratory syndrome in the context of nCoronovirus (SARS-CoV-2) infection: Preliminary safety results of a randomized, double-blinded, phase IIb clinical trial (CloroCovid-19 Study)


Following the publication of these 2 papers (both papers without a required outside peer-review), and each with serious multiple faults, the FDA ignored the submitted Memo for Early-Use Hydroxychloroquine. This is in spite of the disclaimer on the MedRxiv website that specifically states;

*Caution: Preprints are preliminary reports of work that have not been certified by peer review. They should not be relied on to guide clinical practice or health-related behavior and should not be reported in news media as established information.*

Both these papers were seen quickly debunked. Months later, the VA study still remains unpublished and a large petition for retraction is being prepared for the other, in addition to criminal charges that have been filed in Brazil. The timing of these 2 publications in April and the resulting overwhelmingly negative
response and hype by the mainstream media, is temporally linked to the FDA issuing a black box warning for hydroxychloroquine on the 24 April 2020.

This FDA warning cautioned against use of hydroxychloroquine or chloroquine for COVID-19 outside of the hospital setting or in a clinical trial due to the risk of heart rhythm problems. Curiously, this warning did not affect the FDA-approved uses for malaria, lupus, and rheumatoid arthritis (RA) *where periodic doses of hydroxychloroquine were often given to patients with Lupus and RA in much larger doses than that recommended in the US for COVID treatment applications.*

1. The FDA ignored the possibility that the overwhelming pathophysiology exhibited in the **late-phase** COVID patients could be overwhelming any positive effect exerted by the **late** administration of hydroxychloroquine.

2. The FDA seems to have failed to understand that a large percentage of the late COVID-19 patients *not* taking chloroquine or hydroxychloroquine were also showing major cardiac signs and symptoms including heart rhythm irregularities, either from direct COVID virus damage to the muscle and conducting system of the heart, or as a result of myocardial injury as a result of the inflammatory cascade and microvascular damage caused by the patient’s abnormal immune response to the virus.

It is to be noted that the mechanism for delineating viral-induced myocarditis is an endocardial biopsy and this was rarely done, leaving the actual cause of these de-novo arrhythmias in question. This will be discussed more later on.

The immediate effect of these papers and the resulting National Media frenzy, in addition to the FDA’s response, was to destroy the ongoing patient recruitment for the clinical trials that were intended to focus on hydroxychloroquine for the early management of COVID patients and the outpatient use of this drug to prevent disease progression into ICU care.
On June 15, 2020 the U.S. Food and Drug Administration (FDA) revoked the emergency use authorization (EUA) that allowed for the chloroquine phosphate and hydroxychloroquine sulfate donated to the Strategic National Stockpile to be used to treat certain hospitalized patients with COVID-19 when a clinical trial was unavailable, or participation in a clinical trial was not feasible.

The FDA determined that the legal criteria for issuing an EUA were now no longer met. Based on its ongoing analysis of the EUA and emerging scientific data, the FDA determined that chloroquine and hydroxychloroquine are unlikely to be effective in treating COVID-19 for the authorized uses in the EUA.

Additionally, in light of ongoing serious cardiac adverse events and other potential serious side effects, the known and potential benefits of chloroquine and hydroxychloroquine no longer outweigh the known and potential risks for the authorized use.

To quote the withdraw letter: 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.

Considering the timing of the FDA EUA withdraw letter and the FDA’s choice of the words “recent data,” it is assumed the FDA is referring to the now halted HCQ wing of the UK (Randomized Evaluation of COVID-19 Therapy (RECOVERY) study, a trial with several major faults. If not this study then the FDA was likely referring to the Lancet paper that was withdrawn within days for fabricated data.

With respect to the faulty UK RECOVERY Trial, the HCQ dosing regimen used was 12 tablets during the first 24 hours (800mg initial dose, 800 mg six hours later, 400 mg 6 hours later, 400 mg 6 hours later), then 400 mg every 12 hours for 9 more days. This is 2.4 grams during the first 24 hours. This represents a
cumulative dose of 9.2 grams over 10 days. Although the lethal dose of Hydroxychloroquine has not
been well established, the clinical series suggest that 4g of hydroxychloroquine can cause seriously severe
symptoms. Fatalities have been associated with the ingestion of 12g in adults.

- C. Merino Argumànez, I. Sáez de La Fuente, Z. Molina Collado, D. Suárez Piña, B. Mestre Gómez, J.A. Sanchez Izquierdo
  Hydroxychloroquine, a potentially lethal drug. Med Intensiva 2017;41:257-910.1016/j.medine.2016.05.003

The high-dose regimen being used in these trials has no medical justification. This study and other late
studies continue to appear and be cited, and precious weeks have been wasted by investigators who have
refused to concentrate their efforts on EARLY-PHASE patients or have been completely hampered by the
FDA mandate for HCQ use only in hospitalized patients. By the time a patient is hospitalized, tested, and
assigned to receive hydroxychloroquine, given hydroxychloroquine and allowed time for the drug’s
pharmacodynamics to occur following drug ingestion, most patients have already passed into the start of
the LATE-STAGE COVID disease pathogenesis.

In the Recovery study, HCQ was given in non-therapeutic and potentially toxic doses and it was largely
given outside the window of maximum potential effectiveness. The limited collection of any safety data
in this trial obscures any adverse or positive drug effects. The study seems to lack even basic clinical data
such as EKG, Troponin, C-RP, and especially IL-6 level determinations to assess systemic inflammation.
This is in addition to the lack of renal studies, hepatic studies, and no reported assessment of patients for
the Multi-Organ Dysfunction Syndrome (MODS).

This is important because in a recent paper (Not yet peer reviewed), the level of IL-6 was significantly
lowered in severely ill patients given HCQ (from 22.2 (8.3-118.9) pg/mL at the beginning of the treatment
to 5.2 (3.0-23.4) pg/ml (p<0.05) at the end of the treatment) with no change in the untreated group. This
indicates that HCQ treatment even in late-patients may still be exerting a beneficial effect.

Bo Yu, Chenze L, Peng Chen, et al., Hydroxychloroquine application is associated with a decreased
https://doi.org/10.1101/2020.04.27.20073379;this version posted May 1, 2020.

If one is discussing “recent” data, then it is applicable to discuss the 25 June 2020 results of a large
French Study that was recently accepted for publication. This study, like the Ford Study, looked
at 3,737 COVID-19 patients treated with EARLY TREATMENT with HCQ that demonstrated
a mortality of 1.1% with an overwhelming effectiveness in preventing disease progression
with an excellent safety profile in real-life medical experience. This is compared to the halted Oxford UK Study which had a mortality rate of 25%.


The significant association between treatment with HCQ-AZ ≥ 3 days and reduction of risk of death was confirmed to be independent of age and comorbidities. Treatment consisted of the combination of HCQ (200 mg of oral HCQ, three times daily for ten days) and AZ (500 mg on day 1 followed by 250 mg daily for 4 days).

Based on the accumulating results of trials from numerous sources (see below), it is reasonable to believe that the current established procedure for the epidemiological management of COVID-19 be changed from a hospital-based doctrine, to a more focused, community-based approach that involves the outpatient and prophylactic use of Hydroxychloroquine with or without additional antibiotic and/or Zinc supplementation. This use involves the known and potential benefits of early-use hydroxychloroquine which outweigh the known and potential risks of this drug, for the treatment of patients in the EARLY outpatient stage of COVID-19 infection. This is while patients are still ambulatory and do not require supplemental oxygen.

It should be noted that the UK has re-initiated the Hydroxychloroquine arm of the trial and hopefully it has realized the deficiencies in the Oxford RECOVERY study.

The doctrine of “Stay at Home” quarantines and population lockdown without testing, to wait for COVID-infected patients to develop dyspnea and the need for hospitalization as well as the attendant overwhelming of community medical facilities, is unrealistic. It is also not part of the National Pandemic Influenza Plan painstakingly developed by HHS as the prototype response for a large serious respiratory RNA virus infectious disease outbreak.

This is a criticism applicable not only to the United States, but to many countries that refrained from implementing any form of early treatment, such as the UK, Canada, France, and others. (Figure 1) The decision by HHS and Dr. Fauci to recommend lockdown and quarantine while waiting for COVID victims to develop shortness of breath and the onset of the more severe second phase of the COVID-19 disease is not supported by the progressively accumulating early-treatment data that began on 15 February 2020. (Table One).

In contrast to the minimal results of anti-viral therapy in late-stage COVID patients, five published studies, including two controlled clinical trials and three more studies awaiting publication, have all demonstrated a significant major efficacy of hydroxychloroquine as a cheap, antiviral medication when used in the early outpatient stage of COVID-19 infection. This is in addition to over 30 smaller patient trials which demonstrate the same results.
Early use of hydroxymethylchloroquine (HCQ) is a safe medication that appears to halt the progression of patients to the more severe and lethal second-stage of COVID-19 infection with the attending risk of hospitalization, possible ICU admission, invasive intubation and possible death (Table One) (Figure 2)\(^1\)

This is not simply anecdotal data as claimed by Dr. Anthony Fauci of the NIH, who has openly opposed outpatient hydroxychloroquine use in spite of it already being an approved FDA drug with millions of doses already safely prescribed for patients with connective tissue disorders over the last 50-years.

The last hope for some degree of COVID-19 control lies with the initiation of physician-directed hydroxychloroquine outpatient drug therapy, given within the first 7-days of patient symptoms, as well as the pre-exposure prophylactic use of hydroxychloroquine in asymptomatic, uninfected, high-risk Health Care Workers (HCW) and individuals with a high number of inter-personal contacts during their normal daily activities. (Figure 2). Outside of this, there is only the future development of a vaccine for control and thousands of Americans are going to lose their lives during this “immunization gap” with further catastrophic economic damage to the Nation.

**Product Description**

This EUA request is for the outpatient use of hydroxychloroquine sulfate in the formulation of 200 milligram (mg) tablets. As with many of the drugs approved by the FDA for human use, the precise molecular mechanisms involved in the actions of hydroxychloroquine have not been fully elucidated, nor have the effective intracellular micromolar concentrations of these drugs been well established where the different and broad-range of physiological effects are taking place.

Physiologically-Based Pharmacokinetic (PBPK) model simulations of the plasma drug levels and extracellular tissue spaces have been used to estimate the optimal HCQ dosing regimens. However, in reality, it is difficult to observe how these various simulations take into account the slow and accumulative intracellular concentrations of HCQ that varies with the length of time of drug administration, the prolonged 3/4 life of the drug in the human body, as well as the prolonged length of time for various HCQ effects to physiologically appear and then disappear after the cessation of drug intake.\(^2\)

Hydroxychloroquine is known to be able to change the pH at the surface of the cell membrane, inhibit aspects of nucleic acid replication in some cases, interfere with the glycosylation of both receptor and some viral proteins in some viruses, broadly modify the new virus assembly of some viruses, modify new virus particle transport, release, and other processes. Both hydroxychloroquine and its relative chloroquine, appear able to bind to the human ACE-2 protein that serves as the CoV-2 viral receptor and interfere with the viral S protein’s ability to bind to gangliosides.

**FIRST REPORTS ON THE CLINICAL USE OF HCQ OUTSIDE OF ITS ANTI-PARASITIC ROLE, OCCURRED IN SYSTEMIC LUPUS ERYTHEMATOSUS (SLE) PATIENTS MORE THAN 50 YEARS AGO. IN THIS APPLICATION, THE DOSAGE FOR THE OUTPATIENT USE OF HCQ IN SLE IS A LOADING INITIAL DOSE OF 400**
MG ORALLY ONCE OR TWICE A DAY. THE MAINTENANCE DOSE RANGES BETWEEN 200 AND 400 MG PER DAY WITH VARIABLE AVOCATIONS FOR DOsing BASED ON ACTUAL OR IDEAL BODY WEIGHT. ONE STUDY ON SLE USE INDICATES THAT EFFECTIVE HCQ BLOOD LEVELS ARE SIMILAR REGARDLESS OF HEIGHT AND BODY WEIGHT AND THAT A DOSE OF 6.5 MG/KG OF ACTUAL BODY WEIGHT (MAX 400 MG DAILY) IS APPROPRIATE.¹

THE PROTOCOLS FOR RHEUMATOID ARTHRITIS SUGGEST AN INITIAL LOADING DOSE OF 400 TO 600 MG SALT (310 TO 465 MG BASE)/DAY ORALLY DIVIDED IN 1 OR 2 DOSES, WITH A MAINTENANCE DOSE OF 200 TO 400 MG SALT (155 TO 310 MG BASE)/DAY ORALLY DIVIDED IN 1 OR 2 DOSES AND A MAXIMUM DOSE OF 600 MG SALT (465 MG BASE)/DAY OR 6.5 MG/KG SALT (5 MG/KG BASE)/DAY, WHICHEVER IS LOWER, SHOULD NOT BE EXCEEDED. ACCORDINGLY, THE ADVICE IS TO REDUCE THE DAILY DOSE TO BELOW 400 MG PER DAY FOR THOSE WEIGHING LESS THAN 61 KG.²

For COVID-19 the suggested dose of HCQ sulphate is 400mg BID on day 1, followed by 200mg BID on day 2-5. Because of the long elimination half-life of the drug (32–50 days), the duration of treatment should not exceed 5 days to avoid accumulation of hydroxychloroquine concentrations in plasma and tissues, and associated increased risk of toxicity, and because there is no in vitro evidence that longer courses improve drug activity on SARS-CoV-2.³

Safety of Hydroxychloroquine

Hydroxychloroquine has an excellent safety profile. Led by Dr. Dani Prieto-Alhambra, Professor of Pharmaco-and Device Epidemiology at the University of Oxford, a team of researchers from around the world met to analyze the safety profile of hydroxychloroquine. From 26 – 29 March 300 researchers from 30 countries and six continents formed teams to examine the data from fourteen datasets, from six countries: Germany, Japan, the Netherlands, Spain, the UK, and the USA. The research was to provide real-world evidence and inform healthcare decision-making in response to the current global pandemic.

Over 300 international researchers from the Observational Health Data Sciences and Informatics (OHDSI) community described the safety profile and potential harms of Hydroxychloroquine and Azithromycin and found that Hydroxychloroquine had been shown to be a safe drug in over 130,000 patients.⁶ When administered at the doses used for current indications like rheumatoid arthritis and lupus in the developed nations, and amoebic liver abscesses and malaria in the under-developed countries, there were no serious side effects.

It should be noted that that some of the short-term amplified doses of Hydroxychloroquine used in Lupus patients with complications, are much higher than the doses proposed for use in early COVID-19 cases. This study did not find any consistent reason to make them think that the drug Hydroxychloroquine
was anything other than a safe medication in general but urge caution in using it in combination with azithromycin.

The major stated concern of the FDA and NIH advisories and the cardiology opinions restricting use of HCQ and HCQ+AZ, was for a prolongation of QT interval > 500msec leading into a fatal Torsades de Pointes a rare type of ventricular arrhythmias, as well as for cardiac arrhythmias in general.

One Oxford study examined cardiac arrhythmia outcomes and obtained for its random effects meta-analysis result, RR=1.08, P-value=.36 for HCQ + Azithromycin (AZ) use vs HCQ + Amoxicillin use (another broad spectrum antibiotic. The fixed-effects meta-analysis RR=1.04, P-value=.41. This study clearly demonstrates that cardiac arrhythmia adverse events are not appreciably increased by combining HCQ with AZ.6

The same study compared HCQ use to sulfasalazine use and again found no difference in cardiac arrhythmia risk: for HCQ, a slightly lower RR=0.85, P-value=.13. The subjects analyzed in the Oxford study were largely older adults with multiple comorbidities in addition to rheumatoid arthritis. Finally, the Oxford study allows for a direct estimate of the number of arrhythmia events attributable to HCQ+AZ use. Among 306,106 people taking sulfasalazine (which is known not to produce QT prolongation), 877 with cardiac arrhythmias were identified, representing 0.287%. In 320,589 people taking HCQ+AZ, 1,068 had arrhythmias, 0.333%. The difference, 0.047% or 47/100,000 older multi-comorbidity patients taking HCQ+AZ, is attributable to the HCQ+AZ use. These are events, not fatalities. Fatalities according to FAERS comprise <20% of HCQ-related arrhythmia events. The maintenance HCQ dose in the Oxford study patients, 200 mg/day, gives as large or larger plasma drug levels as five days of HCQ at 400 mg/day, the recommended dose for outpatient Covid-19. These very small numbers of arrhythmias, as well as the null results in this very large empirical study, should therefore negate the worry about HCQ causing deaths for the drug itself or in combination with Azithromycin in outpatient use.6

The FDA, NIH and cardiology society warnings about cardiac arrhythmia adverse events, while appropriate for theoretical and physiological considerations about use of these medications, are not borne out in mortality in real-world use. Theoretical calculations about potential adverse events and from measured physiologic changes rather than from current real-world mortality experience with these medications suggest it would be incumbent upon all three organizations to reevaluate their positions as soon as possible.7

It is unclear why the FDA, NIH and cardiology societies made their recommendations about HCQ+AZ use now, when the Oxford study analyzed 323,122 users of HCQ+AZ compared to 351,956 users of HCQ + amoxicillin, i.e., that the combination of HCQ + AZ has been in widespread standard-of-care use in the US and elsewhere for decades, use comparable to HCQ + Amoxicillin as if it just involved an alternate antibiotic choice, this use predominantly in older adults with multiple comorbidities, with no such strident warnings about the use given during that time.7

Baseline EKG is not recommended for Rheumatoid Arthritis, Scleroderma, or SLE patients starting hydroxychloroquine therapy, and HCQ is one of the few drugs not contraindicated in pregnancy and nursing mothers.
It is also curious the recommendation for remdesivir use as early as possible was made without either FDA approval or RCT evidence of efficacy in the outpatient context at this time or exactly how IV medication would be provided to hundreds of patients nationwide each day when FEMA has difficulty simply distributing N-95 masks to hospitals. Their recent performance during the U.S. COVID crisis has not been exactly efficient and exemplary.

In a recent COVID treatment study, 3,119 French patients were treated with a higher dose of HCQ-AZ (200 mg of oral HCQ, three times daily for ten days and 500 mg of oral AZ on day 1 followed by 250 mg daily for the next four days, respectively) for at least three days and 618 (16.5%) patients treated with other regimen (“others”). Outcomes were death, transfer to the intensive care unit (ICU), ≥10 days of hospitalization and viral shedding.7 Treatment with HCQ-AZ was associated with a decreased risk of transfer to ICU or death (Hazard ratio (HR) 0.18 0.11–0.27), decreased risk of hospitalization ≥10 days (odds ratios 95% CI 0.38 0.27–0.54). QTc prolongation (>60 msec) was observed in 25 patients (0.67%) leading to the cessation of treatment in 12 cases including 3 cases with QTc> 500 msec. No cases of torsade de pointe or sudden death were observed. Overall, the case fatality rate among the 3,737 patients was 1.1%. This can be contrasted with the hospital-level case fatality rates of roughly 25%, in the Oxford University RECOVERY clinical trials.7

Recently a French Medical Panel petitioned their national government to allow HCQ+AZ and HCQ + Doxycycline for outpatient use in early COVID cases. Their assessment was that this medication was generally safe for short-term use in the early treatment of most symptomatic high-risk COVID outpatients, where not contraindicated, and that they are effective in preventing hospitalization for the overwhelming majority of such patients. Their assessment was that if these HCQ-combined medications become the standard-of-care, they would save an enormous number of lives that would otherwise be lost to this Pandemic disease.8

Supporting Documentation and Clinical Trials

Symptomatic outpatient infection is a pathologically and clinically different disease than the life-threatening inpatient acute respiratory distress syndrome seen in some hospitalized patients caused by SARS-CoV-2, thus there is little reason to think that the same treatment would be useful for both early and late COVID-19 disease where different pathophysiological processes are involved. In this respect, the first Western study of HCQ+AZ (24) was controlled but not randomized or blinded, and involved 42 patients in Marseilles, France.


This study showed that the sooner these medications are used, the better their effectiveness, as would be expected for viral early respiratory disease. The average start date of medication use was day-4 of symptoms. This study has been criticized on various grounds that are not germane to the science, but the most salient criticism is the lack of randomization into the control and treatment groups. This is a valid general scientific criticism, but it does not represent epidemiologic experience in this instance. If this
study had shown a 2-fold or perhaps 3-fold benefit, that magnitude could be postulated to have occurred because of subject-group differences from lack of randomization. However, the 25-fold or 50-fold benefit found in this study is not amenable to lack of randomization as the sole reason for such a huge magnitude of benefit.

Further, the study showed a significant 7-fold benefit of taking HCQ+AZ over HCQ alone, (P-value =.035), which cannot be explained by differential characteristics of the controls, since it compares one treatment group to the other. In addition, the treated subjects receiving AZ had more progressed pneumonia than the treated subjects receiving HCQ alone, which should otherwise have led to worse outcomes.

The study size has been described as “small,” but this criticism only applies to studies not finding statistical significance. Once a result has exceeded plausible chance finding, greater statistical significance does not contribute to evidence for causation.¹ No different conclusion would have resulted had a study with 1000 patients found the same 50-fold benefit but with a P-value of 10⁻¹⁰. Small study size limitations only apply to studies having a finding within the play of chance. That is not the case here. A second study by the Marseilles group involved 1061 patients tested positive for SARS-CoV-2 treated with HCQ+AZ for at least 3 days and followed for at least 9 days.


The authors state “No cardiac toxicity was observed.” Good clinical outcome and virological cure were seen in 973 patients (92%). Five patients died, and the remainder were in various stages of recovery.

A third piece of evidence for the effect of hydroxychloroquine given to COVID patients still in the very early stage of their infection, involves the cohort of 1450 patients treated by a private physician in New York.


His two-page report describes his clinical reasoning and procedures, dosing regimen, and patient results through April 28, 2020. Symptomatic patients were treated with five days of HCQ + AZ + zinc sulfate if they were considered high-risk, as evidenced by one or more of: age 60 years or older; high-risk comorbidities; body-mass index > 30; mild shortness of breath at presentation. Patients were considered to have Covid-19 based on clinical grounds and started treatment as soon as possible following symptom onset, rather than delaying for test results before starting treatment.

Of the 1450 patients, 1045 were classified as low-risk and sent home to recuperate without active medications. No deaths or hospitalizations occurred among them. Of the remaining 405 treated with the
combined regimen, 6 were ultimately hospitalized and 2 died. No cardiac arrhythmias were noted in these 405 patients.


The fourth relevant study was a controlled non-randomized trial of HCQ+AZ in 636 symptomatic high-risk outpatients in São Paulo, Brazil. All consecutive patients were informed about the utility and safety profile of the medications and offered the treatment, and those who declined (n=224) comprised the control group. Patients were monitored daily by telemedicine. The study outcome was the need for a patient to be hospitalized as defined by a clinically worsening condition or significant shortness of breath (blood oxygen saturation <90%).

Even though the severity of all early signs and symptoms and comorbidities (diabetes, hypertension, asthma, stroke) were substantially greater in the treated patients than the controls, the need for hospitalization was significantly lower, 1.2% in patients starting treatment before day 7 of symptoms, 3.2% for patients starting treatment after day 7, and 5.4% for controls, P-value <0.0001. No cardiac arrhythmias were reported in the 412 treated patients. The most common side effect of treatment was diarrhea (16.5%), but 12.9% of treated patients presented with diarrhea before treatment began.

Although new data from the Mt. Sinai medical system has just been published, the last study to relate here is the Henry Ford Hospital System which examined 2,662 patients entering its five-hospital system in southeast Michigan from March 10, 2020 to May 2, 2020. This patient universe was subdivided into four groups: a control group, a hydroxychloroquine group, a hydroxychloroquine with azithromycin group and an azithromycin-only group.

A key feature of this study is that it provides the best “early treatment” study to date. Median time from hospital admission to receipt of hydroxychloroquine and other medicines was just a single day.

As the study notes: “The postulated pathophysiology of Covid-19 of the initial viral infection phase followed by the hyperimmune response suggests potential benefit of early administration of hydroxychloroquine for its antiviral and antithrombotic properties.” [Emphasis added]

This Ford study initially found at a statistically significant level that the hydroxychloroquine alone group was associated with a significantly lower mortality rate compared to patients not receiving hydroxychloroquine. While the mortality rate for the 487 patients in the control group receiving no medicine was 23.0%, it was 13.5% for the 1,234 patients receiving hydroxychloroquine alone.

This compared to a rate of 19.9% for the HCQ/Azithromycin group and 21.7% for the azithromycin only group. Later data and statistics equate the administration of HCQ with a 51% improvement in mortality in
treated patients. This study has been accepted for publication but because of the expected media problems, it will only be published at the end of next week.

These results, in turn, suggest that of the more than 100,000 Americans who have lost their lives to the China virus, tens of thousands of them might have survived with an early treatment regime of hydroxychloroquine.

As a note, an accompanying safety study has been submitted for publication and further evidence to the safety of HCQ comes from the recent data from Wang and McKinnon, et.al. 2020 North American Consortium of Hydroxychloroquine Randomized Clinical Trials for Prevention of COVID-19: Release of Data Safety Monitoring Board Data. Submitted for peer review.

“Since March 17, 2020, a total of 1966 participants have been enrolled across the 7 RCTs. DSMB and independent review events were collected from these RCTs. To date, there have been no SAE, no deaths related to hydroxychloroquine. No study participant has required hospitalization due to the drug. There have been no significant adverse cardiovascular events”.


This is not simply anecdotal evidence and continuing accumulating data on HCQ continues to demonstrate its efficacy in improving clinical status in observational or randomized clinical trials for COVID-19 treatment modalities.

This also suggests that an even greater benefit might be obtained by using hydroxychloroquine as both a post-exposure and a pre-exposure prophylactic therapy for health care workers. Because of the uncertainties of the time of infection of secondary cases, the post-exposure individuals placed on hydroxychloroquine treatment may still become ill with COVID, but in the majority they should only require quarantine and general outpatient care.

Preliminary studies in India have prompted the Indian Council of Medical Research to state that the low-dose pre-exposure prophylactic administration of HCQ in healthcare workers, combined with the use of PPE, may provide a greater than 80% reduced chance of contracting COVID-19.10, 11, 12 Plans are now underway for the mass prophylaxis of 100,000 residents in the slum areas of Mumbai.

This is while further Early use data continues to appear. On 23 June 2020, Nigerian authorities in the National Capitol released a statement concerning their preliminary trials on the use of chloroquine and hydroxychloroquine for prophylaxis for COVID-19. Their studies will be expanded to encompass pre-exposure prophylaxis, post-exposure prophylaxis, and ambulatory as well as inpatient care.19
Finally, a small study is ongoing in a long-term care facility in Long Island, NY. This study has been employing HCQ + doxycycline rather than HCQ+AZ for treatment of high-risk Covid-19 patients. Doxycycline itself has antiviral activity against SARS-CoV-2 at in vitro concentrations 5.6μM median (30). Among the first 54 residents treated in the Long Island study, 6 were hospitalized and 3 (5.6%) died (31). An unofficial update of these data indicates that of about 200 high-risk patients treated with HCQ + doxycycline, 9 (4.5%) have died.

Non-randomized but controlled trials provide important evidence, if not “proof,” for the major efficacy of early use of HCQ+AZ against SARS-CoV-2 infection in symptomatic high-risk outpatients. What can be said about the uncontrolled large case series of treated patients? Standard published case reports provide clinical evidence of the possibility of an exposure-outcome relationship, but not of the regularity, magnitude or representativeness of such a relationship. The same can be said of case series reports, meaning that subject entry into the series is not necessarily well-defined and no denominator information is provided from which to gauge what the series represents. However, a large series in the context of known risks of mortality or adverse events can allow for ballpark estimates of the denominator and thus provide a reasonable frame of reference for whether the outcomes likely represent beneficial or harmful.3

Summary

A summary of the FDA’s reasons for the withdraw of its EUA for hydroxychloroquine are non-valid with respect to the Early Use effects of this drug in COVID-19. Let us comment on each of these points in some detail.

- The suggested dosing regimens for CQ and HCQ as detailed in the Fact Sheets are unlikely to produce an antiviral effect.

With respect to the studies on CQ and HCQ dosing regimens, the FDA letter refers to computer simulations of the plasma drug levels and extracellular tissue spaces. It is difficult to observe where these simulations take into account the slow and accumulative intracellular concentrations of both CQ and HCQ that vary with the length of time of drug administration, the prolonged ½ life of both drugs in the human body, as well as the prolonged length of time for various CQ / HCQ effects to physiologically appear and disappear after the cessation of drug intake.

Although simple diffusion may account for the entry of these drugs into the cell, there seems to be an as yet undescribed intracellular mechanism for retaining and concentrating chloroquine (CQ) and hydroxychloroquine (HCQ) inside the various human cell subtypes. Therefore, it is entirely probable that an effective antiviral end-point concentrations of these drugs in fact accumulate intracellularly to an effective therapeutic concentration under the current suggested dosing regimens for CQ and HCQ.
As with many of the drugs approved by the FDA for human use, the molecular mechanisms for the actions of chloroquine and hydroxychloroquine have not been fully elucidated, nor has the intracellular micro-molar concentrations of these drugs been well established inside the cell where these different and broad-range of physiological effects are taking place.

Both chloroquine and hydroxychloroquine have been described to be able to change the pH at the surface of the cell membrane, inhibit aspects of nucleic acid replication in some cases, interfere with the glycosylation of both receptor and some viral proteins in some viruses, and broadly modify new virus assembly, modify new virus particle transport, virus release, and other processes. Both drugs appear able to bind to the ACE-2 protein which serves as the CoV-2 viral receptor and interfere with the viral S protein’s ability to bind to gangliosides.

As the physiological effects are varied, so would the required minimum molar intracellular concentrations of HCQ be expected to also vary with respect to producing these different physiological effects, some of which would be considered antiviral.

If the suggested FDA dosing regimens for CQ and HCQ for COVID treatment are unlikely to produce an antiviral effect as the FDA now claims, then why has positive data been constantly accumulating with respect to pre-exposure HCQ prophylaxis and positive data accumulating concerning the very early use of hydroxychloroquine in COVID patients? Some of this data shows a dose-dependent effect with time.

• 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.

This sentence in the FDA letter refers to one type of anti-viral effect based on either treatment or as a result of the patient’s own immune system clearing active replicating viral particles from the body. However, the randomized studies that this FDA statement refers to, concerns the finding of viral PCR-amplified fragments in both active and convalescing COVID patients.

This is NOT live virus shedding and the failure of the negative conversion of a positive PCR result has absolutely nothing to do with a lack of viral clearance.

South Korea’s Center for Disease Control addressed this issue months ago when their scientists followed up with nearly 800 recovered patient personal contacts such as family members. They found no evidence that they had contracted the virus from the people who had a fresh positive PCR result. The scientists also tried to culture the virus in secretions from the recovered patients. They could not.

As a result of these findings, published online, the South Korean CDC no longer recommends that people in this situation be isolated. Their contacts do not need to be quarantined, though health officials do plan
to continue investigating cases of people who have tested positive again after having had a negative test. As a result of these findings, this study is shedding some light on the natural course of COVID-19 and the South Korean CDC published a notice:

As effective at 0:00 on 19 May 2020, the management of confirmed-PCR positive test after case discharge from isolation or the management of re-positive cases will no longer be conducted. Date 2020-05-19 @ 22:55m Update 2020-06-03 21:31 Korean Center for Disease control; Division of Risk assessment and International cooperation. Notice 2020-05-19 ~ 2020-12-31

These findings have been repeated in a Wisconsin study that is apparently still under peer review:

William R Hartman, Aaron S Hess, Joseph Connor. Prolonged viral RNA shedding after COVID-19 symptom resolution in older convalescent plasma donors medRxiv 2020.05.07.20090621; doi: https://doi.org/10.1101/2020.05.07.20090621

The prolonged persistence of virus PCR positivity in some COVID-19 cases seems to be normal and simply representative of the continued removal of non-viable genetic viral debris from the body of recovering individuals. To state that continued positive PCR results are indicative of a failure of live virus clearance demonstrates a profound misunderstanding of the COVID PCR test. The gold-standard for assuring viral clearance still remains the successful tissue culture isolation of live infective virus from a non-immunologically isolated body site.

These cell culture isolation studies were the standard used in the French papers that first related Chloroquine / HCQ to COVID viral clearance. PCR techniques were used later for simple convenience.

• 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.

What this sentence describes is that the FDA is using its own misconceived guidelines to make a recommendation for following the other misconceived guidelines emanating from the NIH.

By following these recommendations, the FDA is assuring that the narrow treatment window for maximum hydroxychloroquine effectiveness is missed. The requirement for hospitalization itself - ensures that many patients are already entering the second stage of the disease by the time they are given the drug.

Please note that several of the major peer-reviewed references still cited in the NIH COVID Treatment Panel Guidelines are papers that have never been peer reviewed. Several of these have now been debunked. Other papers cited by the NIH have serious flaws. One of these retracted papers is discussed on page 11 of this letter’s Memorandum but there is no mention of the fact it is still included in
the NIH guidelines. Why is this not mentioned? It should be added that the NIH Guidelines also still refer to the discredited VA study which the FDA apparently used to assess its issuance of a black box label. This paper has never been peer-reviewed and remains unpublished months later.

* 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.

Considering the timing of the FDA EUA withdraw letter and the FDA’s choice of the words “recent data,” it is assumed the FDA is referring to the now halted HCQ wing of the UK (Randomized Evaluation of COVID-19 Therapy RECOVERY) study, a trial with several major faults. This has already been discussed.

With respect to “recent data” the “recent” Ford study found at a STATISTICALY SIGNIFICANT level, that its hydroxychloroquine-alone group was associated with a significant lower mortality rate compared to patients not receiving hydroxychloroquine. While the mortality rate for the 487 patients in the control group receiving no medicine was 23.0%, it was 13.5% for the 1,234 patients receiving hydroxychloroquine alone.1

The findings translate into a 40% reduction in the mortality rate for patients receiving an early treatment based on hydroxychloroquine. Further data accumulated and analyzed has now brought this figure up to a 51% reduction in hospitalized COVID mortality.

As discussed, on 25 June 2020, the results of a large French Study finished peer review and was accepted for publication. This study, like the Ford Study, looked at 3,737 COVID-19 patients treated with EARLY TREATMENT with HCQ that demonstrated a mortality of 1.1% with an overwhelming effectiveness in preventing disease progression with an excellent safety profile in real-life medical experience. This is compared to the halted Oxford UK Study which had a mortality rate of 25%.

IHU-Marseille Research on 3,737 COVID-19 Patients Published
Finally, a recent meta-analysis of 20 available reports, including 105,040 patients has demonstrated that in clinical studies, chloroquine and its derivatives improve clinical and biological outcomes and reduce mortality by a factor 3 in COVID-19 patients.


This is not simply anecdotal evidence and continuing accumulating data on HCQ continues to demonstrate its efficacy in improving clinical status in observational or randomized clinical trials for COVID-19 treatment modalities. These results, in turn, suggest that thousands of Americans who have lost their lives to COVID-19, might have survived with an EARLY treatment regime of hydroxychloroquine.

This also suggests that an even greater benefit might be obtained by using hydroxychloroquine as both a post-exposure and a pre-exposure prophylactic therapy for health care workers. Because of the uncertainties of the time of infection of secondary cases, the post-exposure individuals placed on hydroxychloroquine treatment may still become ill with COVID, but in the majority they should only require quarantine and general outpatient care.

Preliminary studies in India have prompted the Indian Council of Medical Research to state that the low-dose pre-exposure prophylactic administration of HCQ in healthcare workers, combined with the use of PPE, may provide a greater than 80% reduced chance of contracting COVID-19.


- Revised advisory on the use of Hydroxychloroquine (HCQ) as prophylaxis for SARS-CoV-2 infection (in supersession of previous advisory dated 23rd March, 2020) India Council of Medical Research.

Plans are now underway for the mass prophylaxis of 100,000 residents in the slum areas of Mumbai.

This is while further Early use data continues to appear. On 23 June 2020, Nigerian authorities in the National Capitol released a statement concerning their preliminary trials on the use of chloroquine and hydroxychloroquine for prophylaxis for COVID-19. Their studies will be expanded to encompass pre-exposure prophylaxis, post-exposure prophylaxis, ambulatory and inpatient care.
In Brazil, an early use study involving outpatient 636 symptomatic outpatients, 412 started treatment with hydroxychloroquine and azithromycin and 224 refused medications (control group). Need for hospitalization was 1.9% in the treatment group and 5.4% in the control group (2.8 times greater) and number needed to treat was 28 (NNT = 28). In those who started treatment before versus after the seventh day of symptoms, the need for hospitalization was 1.17% and 3.2%, respectively.

The Ethics Committee approved study number - CONEP/Plataforma Brasil CAAE: 30586520.9.0000.0008 (Número Parecer:3.968.699) ClinicalTrials.gov Identifier: NCT04348474

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.

This is a completely false statement. If oral formulations of hydroxychloroquine are not effective in treating COVID-19, how do you explain the Detroit, French, South Korean, Indian, and other positive HCQ studies that have focused on the early use HCQ? The difference is in the early administration of the drug.

If hydroxychloroquine is such a dangerous drug, how does the FDA explain the large scale findings reported on 2 April 2020 by the Department of Pharmaco-and Device Epidemiology at the University of Oxford which found that Hydroxychloroquine had been shown to be a safe drug in over 130,000 patients. It should again be noted that that some of the short-term amplified doses of Hydroxychloroquine used in Lupus or RA patients with complications, are much higher than the doses proposed for use in early COVID-19 cases.

As discussed, further evidence to the safety of HCQ comes from the recent data from Wang and McKinnon, et.al. 2020 North American Consortium of Hydroxychloroquine Randomized Clinical Trials for Prevention of COVID-19: Release of Data Safety Monitoring Board Data. Submitted for peer review

“Since March 17, 2020, a total of 1966 participants have been enrolled across the 7 RCTs. DSMB and independent review events were collected from these RCTs. To date, there have been no SAE, no deaths related to hydroxychloroquine. No study participant has required hospitalization due to the drug. There have been no significant adverse cardiovascular events”.

Finally, in its BARDa letter, the FDA mentions the danger of several newly reported cases of methemoglobinemia in COVID-19 patients as further justification for its EUA withdraw and this needs to
be addressed. This was mentioned again later in the attached Memorandum to the BARDA letter, we believe it is important to address the question of Methemoglobinemia at this time.

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 criteria for issuance of an authorization are no longer met and is revoking EUA 039.

The FDA is treating several newly reported cases of methemoglobinemia in COVID-19 patients exposed to hydroxychloroquine, as a major concern and further grounds for an EUA withdraw. Methemoglobinemia is an adverse event which was not included in labeling for either Chloroquine or Hydroxychloroquine and it has now been reported in the setting of a few late stage hospitalized COVID-19 patients. This concern comes from a recent case series described in a short Correspondence Letter to the American Journal of Hematology on 15 May 2020:


This correspondence describes the occurrence of 3 cases of significant and 5 cases of mild methemoglobinemia in COVID-19 patients. The 3 serious cases comprised very ill late stage COVID patients; two with Acute Hypoxic Respiratory Failure requiring mechanical ventilation, one of whom received an in hospital diagnosis of inherited G6PD-deficiency, and one 52-year old male diabetic with signs of sepsis requiring invasive ventilation.

The condition Methemoglobinemia occurs when the iron molecule in the porphyrin group of heme is oxidized from its ferrous state. The most common causes of this are oxidizing reactions to cocaine-derived local anesthetics such as benzocaine and lidocaine, or to antibiotics such as dapsone and other sulfonamides, and to gases, such as nitric oxide or the run-off nitrates in well water. The administration of primaquine (PQ), an essential drug for the treatment of malaria, can lead to methemoglobin formation as well as life-threatening hemolysis in glucose-6-phosphate dehydrogenase-deficient patients.

Rare genetic methemoglobinemia predispositions are known to occur with high frequency in some small ethnic groups and rare autosomal recessive mutations of methemoglobin reductase or mutations in the CYBSR3 gene have been described, as well as rare mutations in the actual hemoglobin molecule.

Chloroquine and primaquine have been described as triggers for the presence of the heterozygous state methemoglobinemia. Out of the 9,087,000 military personnel who served on active duty during the
Vietnam Era, six cases of methemoglobinemia were described in American soldiers while taking antimalarial drugs. Investigations of these and two additional subjects revealed a genetically decreased concentration of NADH methemoglobin reductase in these individuals.


However, in spite of millions of doses of HCQ issued over the years, there was never an FDA label for methemoglobinemia for CQ or HCQ and to our knowledge, no reports methemoglobinemia in lupus, RA, or scleroderma patients on treatment with these drugs.

The United States has not seen a large pandemic involving the Cytokine Release Syndrome or “Cytokine Storm” since the H1N1 Influenza scenario in 1918. However, many lines of evidence indicate this syndrome plays a major role in the pathogenesis of late-stage SARS-CoV infection and death. Consequently we agree with Naymagon, Berwick, Kessler, et.al., that the dramatic increase in use of hydroxychloroquine in Late-Stage COVID-19 patients undergoing a Cytokine Release Syndrome, may make this a more common complication.

Although this same situation has been seen before in cases of sepsis that were not on hydroxychloroquine it is easily reasonable to agree that the level of critical illness and oxidative stress among many COVID-19 patients, leaves them more susceptible to medication-induced methemoglobinemia.


On the other hand however, hydroxychloroquine also appears to have a role in diminishing a developing vasculitis and “cytokine storm” in late COVID patients. This appears to occur by the drug’s ability to modulate IL-6, an interleukin molecule which appears central to this aspect of COVID pathogenesis.

We have already mentioned a recent paper (Not yet peer reviewed), where the measured level of IL-6 was significantly lowered in severely ill patients given HCQ (from 22.2 (8.3-118.9) pg/mL at the beginning of the treatment to 5.2 (3.0-23.4) pg/mL (p<0.05) at the end of the treatment) with no change in the untreated group.


Paradoxically, early-use HCQ in COVID-19 may actually be less likely to induce methemoglobinemia than its FDA-approved administration to late-stage COVID-19 patients as the data to date indicates
that early treatment with either CQ or HCQ may help prevent the progression of COVID to this critical, life-threatening state.

While indeed of legitimate concern in late COVID cases, we consider the repeated, isolated, mentioning of methemoglobinemia without context, as evidence that the FDA is desperate to intentionally undermine any suggestions that CQ and HCQ may have any role in the management of COVID-19. It seems that the FDA is grasping at straws to justify their case against hydroxychloroquine.

**Stephen Hahn Report to the House on 6/23/2020**

**Hahn Seeks Congressional Help To Advance Use Of Real-World Evidence**

*By Beth Wang / June 24, 2020 at 3:00 PM*

In his report to House lawmakers on Tuesday (June 23), the FDA chief Stephen Hahn said the COVID-19 pandemic has shed light on the need for increased use of real-world evidence to help regulators make decisions in real time, and he asked Congress to provide more support for advancing generation of RWE.

“We have an access-to-information issue,” Hahn told “We have learned that we need to collect real-world evidence in real time during an emergency just like a doctor would do during an emergency, to inform.....”

In reality, Dr. Hahn could have availed himself at any time as to what the “real world evidence” was saying about the use of HCQ.

In April the COVID-19 Task Force /FDA was sent a Memo outlining that EARLY use of HCQ was essential for managing COVID-19 patients. Director Hahn could have been briefed at any time on this “real world evidence”. Instead, he chose to place a Black Box warning on Chloroquine and Hydroxychloroquine, virtually restricting its use to hospitalized patients and guaranteeing that the clinical trials of this drug would fail, as they failed for remdesivir (for the patients that actually managed to stay on the drug without discontinuing side effects), and as they would fail for any antiviral drug given to late COVID patients. The pathophysiology is different in late COVID cases. The key is early antiviral treatment before the patients has a chance to start to develop the secondary pathophysiology, which can develop after day 7 from symptom onset and progress to a life support requirement within hours.

**Thousands of Americans have either died or are right now facing a preventable death because of the direct actions of the FDA and its now supposed issue of "Access to Real World Information."**

There are a number of other curious aspects to the FDA’s handling of the hydroxychloroquine issue which seems by design to effectively regulate its use to hospitalized patients which are near or outside the therapeutic window for hydroxychloroquine.
Unlike the rapid EUA for the experimental drug *remdesivir* which had no prior FDA approval, hydroxychloroquine required two months from the reports of its successful use in China and South Korea to get its March 28 FDA EUA for use in COVID-19 patients. Such a delay is inexcusable in a fast-moving pandemic.

Even more outrageous is that the granted EUA for HCQ did not, however, expand its availability, but rather imposed FDA restrictions to prevent non-hospitalized (and hence early-stage) patients from accessing the government’s stockpile of the drug.

The black border warning which was later applied to hydroxychloroquine is also curious. It is our understanding that FDA data shows only 62 cardiac deaths attributed to HCQ out of more than 50 million prescriptions, or 0.000124 percent (1.2 out of each 1 million Rx). Stated again, *Rheumatology Society guidelines for lupus and rheumatoid arthritis do not even require baseline electrocardiograms before prescribing HCQ, because the cardiac risk involved is so minimal.*

Given the scope of the potential of lives possibly being saved, it is critical that this nation move forward with emergency use of the hydroxychloroquine under the sanctity of the doctor-patient relationship. It is equally important that the medical community move briskly forward with the conduct of robust randomized, blinded, and controlled early treatment clinical studies. At present, however, both of these goals are being thwarted by the current climate of “Hydroxy Hysteria” among both patients and doctors as a result of the FDA’s poor decisions and lack of understanding of COVID-19 pathogenesis.

**Scope of Authorization Requested**

- It is essential that Physicians be allowed to prescribe HCQ, with or without antibiotic additions, after assessment of indications, contraindications and under reasonable dosages based on their clinical judgement.

- It is essential that studies evaluating HCQ for pre, post and early treatment, (including early hospital treatment) of HCQ be supported without the need for IND requirement as a limiting potential for studies to be initiated.

- A program of prophylactic HCQ based on the Indian and/or Henry Ford dosing rates should be initiated for all Health Care Workers that wish this and that do not have contraindications.

- Physicians or nurse practitioners / physician assistants, should be added to case-contact tracing teams and allowed to administer a post exposure treatment dose of Hydroxychloroquine with or without antibiotic supplementation to close contacts of infected patients.

- Hydroxychloroquine prophylaxis should be offered to all individuals who are in close contact with others during their normal daily activities, to include bus drivers, police, fire, EMS, first responders and other high-risk groups.
PRODUCTION OF DOCUMENTS PURSUANT TO SCHEDULE “I” OF THE SUBPOENA
DATED SEPTEMBER 23, 2021, SERVED UPON DR. STEVEN J. HATFILL, ADJUNCT
ASSISTANT PROFESSOR OF MICROBIOLOGY, IMMUNOLOGY, AND TROPICAL
MEDICINE, GEORGE WASHINGTON UNIVERSITY
Thursday, October 7, 2021
11:07 am Eastern Standard Time

Summary

1. The FDA seems to have failed to keep informed on the current literature and the basic 2-phase
pathogenesis of COVID-19. It has either ignored or failed to make accurate conclusions in the data
indicating the early use of hydroxychloroquine, instead has relied on its information from non-peer
reviewed publications and the unsubstantiated statements in the reporting by the Mainstream Media.

2. By insisting hydroxychloroquine be administered to only hospitalized patients, the FDA effectively
blocked any use of this drug during its narrow window for maximum effectiveness against COVID-19. This
has been apparent since mid-April in the scientific literature and from discussions with Intensive Care
physicians, and an April Memo to the COVID-19 Task Force outlined the need for Early-Treatment with
hydroxychloroquine.

3. The FDA’s inaccurate black box warning, not substantiated by real world data, helped to destroy patient
recruitment for urgent early-use hydroxychloroquine trials. Its recent withdraw of the EUA has effectively
blocked any further recruitment to conduct these necessary early-use trials.

4. These trials would have been characterized by the outpatient use of hydroxychloroquine where the
presenting patient was still ambulatory, did not require supplemental O2 to maintain their blood oxygen
saturation, with lesions in 3 or less lobes of the pulmonary system. The study goals were to prove that
HCQ could keep patients out of the ICU, off invasive mechanical ventilation, and reduce the associated
horrendous mortality rate associated with invasive ventilation in severe COVID-19 disease management.

In the last week of 1 July alone, 2 major U.S. studies by major medical systems (Ford in Detroit and Mt.
Sinai in NYC), have provided evidence for a 51% and 50% (respective) reduction in COVID mortality for
patients given hydroxychloroquine given in the very early phase of disease pathogenesis. A successful
French study of 3,737 early treatment cases was published, and Zelenko has released his successful
retrospective case series study. Serious cardiac events have not been a factor in these early use COVID
patient studies.

Hydroxychloroquine, Azithromycin, and Combination in Patients Hospitalized with
COVID-19. Int. Journ Inf Diseases Open Access Published: July 01, 2020
DOI:https://doi.org/10.1016/j.ijid.2020.06.099

- Mikami, T., Miyashita, H., Yamada, T. et al. Risk Factors for Mortality in Patients with
https://doi.org/10.1007/s11606-020-05983-z
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DATED SEPTEMBER 23, 2021, SERVED UPON DR. STEVEN J. HATFILL, ADJUNCT
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Thursday, October 7, 2021
11:07 am Eastern Standard Time

  Published at http://covexit.com/ihu-marseille-research-on-3737-covid-19-
patients-published/

- Scholz, M.; Derwand, 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).

Based on the totality of scientific evidence, including data from adequate and well-controlled clinical trials,

it is unreasonable to believe that the current HHS/NIH doctrine of individual case isolation until a patient

requires hospitalization, and then the initiation of hospital-based antiviral drug treatment in the LATE

stages of infection, may have any practical effect in halting the epidemiological spread and significantly

reducing the mortality rate associated with COVID-19 caused by the SARS-CoV-2 Virus.

This doctrine is in a complete contradiction to the United States National Pandemic Influenza Plan which

was to have served as the general guidance for management of an emerging pandemic respiratory RNA

virus. The decision by HHS and the NIH to recommend lockdown and quarantine while waiting for COVID

victims to develop shortness of breath and the onset of the more severe second phase of COVID-19

disease pathogenesis is not supported by the progressively accumulating early-treatment data that began

on 15 February 2020. (Table One).

The early use of hydroxychloroquine is not simply anecdotal data as claimed by Dr. Anthony Fauci, who

has openly opposed hydroxychloroquine use in spite of it already being an approved FDA drug. Oral

hydroxychloroquine represents a vital and proven part of the pandemic control strategy for COVID. Its

safety for early use COVID patients is backed by millions of doses already safely prescribed for patients in

a wide age range and varying co-morbidities suffering from connective tissue disorders over the last 50-

years.

The last hope for some degree of COVID-19 control lies with the initiation of physician-directed

hydroxychloroquine outpatient drug therapy, given within the first 7-days of patient symptoms, (Figure

2), as well as the pre-exposure prophylactic use of hydroxychloroquine in asymptomatic, uninfected, high-

risk Health Care Workers (HCW) and individuals with a high number of inter-personal contacts during their

normal daily activities.

Outside of this, there is only the future development of a vaccine for pandemic control and thousands of

Americans are going to lose their lives during this “immunization gap” with further catastrophic economic
damage to the Nation.
On a last topic, we note that the EUA withdraw was communicated to Gary L. Disbrow Ph.D., Deputy Assistant Secretary Director at BARDA by RADM Denise M. Hinton, Chief Scientist, Food and Drug Administration.

We assume that the Admiral convened a specialist panel of Physicians and Scientists to examine the hydroxychloroquine data before the FDA made its EUA recall, and we would welcome the chance at any time to meet with this panel to review the early-use hydroxychloroquine studies and discuss the latest pathophysiology of COVID-19.

For the reasons listed above, an Emergency Use Authorization is respectfully requested.

Dr. Steven Hatfill MD  June 30, 202

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