Simone Gold, MD, JD
America's Frontline Doctors
2934 1/2 Beverly Glen Circle #314
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November 16, 2022

Re: Docket No. FDA-2020-P-2066

Dear Dr. Gold:

This letter responds to your citizen petition (Petition) received on October 13, 2020. In the Petition, you request that the Food and Drug Administration (FDA, Agency, or we) "switch from prescription to over-the-counter (OTC) status the FDA-approved drugs Plaquenil™ and any equivalent hydroxychloroquine sulfate based drug."[1] Specifically, you ask FDA to "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"[2] to enable "more people to use [these drug products] for prophylaxis of COVID-19 [Coronavirus Disease 2019]."[3]

We have carefully considered the Petition and other information available to us. For the reasons stated below, the Petition is denied. We note, however, that we evaluate marketing applications for drug products on a case-by-case basis. Sponsors interested in exploring drug product development can meet with us to discuss development of the data necessary to support such applications.

I. BACKGROUND

A. Plaquenil

Plaquenil (hydroxychloroquine sulfate) (NDA 009768) is an antimalarial and antirheumatic indicated for the:

- Treatment of uncomplicated malaria due to *Plasmodium falciparum*, *Plasmodium malariae*, *Plasmodium ovale*, and *Plasmodium vivax* in adult and pediatric patients
- Prophylaxis of malaria in geographic areas where chloroquine resistance is not reported in adult and pediatric patients
- Treatment of rheumatoid arthritis in adults
- Treatment of systemic lupus erythematosus in adults
- Treatment of chronic discoid lupus erythematosus in adults[4]

[1] Petition at 1.
[2] Id.
[3] Id. at 2.
[4] See labeling for Plaquenil, NDA 009768, supplement 0056.

Plaquenil was first approved under a new drug application (NDA) in the United States on April 18, 1955. Plaquenil (hydroxychloroquine sulfate) is available as a 200 milligram (mg) tablet. Currently, there are two approved NDAs and multiple abbreviated new drug applications (ANDAs) for tablets containing hydroxychloroquine sulfate in different strengths.[5] Plaquenil and the other approved tablets containing hydroxychloroquine sulfate are available by prescription.

The approved labeling for Plaquenil and the other approved tablets containing hydroxychloroquine sulfate include numerous warnings and precautions regarding its use for the approved indications, including the following:

- fatal or life-threatening cardiomyopathy and ventricular arrhythmias
- retinal toxicity
- serious skin reactions
- worsening of psoriasis and porphyria
- hematologic toxicity
- renal toxicity
- skeletal muscle myopathy or neuropathy
- neuropsychiatric reactions including suicidality
- hypoglycemia[6]

Other important risk information for Plaquenil and the generic versions of Plaquenil, including drug interactions, are available in the approved labeling.

On March 28, 2020, FDA granted an emergency use authorization (EUA) to allow 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.[7] On June 15, 2020, FDA revoked this EUA after determining that the legal criteria for issuing an EUA were no longer met.[8] FDA has not approved any prescription or nonprescription drug products containing hydroxychloroquine sulfate for use in the prophylaxis of SARS-CoV-2/COVID-19.

B. COVID-19

An outbreak of an infectious respiratory disease caused by a novel coronavirus began in December 2019 and was declared a public health emergency in the United States on January 31,

[5] Search results can be obtained by using FDA's *Approved Drug Products with Therapeutic Equivalence Evaluations* (the Orange Book), which is available online at https://www.accessdata.fda.gov/scripts/cder/ob/index.cfm.
[6] See footnote 4. See also labeling for Hydroxychloroquine Sulfate, NDA 214581.
[7] See *Coronavirus (COVID-19) Update: FDA Revokes Emergency Use Authorization for Chloroquine and Hydroxychloroquine*, dated June 15, 2020, available at https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-revokes-emergency-use-authorization-chloroquine-and.
[8] See *Memorandum Explaining Basis for Revocation of Emergency Use Authorization for Emergency Use of Chloroquine Phosphate and Hydroxychloroquine Sulfate*, dated June 15, 2020.

2020,[9] and a national emergency on March 13, 2020.[10] The virus is named "SARS-CoV-2" and the disease it causes is named "Coronavirus Disease 2019" (COVID-19).[11] COVID-19 most often causes respiratory symptoms that can feel much like a cold, a flu, or pneumonia.[12] COVID-19 may affect other parts of the body besides the lungs and respiratory system. Most people infected with COVID-19 have mild symptoms, but some people become severely ill requiring hospitalization.[13] There have been more than one million deaths involving COVID-19 in the United States.[14] In addition, some people who have been infected with COVID-19 can experience long-term effects from their infection.[15]

Patients today have a variety of treatment options for COVID-19. FDA has approved two drug treatments for COVID-19 and has authorized others for emergency use during this public health emergency. Specifically, FDA has approved the antiviral drug Veklury (remdesivir) for certain adult and pediatric patients with COVID-19 and the immune modulator Olumiant (baricitinib) for certain hospitalized adults with COVID-19.[16] In addition, more therapies are being tested in clinical trials to evaluate whether they are safe and effective against COVID-19.

During public health emergencies, FDA may authorize the use of unapproved drugs or unapproved uses of approved drugs under certain conditions by issuing an EUA under section 564 of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 360bbb-3), after the requisite declaration has been made under section 564(b)(1) of the FD&C Act. FDA has a responsibility to regularly review the appropriateness of an EUA and to revise or revoke an EUA when appropriate to do so under section 564(g)(2) of the FD&C Act.

FDA issued EUAs for two oral antiviral pills, Paxlovid and Lagevrio (molnupiravir), for certain patients with mild-to-moderate COVID-19.

In addition, multiple FDA-approved or authorized vaccines for COVID-19 are widely available in the United States.[17] Available evidence suggests that the currently approved or authorized

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[9] See Secretary of Health and Human Services Alex M. Azar II, *Determination that a Public Health Emergency Exists*, dated January 31, 2020, available at https://www.phe.gov/emergency/news/healthactions/phe/Pages/2019-nCoV.aspx.

[10] See *Declaring a National Emergency Concerning the Novel Coronavirus Disease (COVID-19) Outbreak*, Federal Register (85 FR 15337, March 18, 2020).

[11] *Proclamation on Declaring a National Emergency Concerning the Novel Coronavirus Disease (COVID-19) Outbreak*, March 13, 2020, available at https://www.whitehouse.gov/presidential-actions/proclamation-declaring-national-emergency-concerning-novel-coronavirus-disease-covid-19-outbreak/.

[12] See Centers for Disease Control and Prevention, *Basics of COVID-19*, available at https://www.cdc.gov/coronavirus/2019-ncov/your-health/about-covid-19/basics-covid-19.html.

[13] See id.

[14] See Centers for Disease Control and Prevention, *Weekly Updates by Select Demographic and Geographic Characteristics*, accessed November 15, 2022, available at https://www.cdc.gov/nchs/nvss/vsrr/covid_weekly/index.htm.

[15] [15] See Centers for Disease Control and Prevention, *Long COVID or Post-COVID Conditions*, available at https://www.cdc.gov/coronavirus/2019-ncov/long-term-effects/index.html.

[16] See FDA's *Coronavirus (COVID-19) Drugs*, available at https://www.fda.gov/drugs/emergency-preparedness-drugs/coronavirus-covid-19-drugs.

[17] See FDA's *COVID-19 Vaccines*, available at https://www.fda.gov/emergency-preparedness-and-response/coronavirus-disease-2019-covid-19/covid-19-vaccines#authorized-vaccines.

COVID-19 vaccines are highly effective at preventing hospitalization and death for a variety of COVID-19 strains.[18]

II. LEGAL AND REGULATORY FRAMEWORK

A. New indication for an approved drug product

The FD&C Act and FDA regulations require that a person seeking to market a new drug, including a new indication for an approved drug, submit an application to FDA for review, in addition to paying any applicable user fee.[19] To be approved, an NDA submitted under section 505(b) of the FD&C Act must, among other things, be supported by investigations showing the drug product to be safe and effective for its intended use(s).[20]

Section 505(d) of the FD&C Act (21 U.S.C 355(d)) and FDA's regulation in 21 CFR 314.125(b) provide grounds for refusing to approve an application. FDA will refuse to approve an application if, among other grounds, the applicant fails to provide substantial evidence of effectiveness for the drug for its intended use(s) and adequate tests showing the drug is safe for use under the conditions in the proposed labeling.

FDA reviews new indications and new dosage information for currently approved drug products under its new drug approval process. As described above, the Petition requests that FDA approve Plaquenil and any equivalent hydroxychloroquine sulfate-based drug for over-the-counter use "for prophylaxis of COVID-19."[21] Plaquenil and the ANDAs that reference Plaquenil are not currently approved for this indication.

To support the addition of a new indication to a drug product's FDA-approved labeling, the holder of the NDA for the drug product would submit a supplemental application requesting a new indication.[22] FDA would approve a supplemental application only if the Agency finds that the drug product is safe and effective for the proposed indication.[23]

Only the holder of an approved application may submit a supplement to an application.[24] Therefore, if the person seeking a new indication for an approved drug product is not the

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[18] See Centers for Disease Control and Prevention, *Science Brief: COVID-19 Vaccines and Vaccination*, available at cdc.gov/coronavirus/2019-ncov/science/science-briefs/fully-vaccinated-people.html.
[19] Section 505(a) of the FD&C Act (21 U.S.C. 355(a)), 21 CFR part 314, and section 736(a)(1) of the FD&C Act.
[20] See § 314.50 (d)(5) (21 CFR 314.50(d)(5)).
[21] Petition at 2.
[22] §§314.71(b) and 314.50(d)(5). See also FDA final guidance, *Submitting Separate Marketing Applications and Clinical Data for Purposes of Assessing User Fees* (Dec. 2004), at 6. We update guidances periodically. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.
[23] See section 505(d) of the FD&C Act.
[24] §314.71(a).

application holder for the drug, that person would need to submit a separate, original application for approval of a new drug with the new indication.[25]

To support a finding of safety and effectiveness for a new indication, FDA would require, among other information, that an applicant provide adequate clinical data to support the new indication. The clinical studies must show effectiveness of the drug for the proposed indication and the application (original application or supplemental application) generally would contain complete, primary data that support a determination that the studies were adequately designed and conducted.[26] The study data should be capable of independent substantiation.[27]

B. Marketing Nonprescription Drug Products

As set forth in section 503(b)(l) of the FD&C Act (21 U.S.C. 353(b)(l)), a prescription drug is:

> a drug intended for use by man which (a) because of its toxicity or other potentiality for harmful effect, or the method of its use, or the collateral measures necessary to its use, is not safe for use except under the supervision of a practitioner licensed by law to administer such drug; or (b) is limited by an approved application under section 505 to use under the professional supervision of a practitioner licensed by law to administer such drug…

Under section 503(b) of the FD&C Act, a drug that is not safe for use except under the supervision of a practitioner licensed by law to administer the drug may be dispensed by prescription only. Drugs that do not meet the description set forth in section 503(b)(l) of the FD&C Act are nonprescription drugs. To be nonprescription, a particular drug must be determined by FDA to be safe and effective for use without the supervision of a licensed healthcare practitioner.[28]

Under the FD&C Act and FDA's regulations, a drug product can be made available without a prescription pursuant to an approved NDA under section 505 of the FD&C Act.[29, 30] As part of such an application, the applicant must submit data to satisfy the applicable statutory and regulatory requirements for approval of a new drug application. An NDA must include adequate tests to show that the drug is safe for use under the conditions prescribed, recommended, or

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[25] An application under section 505(b)(1), also called a "stand-alone NDA," requires that the application contain, among other information, "full reports of investigations" to show that the drug is safe and effective for its intended use.

[26] See § 314.126.

[27] The Agency has described the type of documentation it recommends for ensuring the adequacy of the scientific evidence in the draft guidance for industry entitled *Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products* (December 2019), as well as the preceding, related final guidance *Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products* (May 1998). When finalized, the draft guidance will represent FDA's current thinking on this topic but will supplement, not replace, the 1998 guidance. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/regulatoryinformation/search-fda-guidance-documents.

[28] See section 503(b) of the FD&C Act.

[29] See section 505(b) and (G) of the FD&C Act.

[30] We also note that products marketed in compliance with an OTC monograph and other applicable requirements are not required to have approved NDAs.

suggested in the proposed labeling,[31] and there must be substantial evidence that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling.[32] A drug product may be approved as a prescription or nonprescription product, or may be switched from prescription to nonprescription status, under the applicable legal and regulatory standards. The prescription-to-nonprescription switch process is described in further detail below.

C. Prescription-to-Nonprescription Switch

Section 503(b)(3) of the FD&C Act states, "The Secretary may by regulation remove drugs subject to section 505 from the requirements of paragraph (1) of this subsection when such requirements are not necessary for the protection of the public health." FDA's regulations in § 310.200 (21 CFR 310.200) identify processes for initiating consideration of a prescription-to-nonprescription switch. Under § 310.200, the Commissioner must make a twofold finding before exempting a drug product with an approved NDA from prescription status. First, the Commissioner must find that the prescription-dispensing 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."[33] Second, the Commissioner must find that the drug is "safe and effective for use in self-medication as directed in proposed labeling."[34] A proposal to exempt a prescription drug from prescription-only requirements can be initiated by the drug sponsor submitting an application or by a third party petitioning FDA to initiate rulemaking pursuant to section 503(b)(3) of the FD&C Act.[35]

III. DISCUSSION

A. New indication for an approved drug product

The Petition requests that FDA approve Plaquenil and any equivalent hydroxychloroquine sulfate-based drug for over-the-counter use "for prophylaxis of COVID-19."[36] Plaquenil and the approved drug products that contain hydroxychloroquine sulfate are not currently approved for this indication. FDA interprets the Petition to be requesting the approval of a new indication "prophylaxis of COVID-19" for Plaquenil. The Petitioner is neither the holder of the Plaquenil application nor any other approved application for a drug product containing hydroxychloroquine sulfate.

As explained above, only the holder of an approved application may submit a supplemental application requesting a new indication.[37] A person seeking a new indication for an approved drug product, who is not the application holder for the drug, must submit a separate, original application requesting approval of a new drug with the new indication.[38]

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[31] See section 505(d)(l) and (2) of the FD&C Act.
[32] See section 505(d)(5) of the FD&C Act.
[33] § 310.200(b).
[34] Id.
[35] ld.; 21 U.S.C. 353(b)(3).
[36] Petition at 2.
[37] §§314.71(b) and 314.50(d)(5).
[38] See section 505(b)(1)-(2) of the FD&C Act.

FDA denies your request for approval of the new indication, prophylaxis of COVID-19, for Plaquenil because a petition to FDA under 21 CFR 10.30 is not the correct procedure to request approval of a new indication for an approved application. In addition, this Petition does not constitute a new drug application that FDA can evaluate to determine whether the approval standard for a new drug application has been met.[39] We note, however, that we evaluate marketing applications for drug products on a case-by-case basis. Sponsors interested in exploring drug product development can meet with us to discuss development of the data necessary to support such applications. We further note that the Petition did not provide evidence that supports the safety or effectiveness of Plaquenil when used for prophylaxis of COVID-19.

B. Prescription-to-Nonprescription Switch

To initiate a prescription-to-nonprescription switch of the type requested by your Petition, FDA would also need sufficient data to support the safe and effective nonprescription use of Plaquenil and the equivalent hydroxychloroquine sulfate approved drug products. Your Petition, however, does not present such data. Moreover, the arguments in your Petition are insufficient to persuade FDA to initiate rulemaking for a switch of Plaquenil and the equivalent hydroxychloroquine sulfate approved drug products at this time. Consequently, your Petition is denied.

FDA will continue to monitor and review new studies and data, as they become available regarding Plaquenil and the equivalent hydroxychloroquine sulfate approved drug products. We are open to evaluating marketing applications for drug products for nonprescription use.

1. Evidence Needed to Support a Prescription-to-Nonprescription Switch

Data to support a prescription-to-nonprescription switch generally come from the following sources: (1) safety and effectiveness data in an original NDA for the prescription drug; (2) other available safety and effectiveness data;[40] and (3) data from trials conducted to support an NDA supplement for nonprescription use (e.g., actual use, self-selection, and label comprehension studies). Often, consumer studies are required to demonstrate that products can be used safely and effectively in a nonprescription setting. Actual use, self-selection, and label comprehension studies may be required to evaluate proposed nonprescription drug product labeling and to demonstrate that the drug is safe and effective for use in self-medication, as directed in proposed labeling as required under § 310.200(b).[41] In addition, consumer studies are generally required when, as here, the drugs at issue would be the first in their class to enter the nonprescription market. The less that is known about the use of a medication without the oversight of a health care professional, the more data typically will be required.

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[39] See, e.g., § 314.50.

[40] Safety assessments typically rely on information presented in an NDA, worldwide databases, FDA's Adverse Event Reporting System, and literature.

[41] See e.g., FDA's guidances for industry called "Self-Selection Studies for Nonprescription Drug Products," and "Label Comprehension Studies for Nonprescription Drug Products."

Currently, patient information is provided for prescription hydroxychloroquine sulfate in detailed package inserts. Converting the necessary information into appropriate nonprescription labeling could present challenges and would require evidence to demonstrate that hydroxychloroquine sulfate can be used safely and effectively in a nonprescription setting. Demonstrating that hydroxychloroquine sulfate could be used safely and effectively without prescriber oversight would likely require testing to address certain considerations. For example:

- Consumer ability to recognize warnings and contraindications that would require them to consult with a health care provider before use or to avoid use altogether. This is particularly relevant for patients with comorbidities and concomitant drugs that could increase the risks associated with hydroxychloroquine sulfate use.

- Consumer understanding of serious side effects that may be associated with the use of hydroxychloroquine sulfate, including symptoms of those side effects and the need to seek prompt medical attention.

In sum, marketing applications or rulemaking to switch hydroxychloroquine sulfate to nonprescription use would likely need to be supported by results from adequately designed consumer studies that address the adequacy of labeling and whether consumers can adequately self-select and safely and effectively use hydroxychloroquine sulfate.

2. Your Petition's Arguments and Evidence Supporting a Switch to Nonprescription Use

At this time, the arguments set forth in your Petition, in view of the evidence available to FDA, are insufficient to persuade FDA to initiate rulemaking to switch hydroxychloroquine sulfate from prescription to nonprescription.

You suggest that hydroxychloroquine sulfate

> 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.[42]

You suggest that hydroxychloroquine sulfate is "effective when self-administered" because administration "relies only on the person's assessment of potential exposure to persons infected with" COVID-19.[43] You suggest that "any interaction between low-dose [hydroxychloroquine sulfate] and other drugs would be unlikely to seriously affect [hydroxychloroquine sulfate]'s efficacy or a person's well-being."[44] You also suggest that "the patient labeling for [hydroxychloroquine sulfate] can be easily tailored to self-administration" because "it requires only once per week dosing of 2 pills (400 mg)."[45]

[42] Petition at 2.
[43] Id.
[44] Id.
[45] Id.

To support the assertions that hydroxychloroquine sulfate can be self-administered safely and effectively, the Petition references a hydroxychloroquine patient fact sheet issued by the American College of Rheumatology;[46] an article on the risk of hydroxychloroquine alone and in combination with azithromycin in the treatment of rheumatoid arthritis;[47] an article on early outpatient treatment of symptomatic, high-risk covid-19 patients;[48] the Center for Disease Control's webpage on malaria; and an article describing a case of fatal hydroxychloroquine overdose.[49] In addition, the Petition provides a declaration by Dr. Simone Gold of the America's Frontline Doctors.[50]

While certain references in the Petition provide some evidence regarding the general safety and effectiveness of hydroxychloroquine sulfate, the Petition provides no evidence regarding the safety or effectiveness of hydroxychloroquine sulfate when used for prophylaxis of COVID-19. Furthermore, 400 mg once a week is the approved dose for the prevention of malaria, but the Petition provides no evidence to support the same dosing regimen would be safe and effective for prophylaxis of COVID-19.

In addition, an application for nonprescription marketing for a hydroxychloroquine sulfate drug product for prophylaxis of COVID-19 would require considerably more specific information than the minimal, general information provided by the Petition. The references supporting the Petition do not establish that the prescription-dispensing requirements for hydroxychloroquine sulfate 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" nor do they establish that hydroxychloroquine sulfate is "safe and effective for use in self-medication as directed in proposed labeling."[51] There are contraindications and adverse reactions associated with hydroxychloroquine sulfate use. These risks are discussed in the approved labeling. Without data from consumer studies and without proposed nonprescription labeling, FDA cannot evaluate whether hydroxychloroquine sulfate can be used safely and effectively in the nonprescription setting.

IV. CONCLUSION

For the reasons stated above, your Petition is denied. FDA will evaluate applications for hydroxychloroquine sulfate for prophylaxis of COVID-19 (for prescription or nonprescription

[46] Hydroxychloroquine (Plaquenil) Patient Fact Sheet, American College of Rheumatology, April 2020.
[47] The Petition references a preprint version of the article, which is available at https://www.medrxiv.org/content/10.1101/2020.04.08.20054551v2. The article has since been published: Lane JCE, Weaver J, Kostka K, et al. Risk of Hydroxychloroquine Alone and in Combination with Azithromycin in the treatment of Rheumatoid Arthritis: A Multinational, Retrospective Study. Lancet Rheumatol. 2020;2(11):e698-711.
[48] Risch HA. Early Outpatient Treatment of Symptomatic, High-Risk COVID-19 Patients That Should Be Ramped Up Immediately as Key to the Pandemic Crisis. Am J Epidemiol. 2020;189(11):1218–1226.
[49] Fung HT. A Case of Hydroxychloroquine Overdose. Hong Kong Journal of Emergency Medicine. January 2007, volume 14(1).
[50] Petition at 4.
[51] § 310.200(b).

use) on a case-by-case basis. FDA is available to meet with interested parties to discuss initiating a program to develop the data necessary to support such an application.

Sincerely,

Douglas C. Throckmorton -S

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Date: 2022.11.16 11:27:36 -05'00'

Patrizia Cavazzoni, M.D.
Director
Center for Drug Evaluation and Research