October 12, 2020

Dockets Management Branch Food and Drug
Administration Department of Health and Human Services
Room 10-61 5630 Fishers Lane
Rockville MD 20857

CITIZEN'S PETITION

The America's Frontline Doctors, Association of American Physicians and Surgeons and other petititoners, submit this petition pursuant to 21 C.F.R. § 10.30 (1999), to request that the Food and Drug Administration (FDA) switch from prescription to over-the-counter (OTC) status the FDA-approved drugs Plaquenil™ and any equivalent hydroxychloroquine sulfate based drug. Such a switch is authorized under 21 U.S.C. § 353(b)(3) and 21 C.F.R. § 310.200(b) because, as set forth below and in the supporting declaration of Dr. Simone Gold, hydroxychloroquine (HCQ) is safe and effective for OTC use. Accordingly, the FDA should grant this Petition and exempt HCQ from prescription dispensing limitations.

ACTION REQUESTED

Petitioners request that the FDA exempt from prescription-dispensing requirements, pursuant to 21 U.S.C. § 353(b)(3) and 21 C.F.R. § 310.200(b), Plaquenil™ and equivalent hydroxychloroquine sulfate based drugs.

STATEMENT OF GROUNDS

Under the Food, Drug and Cosmetic Act and FDA regulations, "[a]ny drug limited to prescription use...shall be exempted from prescription-dispensing requirements when the Commissioner finds such requirements are not necessary for the protection of the public health by reason of the drug's toxicity or other potentiality for harmful effect, or the method of its use, or the collateral measures necessary to its use, and he finds that the drug is safe and effective for use in self-medication as directed in proposed labeling.'' 21 C.F.R. § 310.200(b); see also 21
U.S.C. § 353(b)(3) ("The Secretary may by regulation remove drugs subject to sections 352(d) and 355 of this title from the requirements of paragraph (1) of this subsection when such requirements are not necessary for the protection of the public health."). FDA regulations also explicitly authorize the use of a citizen's petition to seek a switch from prescription to OTC status: "A proposal to exempt a drug from the prescription-dispensing requirements of section 503(b)(1)(C) of the act may be initiated by...any interested person....fil[ing] a petition...pursuant to Part 10 of this chapter... .'' 21 C.F.R. § 310.200(b).

Limiting HCQ to prescription use is not necessary for the protection of public health. As set forth in greater detail in the accompanying Declaration of Dr. Simone Gold, HCQ meets all the criteria for OTC availability. In general, an approved drug is suitable for OTC use when:

(I) the drug is safe for self-medication, 21 C.F.R. § 310.200(b)(1999); 21 C.F.R. § 330.10(a)(4)(i) (1999); Tamar Nordenberg, *Now Available Without a Prescription*, FDA Consumer 7, 9 (Nov. 6, 1996); Marian Segal, *Rx to OTC: The Switch is On*, www.fda.gov/bbs/topics/consumer/ CN00012c.html (March 1991); R. William Soller, "*OTCness*", 32 Drug Information Journal 555, 556-58 (1998); Debra L. Bowen, *Making the Switch to OTC*, III Cosmetics & Toiletries 102 (May 1996); Nancy L. Buc, *The Switch from Prescription to Over the Counter, in* The Pill: From Prescription to Over the Counter 237, 238-39 (eds. Samuels & Smith 1994); (2) the drug is effective when self-administered, 21 C.F.R. § 310.200(b)(1999); 21 C.F.R. § 330.10(a)(4)(ii)(1999); Soller, *supra* at 556, 558-59; Bowen, *supra*; Buc, *supra*; Nordenberg, *supra* at 7; (3) the condition to be treated is self-diagnosable, Segal, *supra*; Bowen, *supra*, Buc, *supra*; and (4) the drug's labeling is tailored to self-administration, 21 C.F.R. § 310.200(b)(1999); 21 C.F.R. § 330.10(a)(4)(v)(1999); Soller, *supra*, at 559-60; Segal, *supra*; Bowen, *supra*; Buc, *supra*; Nordenberg, *supra* at 7-8, 9, 11.

First, HCQ is safe for self-medication because it is not toxic in adults, including in pregnant or breastfeeding women; it has a low risk of abuse or overdose; overdose is unlikely to lead to serious consequences; and its side effects are minor and well-known after greater than 65-years of FDA-approved use.

Second, HCQ is effective when self-administered, as its administration is simple and relies only on the person's assessment of potential exposure to persons infected with SARS-CoV-2, which can be determined without consulting a physician.

Third, any interaction between low-dose HCQ and other drugs would be unlikely to seriously affect HCQ's efficacy or a person's well-being. HCQ is one of the most prescribed medications in the USA with an estimated five million prescriptions annually and is routinely prescribed to persons taking a plurality of prescription medications for other ailments.

Fourth, the patient labeling for HCQ can be easily tailored to self-administration in simple, clear and comprehensive instructions as it requires only once per week dosing of 2 pills (400 mg). Finally, because contacting a physician and obtaining and filling a prescription hinder people from obtaining HCQ in a timely fashion which is critical, making HCQ available OTC will allow more people to use it for prophylaxis of COVID-19.

Finally, the condition HCQ treats—exposure prophylaxis to COVID-19—is widespread resulting in unnecessary deaths, long-lasting disease sequelae, excessive burdens on hospital systems, trepidation among healthcare workers, teachers and first responders, mandated lockdowns, social isolation, loss of education from indefinite school closures and, ultimately, restriction on the American way of life never seen before in the nearly 250 years since the USA was founded.

Switching HCQ to OTC status will promote public health because it will decrease hospitalizations and deaths from COVID-19 and decrease the transmission of SARS-CoV-2. This allows better protection from SARS-CoV-2 infection for teachers, healthcare

personnel, police force, and the hundreds of other occupations in disarray due to employee quarantines and mandatory lockdowns. Accordingly, America's Frontline Doctors and the Association of American Physicians and Surgeons as well as hundreds of board-certified physicians have publicly supported efforts to make HCQ widely available. Because limiting HCQ to prescription dispensing is not necessary for the protection of public health, the FDA should exempt it from that limitation. 21 C.F.R. § 310.200(b) (a drug "shall be exempted from prescription-dispensing requirements when the Commissioner finds such requirements are not necessary for the protection of the public health").

ENVIRONMENTAL IMPACT

The proposed action is exempt from the requirement of an environmental impact statement under 21 C.F.R. §§ 25.24(a)(8) and (c)(6).

ECONOMIC IMPACT

The economic impact from COVID-19 is nearly unprecedented, resulting in record numbers of unemployment claims, permanent closure of over one hundred thousand small businesses, and losses in billions of dollars for surviving businesses. To combat this economic destruction, bailout loans and stimulus packages in the amount of over three trillion dollars were approved by the federal government. With the potential of a second wave of SARS-CoV-2 infections in the rapidly approaching flu season, it is possible for the above destruction to dramatically worsen with disastrous, long-lasting consequences for the American economy and value of the US dollar.

CERTIFICATION

America's Frontline Doctors and the Association of American Physicians and Surgeons counsel for petitioners certifies that, to the best of its knowledge and belief, this petition includes all information and views on which the Petition relies. The petitioners know of no data unfavorable to the petition.

PETITIONERS

1. Simone Gold, MD, JD, Founder, America's Frontline Doctors
2. James Todaro, MD, Investigative Physician, America's Frontline Doctors
3. Richard Urso, MD, Science Liason, America's Frontline Doctors
4. Paul M. Kempen, MD, PhD, President, AAPS
5. Jane M. Orient, MD, Executive Director, AAPS
6. Brian Tyson, MD
7. Lionel Lee, DO
8. Brian Procter McKinney, MD
9. Dennis Spence, MD
10. Robin Armstrong, MD

Declaration of Simone Gold, MD, JD

1. I am a board-certified emergency medicine physician with a dual medical and law degree. I am licensed to practice in California and am clinically active. I serve as the founder of America's Frontline Doctors and have been treating COVID-19 patients since March 2020.

2. In the past eight months, there has been mounting evidence that hydroxychloroquine (HCQ) is effective for prophylaxis and early treatment of COVID-19. Prophylaxis consists of two doses taken simultaneously once per week (400mg per week).

3. I write to advocate an immediate switch of these regimens from prescription to over-the-counter (OTC) status. My reasoning is based on two considerations: first, the prescription requirement limits access to HCQ, which prevents effective use of the treatment, and second, no medical justification exists for maintaining prescription status.

4. COVID-19 is a major public health problem in the United States. As of today, there have been over seven million confirmed cases of COVID-19. The number of US deaths from COVID-19 is stated to be over 200,000. This does not account for the unprecedented rise in deaths from suicide, drug overdoses and domestic violence as a result of mandated lockdowns, stay-at-home orders and financial stressors in a shuttered economy. The public health problem extends even further on down to our children. With school closures, suspension of games/sports/activities and stay-at-home orders, children of all ages were suddenly thrown into social isolation and confinement during a critical time of their growth and maturity. The psychological consequences of social isolation and persistent fear from an invisible disease in millions of children across the country will likely haunt parents, therapists and public health experts for years to come.

5. HCQ has the potential to reduce the transmission of SARS-CoV-2 as well as reduce hospitalizations and deaths from COVID-19. As a prophylactic, HCQ may prevent up to 75% of individuals from becoming infected with SARS-CoV-2. This can be an additional layer of protection for not just healthcare workers and first responders, but also for the American people as they go back to work. Early treatment with HCQ can decrease viral load, hospitalization and mortality. By decreasing viral load, there will be a decreased chance and shorter period of time that an infected person can transmit the disease to healthy persons. By reducing need for hospitalization, hospital systems will be less likely to become overwhelmed with COVID-19 patients—effectively "flattening the curve" without the need for lockdowns and stay-at-home orders. Lastly, HCQ will decrease mortality, particularly in older vulnerable populations such as those in nursing homes.

6. These benefits can be realized, however, only if Americans have ready access to the therapy. For best results, it is critical that prophylaxis is started immediately after or even before exposure and that early treatment is initiated immediately upon symptom onset. Any delay reduces efficacy, leading to an increased risk of prophylaxis or treatment failure and consequent unnecessary infection, hospitalization or death.

7. Prescription status is a major barrier to access to HCQ. Patients are often unable to see or contact a health care provider quickly to obtain a prescription, especially on weekends and in evenings. Removing the prescription requirement and allowing the purchase of HCQ directly over the counter is the most expedient way to ensure that people can obtain and use them immediately after exposure to COVID-19 or symptom onset.

8. In addition, prescription status is medically unwarranted. Both HCQ regimens fulfill all the customary criteria for over-the-counter distribution:

A. Low toxicity. The last medication granted OTC status from a citizen's petition—oral contraceptive pills—had been used in varying hormonal formulations by tens of millions of women for over three decades. This history of use pales in comparison to hydroxychloroquine. Quinine has been used since the 1600s when it was first used to treat malaria in Rome. A derivative of quinine, hydroxychloroquine was first synthesized in the 1940s, approved by the FDA since 1955 and on the World Health Organization's list of safe, essential medicines for decades. Billions of doses have been taken worldwide with over five million annual prescriptions in the USA alone.

Given its known safety profile, in many parts of the world, HCQ is already available OTC, including in Mexico and Iran. It is well tolerated in the vast majority of patients and is prescribed in healthy persons for malaria prophylaxis. It is also a first line treatment option for autoimmune disorders such as rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE). Rheumatologists have referred to hydroxychloroquine as the equivalent of a "daily multivitamin for people with mild to moderate lupus." Moreover, COVID-19 prophylaxis dosages are considerably lower than those used in treatment of RA or SLE—about $1/7^{th}$ to $1/10^{th}$ the weekly dose given for those autoimmune disorders.

The most common side effects include gastrointestinal distress, headache and itching. Ocular adverse effects are rare with HCQ primarily only a risk factor for retinal toxicity after approximately five years of daily consumption of at least 400mg. Cardiac adverse effects are also rare with only a handful of drug-related deaths due to cardiovascular issues among millions of patients over decades. In the largest study to date on the subject, HCQ has been shown to not increase heart (cardiac) risk.

Hydroxychloroquine is commonly prescribed to all members of the population, including children, the elderly, and pregnant and breastfeeding women. HCQ is certainly safer than many drugs currently sold over the counter in the United States. For example, hundreds of deaths, over 50,000 emergency room visits and about 2,500 hospitalizations occur annually in the USA from overdoses of acetaminophen (e.g. Tylenol) alone. To allow unrestricted access to Tylenol while requiring a physician's prescription for HCQ makes no sense.

B. Low potential for overdose and no potential for addiction. Death from overdose of hydroxychloroquine is exceedingly difficult to do. It is so rarely toxic that there are only isolated case reports of toxicity. A 2007 study published in Hong Kong reviewed the literature up until that time, and when death occurred it required extraordinarily large

amounts such as 10, 12, 14, or 20 grams. Even with these extreme amounts, the result typically was *not* fatal. In the USA such dosages would require an ingestion of 50 to 100 tablets. This must be compared to acetaminophen (Tylenol), which is sold over the counter in unlimited lethal quantities. Medlineplus.gov states that 14 ES-Tylenol tablets in a day would be a severe overdose and 40 extra-strength Tylenol would be fatal, but nonetheless, it is routinely sold everywhere in bottles of 100 and Costco even sells them in bottles of 400 pills. HCQ is not addictive.

C. No teratogenicity or danger in pregnant or breastfeeding women. Extensive studies over decades have confirmed that use of HCQ during pregnancy carries no risk of damage to an embryo and no risk of damage to infant during breastfeeding.

D. No contraindications requiring screening by a medical professional. The package label for HCQ approved by the FDA list a number of contraindications. However, none of these contraindications are supported by medical evidence for low-dose prophylaxis with HCQ. These contraindications are more relevant for higher doses given in treatment of RA and SLE given continuously for many months or years.

E. No need for screening to recognize indication for therapy. The only indication for use of HCQ is exposure to SARS-CoV-2. Identification of this indication does not require professional expertise.

F. No need for professional monitoring of treatment. Although the half-life of HCQ is about one month, there is little accumulation in prophylactic doses that are about $1/10^{th}$ the amount commonly prescribed for autoimmune disorders. If HCQ prophylaxis fails, the individual will eventually recognize on her own that she has symptoms of a respiratory illness and seek medical help. Professional monitoring will neither reduce the incidence of side effects nor increase the efficacy of therapy and is unnecessary.

G. Same dose for all adults. HCQ prophylaxis consists of two equal doses taken simultaneously once a week. Because this dose is applicable to everyone, professional expertise is not needed to determine the correct dose. In this respect, HCQ is much simpler than medications currently sold over the counter which require tailoring of dose based on patient characteristics (such as age) or therapeutic response.

H. Simplicity of prophylaxis regimen. The instructions for use of HCQ is straightforward: take two doses prior to or immediately after potential exposure to SARS-CoV-2 and continue to do so weekly while the exposure continues. Consumers regularly follow much more complicated instructions for other over-the-counter medications by reading the package
label.

I. No important drug interactions. Evidence suggests that the efficacy of HCQ may be reduced by concomitant use of certain medications. However, no conclusive information is available on how or even whether the HCQ dose should be adjusted for individuals taking these drugs. The prescription requirement for HCQ does not resolve the problem posed by

this lack of knowledge. Once data on this matter becomes available, labeling of HCQ could be modified to advise persons taking these drugs to alter the HCQ dose appropriately or to consult their physicians.

9. In summary, the requirement for a prescription to obtain HCQ hurts the health of all Americans by posing an unnecessary obstacle to the prompt, effective use of this important therapy. This requirement directly contributes to the COVID-19 epidemic. These outcomes are both antithetical to the mission of the FDA and damaging to public health. No medical reason exists to maintain prescription status for HCQ, as professional intervention is not necessary to ensure safe and correct use. Following the primary principle of medical care "first, do no harm," the prescription requirement for HCQ should be dropped.

I declare under penalty of perjury that the foregoing is true.

Simone Gold

Simone Gold, MD, JD

REFERENCES

1. American College of Rheumatology. No pre-starting medication monitoring. Widely used/safe. : https://www.rheumatology.org/Portals/0/Files/Hydroxychloroquine-Plaquenil-Fact-Sheet.pdf?ver=2020-04-30-154904-073

2. Multi-national database almost one million cases of HCQ use. Conclusion: No excess risk of serious adverse events identified with 30-day usage. Short term HCQ treatment is safe. https://www.medrxiv.org/content/10.1101/2020.04.08.20054551v2

> This is the largest ever analysis of the safety of such treatments worldwide, examining over 900,000 HCQ and more than 300,000 HCQ + azithromycin users respectively. The results on the risk of serious adverse events associated with short-term (1 month) HCQ treatment as proposed for COVID-19 therapy are reassuring, with no excess risk of any of the considered safety outcomes compared to an equivalent therapy.

3. The FDA database shows a total of 640 deaths attributable to HCQ over fifty years. To put this in context "Each year the FDA receives over one million adverse event reports associated with the use of drug products" "This concerns the entirety of HCQ use over more than 50 years of data, likely millions of uses and of longer-term use than the five days recommended for Covid-19 treatment." The 640 deaths represented 0.034% of all the deaths (1,910,212) attributable to medications. https://fis.fda.gov/sense/app/d10be6bb-494e-4cd2-82e4-0135608ddc13/sheet/7a47a261-d58b-4203-a8aa-6d3021737452/state/analysis and https://academic.oup.com/aje/advance-article/doi/10.1093/aje/kwaa093/5847586

4. The CDC has an information sheet about HCQ. That sheet includes the following questions/answers. https://www.cdc.gov/parasites/malaria/index.html

Q: Who can take hydroxychloroquine?
A: Hydroxychloroquine can be prescribed to adults and children of all ages. It can also be safely taken by pregnant women and nursing mothers.

Q: Who should not take hydroxychloroquine?
A: People with psoriasis should not take hydroxychloroquine.

Q: What are the potential side effects of hydroxychloroquine?
A: Hydroxychloroquine is a relatively well tolerated medicine. The most common adverse reactions reported are stomach pain, nausea, vomiting, and headache. These side effects can often be lessened by taking hydroxychloroquine with food. Hydroxychloroquine may also cause itching in some people.

Q: How long is it safe to use hydroxychloroquine?
A: CDC has no limits on the use of hydroxychloroquine for the prevention of malaria. When hydroxychloroquine is used at higher doses for many years, a rare eye condition called retinopathy has occurred. People who take hydroxychloroquine for more than five years should get regular eye exams.

5. A Case of Fatal Hydroxychloroquine Overdose.
https://hkcem.com/html/publications/Journal/2007-1/2007_1_p53-57.pdf