Summary Report

Chloroquine phosphate

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Clinical use of bulk drug substances nominated for inclusion on the 503B Bulks List
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Frequently Used Abbreviations

API	Active Pharmaceutical Ingredient
EMA	European Medicines Agency
EU	European Union
FDA	Food and Drug Administration
IRB	Institutional Review Board
IM	Intramuscular
IV	Intravenous
OTC	Over-the-counter
P. falciparum	*Plasmodium falciparum*
P. malariae	*Plasmodium malariae*
P. ovale	*Plasmodium ovale*
P. vivax	*Plasmodium vivax*
ROA	Route of administration
SC	Subcutaneous
SME	Subject matter experts
UK	United Kingdom
US	United States

INTRODUCTION

This report was created to assist the Food and Drug Administration (FDA) in their evaluation of the use of chloroquine phosphate (UNII code: 6E17K3343P), which was nominated for use as a bulk drug substance in compounding by outsourcing facilities under section 503B of the Federal Food, Drug, and Cosmetic Act.

The aim of this report was to describe how chloroquine phosphate is used in clinical research and practice to diagnose, prevent, or treat disease. Due to the broad, exploratory nature of this aim, scoping review methodology was used. Following the scoping review framework, a systematic literature review was conducted and healthcare practitioners were consulted to identify how chloroquine phosphate has been used historically and currently.[1-3] Assessment of study quality and risk of bias were not performed because the aim of this report was not to make specific recommendations on the use of this substance in clinical practice.[1,4,5] Rather, the aim was to summarize the available evidence on the use of chloroquine phosphate and thereby assist the FDA to determine whether there is a need for the inclusion of this substance on the 503B Bulks List.

REVIEW OF NOMINATION

Chloroquine phosphate was nominated for inclusion on the 503B Bulks List by Fagron for the prophylaxis and treatment of malaria via a 64.5 mg/mL intramuscular (IM) or intravenous (IV) injection.

The nominator provided references from published peer-reviewed literature to describe the pharmacology and support the clinical use of chloroquine phosphate.[6-8]

Reasons provided for nomination to the 503B Bulks List included:

- Chloroquine has been given as an injection for patients who are unable to take oral medication.
- The only FDA-approved product with chloroquine phosphate is a tablet or capsule for oral use. This is an inappropriate source of active pharmaceutical ingredient due to unsuitable excipients.

METHODOLOGY

Background information

The national medicine registers of 13 countries and regions were searched to establish the availability of chloroquine phosphate products in the United States (US) and around the world. The World Health Organization, the European Medicines Agency (EMA), and globalEDGE were used to identify regulatory agencies in non-US countries. The medicine registers of non-US regulatory agencies were selected for inclusion if they met the following criteria: freely accessible; able to search and retrieve results in English language; and desired information, specifically, product trade name, active ingredient, strength, form, route of administration (ROA), and approval status, provided in a useable format. Based on these criteria, the medicine registers of 13 countries/regions were searched: US, Canada, European Union (EU), United Kingdom (UK), Ireland, Belgium, Latvia, Australia, New Zealand, Saudi Arabia, Abu Dhabi, Hong Kong, and Namibia. Both the EMA and the national registers of select EU countries (Ireland, UK, Belgium, and Latvia) were searched because some medicines were authorized for use in the EU and not available in a member country and vice versa.

Each medicine register was searched for chloroquine phosphate; name variations of chloroquine phosphate were entered if the initial search retrieved no results. The following information from the search results of each register was recorded in a spreadsheet: product trade name; active ingredient;

strength; form; ROA; status and/or schedule; approval date. Information was recorded only for products with strengths, forms, and/or ROA similar to those requested in the nominations.

In addition to the aforementioned medicine registers, the DrugBank database (version 5.1.5) and the Natural Medicines database were searched for availability of over-the-counter (OTC) products containing chloroquine phosphate. The availability of OTC products (yes/no) in the US and the ROA of these products were recorded in a spreadsheet. Individual product information was not recorded.

Systematic literature review

Search strategy

A medical librarian constructed comprehensive search strategies for Ovid MEDLINE and Embase. The search strategies used a combination of controlled vocabulary terms and keywords to describe four concepts: chloroquine phosphate, intravenous or intramuscular administration, therapeutic or preventative use, and malaria (refer to Appendix 1 for full search strategies). Keywords for brand or proprietary products were not included in the search strategy because studies that utilized such products were excluded. Results were limited to human studies in English language. Searches were conducted on March 4, 2020. In addition, the ECRI Guidelines Trust® repository was searched on March 4, 2020 for clinical practice guidelines that recommended the use of chloroquine phosphate and provided sufficient information on dosing and administration.

Results were exported to EndNote for Windows version X9.2 (Clarivate Analytics), and duplicates were removed. The de-duplicated results were uploaded to Covidence (Veritas Health Innovation) for screening.

Study selection

Studies in which chloroquine phosphate was used in the nominated dosage form, ROA and/or combination product to diagnose, prevent or treat the nominated disease or condition, or other conditions not specified in the nomination, were included. Studies were excluded if they were: written in a language other than English; reviews or meta-analyses; surveys or questionnaires (cross-sectional design); designed to evaluate cost-effectiveness, mechanism of action, pre-clinical use, safety, or toxicity; or any study design other than a randomized controlled trial conducted in a non-US country. Studies were also excluded if chloroquine phosphate was used as: a brand or proprietary product; an FDA-approved product in the nominated dosage form, ROA, or combination; or a dosage form, ROA, or combination that was not nominated. Studies in which chloroquine phosphate was used to diagnose, prevent, or treat autism were excluded due to a separate project examining the use of compounded substances in individuals with autism. Studies that did not meet the inclusion criteria but provided valuable information about the pharmacological or current or historical use of the substance were noted and put in a separate group in the EndNote library. Two reviewers independently screened titles and abstracts and reviewed full-text articles. A third reviewer reconciled all disagreements.

Data extraction

The following information was recorded in a standard data extraction form: author names; article title; journal; year of publication; country; study type; historical use of chloroquine phosphate; setting; total number of patients; number of patients who received chloroquine phosphate; patient population; indication for use of chloroquine phosphate; dosage form and strength; dose; ROA; frequency and duration of therapy; use of chloroquine phosphate in a combination product; use and formulation of chloroquine phosphate in a compounded product; use of chloroquine phosphate

compared to FDA-approved drugs or other treatments; outcome measures; authors' conclusions. One reviewer extracted data from the included studies; a second reviewer checked the data extraction.

Interviews

Semi-structured interviews with subject matter experts (SME) were conducted to understand how and in what circumstances chloroquine phosphate was used in a clinical setting. The systematic literature review and indication from the nomination were reviewed to identify the following medical specialties that would potentially use chloroquine phosphate: infectious disease, and primary care and internal medicine. Potential SMEs within the relevant medical specialties were identified through recommendations and referrals from professional associations, colleagues' professional networks, and authors of relevant literature. Seventeen SMEs were contacted for interviews, of which 5 accepted and 12 declined. SMEs provided oral informed consent to be interviewed and audio recorded. Interviews lasting up to 60 minutes were conducted via telephone, audio recorded, and professionally transcribed. The transcriptions and notes were entered into NVivo 12 (QSR International) for qualitative data analysis. Several members of the research team independently coded the transcriptions of two representative interviews for themes. The team members discussed the codes that emerged from their independent analysis, as well as those codes that were determined a priori. The code book was developed out of the integration of these coding schemes.

Survey

A survey was distributed to the members of professional medical associations to determine the use of chloroquine phosphate in clinical practice. The online survey was created using Qualtrics® software (refer to Appendix 2 for complete survey). A Google™ search was conducted to identify the professional associations in the US for the relevant medical specialties. An association's website was searched to identify the email of the executive director, regulatory director, media director, association president, board members, or other key leaders within the organization to discuss survey participation. If no contact information was available, the "contact us" tab on the association website was used. An email describing the project and requesting distribution of the survey to the association's members was sent to the identified persons. Associations that declined, did not respond, or did not provide significant data in project Year 1 were not contacted to distribute the project Year 2 surveys.

The survey was posted on the project website and the survey link was distributed to the associations that agreed to participate (refer to Appendix 3 for associations that participated and those that did not).

Participation was anonymous and voluntary. The estimated time for completion was 15 minutes with a target of 50 responses per survey.

The University of Maryland, Baltimore Institutional Review Board (IRB) and the FDA IRB reviewed the interview and survey methods and found both to be exempt. The Office of Management and Budget approved this project.

CURRENT AND HISTORIC USE

Results of background information

- Chloroquine phosphate is not available as an FDA-approved product in the nominated form and ROA.
- Chloroquine phosphate is not available as an OTC product in the US.
- There is a current United States Pharmacopeia (USP) monograph for chloroquine phosphate.
- Chloroquine phosphate is not available in the nominated dosage form and ROA in any of the foreign registries searched. Chloroquine sulfate is available as a 40 mg/mL injectable solution in Abu Dhabi.

Table 1. Currently approved products – US

No approved products in the US

Table 2. Currently approved products – select non-US countries and regions[a]

Active Ingredient	Concentration	Dosage Form	Route of Administration	Approved for Use		
				Country	Status	Approval Date
Chloroquine sulfate	40 mg/mL	Solution	Injectable	Abu Dhabi	Active	–

Abbreviation: "–", not mentioned.

[a]Medicine registers of national regulatory agencies were searched if they met the following criteria: freely accessible; able to search and retrieve results in English language; and desired information (product trade name, active ingredient, strength, form, ROA, and approval status) provided in a useable format. Information was recorded only for products with strengths, forms, and/or ROA similar to those requested in the nominations. See Methodology for full explanation.

Results of literature review

Study selection

Database searches yielded 860 references; 2 additional references were identified from searching ECRI Guidelines Trust® and the references of relevant systematic reviews. After duplicates were removed, 676 titles and abstracts were screened. After screening, the full text of 216 articles was reviewed. Finally, 6 studies were included. Two hundred ten studies were excluded for the following reasons: wrong study design (176 studies); unable to obtain (14); wrong dosage form or ROA (11); chloroquine phosphate used as brand or proprietary product (6); wrong substance (2); duplicate study (1). The global coronavirus disease 2019 (COVID-19) pandemic and subsequent closure of libraries affected the number of articles for which full text was not obtained.

Refer to Figure 1 for the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram.

Characteristics of included studies

The 6 included studies were published between 1949 and 2013. There were 3 experimental studies, 1 observational study, 2 descriptive studies, and 0 clinical practice guidelines. The 6 studies were conducted in the following countries: the Netherlands, US, and Vietnam.

A total of 233 patients participated in the 6 included studies. The number of patients in each study ranged from 1 to 106.

Outcome measures differed among the included studies and included: presence of parasitemia, time to parasitemia after challenge, days to parasite clearance, days to parasite recrudescence, last day of fever, relapse (days after treatment), parasite counts, and toxicity.

Refer to Table 5 for summary of study country, design, patient population, intervention and comparator, and outcome measures.

Use of chloroquine phosphate

Two hundred thirty-three patients received chloroquine phosphate as prophylaxis and/or treatment for malaria, administered intramuscularly in doses ranging from 200 mg/day to 750 mg/day. Duration of treatment ranged from 1 to 3 days.

Refer to Tables 6 and 7 for summaries of dosage by indication.

Chloroquine phosphate was not used as a compounded product.

In 3 studies, the authors' concluding statement recommended the use of chloroquine phosphate for the prophylaxis and treatment of malaria.[9-11] In 2 studies, the authors' concluded that chloroquine phosphate was not recommended or further studies were necessary for the treatment of malaria.[12,13] In 1 study, the authors' concluding statement was not specific to chloroquine phosphate.[14] Refer to Table 5 for summary of authors' conclusions.

Pharmacology and historical use

In addition to the 6 included studies, 17 studies were identified that did not meet the inclusion criteria but provided valuable information about the pharmacology and historical use of chloroquine phosphate.

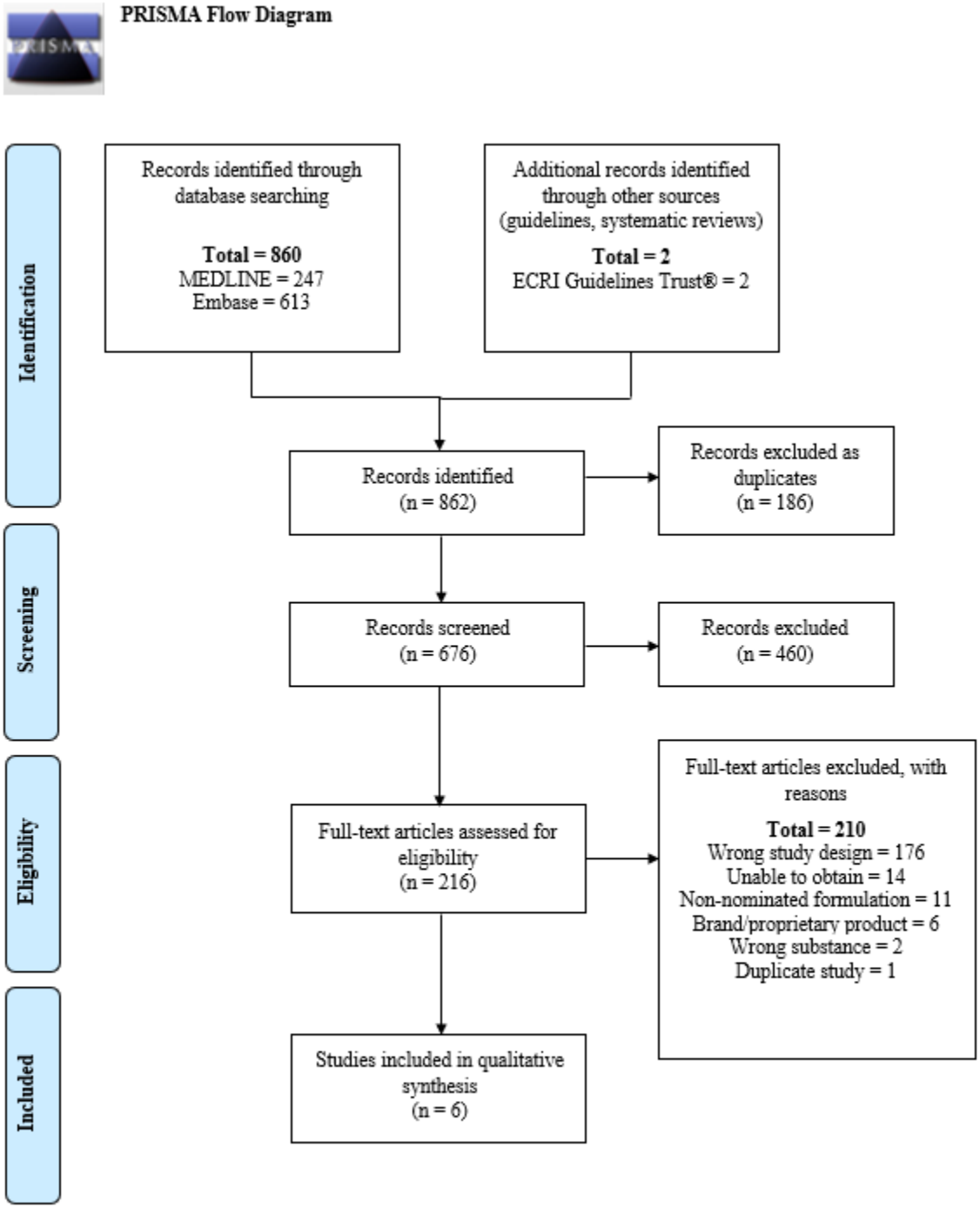
Oral chloroquine is generally well tolerated, with some patients experiencing mild gastrointestinal upset, visual disturbances, headache, and pruritus.[15] However, in 1984, the World Health Organization announced that parenteral chloroquine should not be used due to safety concerns with its arrhythmogenic properties and sudden death in children.[15,16] Some of the deaths were due to IV administration of chloroquine and overdosage in children who previously received chloroquine.[15,16] Rapid IV administration of chloroquine can cause fatal arrhythmias and a bolus IV infusion of chloroquine is never indicated.[15,17,18] For IM and subcutaneous (SC) injections, the dose should be less than 3.5 mg base/kg to prevent hypotension.[19] Dr. NJ White, who wrote several articles in the 1980s and 1990s about the treatment of *falciparum* malaria, stated that parenteral chloroquine can be given safely by IV, IM, and/or SC routes with close monitoring and/or in smaller and more frequent doses.[16]

Several recommendations and/or clinical reviews touching upon parenteral chloroquine were found. In a 1990 written recommendation on the management and prevention of malaria by the Council of Ministers and the Ministry of Health of Vietnam, chloroquine was the drug of choice for chloroquine-sensitive infections because it was possibly more effective and less toxic than cinchona alkaloids.[18] The Council recommended chloroquine IV infusion 10 mg base/kg over 8 hours, then 15 mg base/kg over 24 hours or 5 mg/kg over 4-6 hours every 12 hours.[18] For IM and SC dosing, the Council recommended 2.5 mg/kg every 4 hours.[18] In 1997, the written recommendations from Thailand for treatment and prophylaxis of cerebral malaria described chloroquine as the drug of choice for susceptible strains of *Plasmodium falciparum (P. falciparum)*.[20] These recommendations stated that IM and SC injections are not painful and provide rapid absorption with a bioavailability of greater than 80%.[20] For intensive care units treating a chloroquine-sensitive malaria patient, they recommended 10 mg/kg rate controlled IV infusion over 8 hours, followed by 15 mg/kg over 24 hours or 3.5 mg/kg by IM or SC injection every 6 hours for a total dose of 25 mg/kg.[20] For a rural health clinic treating a chloroquine-sensitive malaria patient, they recommended a 3.5 mg/kg dose every 6 hours or 2.5 mg/kg dose every 4 hours via IM or SC injection.[20] In a 2003 clinical review, parenteral chloroquine was the drug of choice for severe chloroquine-susceptible *P. falciparum* infections and for rare cases of life-threatening malaria caused by *P. ovale, P. malariae,* and *P. vivax*.[21] The suggested dosing was the same as the chloroquine IV infusion dosing recommend by the Council of Ministers and Ministry of Health of Vietnam.

Additional studies mentioned use of parenteral chloroquine that did not meet the literature review inclusion criteria. Almost all of these studies were conducted before the year 2000[22-30] outside the US in places like Gambia,[26,30] Ghana,[23] India,[28] Kenya,[27] Tanzania,[24,25] and Zambia.[29] In 1 study, the authors noted that they used the IM route because effective plasma concentrations were obtained rapidly and could aid in preventing side effects associated with high doses.[24] Another study noted that chloroquine-resistant *P. falciparum* had been seen in non-immune travelers to east Africa since 1987 and had also increased in semi-immune persons.[27] However, chloroquine is still a common malaria treatment in Kenya because it is cheap, safe, and rapid-acting.[27] Several studies referenced a 1987 study done by White et al, in which the toxicity and acute disposition of IV, IM, SC, and oral chloroquine in 60 Zambian *falciparum* malaria patients were studied.[29] White et al. found that the "acute toxicity of parenteral chloroquine is related to transiently high concentrations in blood and result from incomplete distribution out of a relatively small central compartment."[29] IM and SC chloroquine may be safely administered via smaller frequent doses; continuous infusion should be used for IV administration.[29] White et al recommended dosing regimens of 2.5 mg base/kg every 4 hours or 3.5 mg base/kg every 6 hours.[29] IV chloroquine should be given as either a continuous infusion of 5 mg base/kg every 6 hours or as an initial dose of 10 mg base/kg over 8 hours followed

by 5 mg base/kg every 8 hours.[29] White et al noted that the total dose for all parenteral regimens should be 35 mg base/kg, and oral treatment should be substituted in a soon as possible.[29] A more recent 2015 case report from India of a 22 year-old male with *P. vivax* malaria and acute pancreatitis, reported that the patient responded to IV chloroquine and supportive treatment.[31]

Figure 1. PRISMA flow diagram showing literature screening and selection.



Adapted from:
Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *J Clin Epidemiol.* 2009;62(10):1006-1012. Available from: http://www.prisma-statement.org/.

Table 3. Types of studies

Types of Studies	**Number of Studies**
Descriptive[10,14]	2
Experimental[11-13]	3
Observational[9]	1

Table 4. Number of studies by country

Country	**Number of Studies**
The Netherlands[11]	1
US[9,10,13,14]	4
Multiple Countries • Vietnam and US[12]	1
	Total US[a]: 5 Total Non-US Countries[a]: 2

[a]Study 12 counted in both US and non-US total

Table 5. Summary of included studies

Author, Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (# of patients)	Primary Outcome Measure	Authors' Conclusions
Bijker *et al.*, 2013, the Netherlands[11]	Single-center, open-label study	25 patients (not specified, range 19-32 y)	• Groups 1 & 2: chloroquine prophylaxis and exposed to bits of *Plasmodium falciparum (P. falciparum)*-infected mosquitoes (15) • Groups 3 & 4 (control groups): chloroquine prophylaxis (10)	Presence of and time to parasitemia after challenge	Sporozoite immunization via chloroquine chemoprophylaxis with *Plasmodium falciparum* sporozoites protocol may "induce sterile protection entirely mediated by immune responses against the preerythrocytic stages of *P. falciparum*."
Collins *et al.*, 1973, US[9]	–	22 prisoner volunteers infected with either the Philippines or Nigerian strain of *P. malariae* Philippine strain (100%, range 28-38 y) Nigerian strain (not specified, range 26-37 y)	• Philippine strain (7*): o Quinine sulfate (6) o Chloroquine (5) • Nigerian strain (15**) o Quinine (4) o Chloroquine (11) o Not treated (1) *Four patients given both quinine and chloroquine **One patient given both quinine and chloroquine	Days to parasite clearance and days to parasite recrudescence	Both strains of infections treated with chloroquine were curative.
Hall *et al.*, 1974, Vietnam and US[12]	–	106 patients (not specified)	• Intravenous quinine (46) • Oral quinine (42) • Chloroquine (18)	Cure, recrudescence of infection, effect on parasitemia	Combination therapy with chloroquine was less successful than combination therapy with quinine for treatment of falciparum malaria among the US troops in Vietnam. The studies done in the US with volunteers confirmed this.

Author, Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (# of patients)	Primary Outcome Measure	Authors' Conclusions
Jeffery, 1956, US[13]	–	71 patients* (not specified) *Calculated based on number of patients with primary attacks from the information provided in the study tables	• Oral chloroquine (58) o 58 primary attacks o 73 relapses • Intramuscular chloroquine (13) o 13 primary attacks o 21 relapses	Last parasite day, last day of fever, relapse (days after treatment)	Patients treated with oral or intramuscular chloroquine showed "no appreciable difference between the two where the treatment-to-relapse interval was concerned. The severity or duration of the primary attack could not be related to the treatment-to-relapse interval, nor could the number of infective bites used to induce the infection."
Khan *et al.*, 2010, US[14]	–	1 patient (100%, 19 y)	• Chloroquine and primaquine	Resolution of malaria	"Successful treatment of Malaria necessitates accurate diagnosis of the offending Plasmodium species."
Spicknall *et al.*, 1949, US[10]	Cases	8 patients with *P. falciparum* malaria (not specified)	• Oral and intramuscular chloroquine (8)	Parasite counts, toxicity	All patients responded to the treatment and no toxic effects from the drug were observed.

Abbreviations: "– ", not mentioned; *Plasmodium falciparum, P. falciparum*; *Plasmodium malariae, P. malariae*.
[a]As defined by authors.

Table 6. Dosage by indication – US

Indication	Dose	Concentration	Dosage Form	Route of Administration	Duration of Treatment
Malaria treatment[9,10,12-14]	500-750 mg/day	–	–	–	1-3 days
	200-400 mg/day	–	Solution	Intramuscular	Once-Twice

Abbreviation: "– ", not mentioned.

Table 7. Dosage by indication – non-US countries

Indication	Dose	Concentration	Dosage Form	Route of Administration	Duration of Treatment
Malaria prophylaxis[11] and treatment[12]	750 mg/day	–	–	–	–

Abbreviation: "– ", not mentioned.

Table 8. Number of studies by combination

No combination products were nominated

Table 9. Compounded products – US

No compounded products from reported studies

Table 10. Compounded products – non-US countries

No compounded products from reported studies

Results of interviews

Seventeen SMEs were contacted for interviews, of which 5 accepted and 12 declined. Of the 5 SMEs, there were 4 medical doctors and 1 pharmacist. The SMEs specialized and/or were board-certified in infectious disease and primary care and family practice, working in academic medical centers. The SMEs had been in practice for 9 to 30 years.

Chloroquine was first used to treat malaria around World War II. By the 1980s, many countries, first in southeast Asia and South America, stopped using chloroquine due to the amount of resistance. By the early 1990s and the following decade, most sub-Saharan African countries had stopped using chloroquine. One SME expressed that "everyone associates [chloroquine] in Africa with not working and giving you itching." The primary use for chloroquine now is for the treatment of non-falciparum infection, especially for *P. vivax.* In theory, chloroquine could be useful for malaria cases for countries north of the equator such as Costa Rica and Haiti, but people do not use it for *P. falciparum*. Some studies have explored chloroquine resistance in countries that had previously stopped using chloroquine due to the resistance. For example, in Malawi, the first sub-Saharan African country which stopped using chloroquine about 15 years ago, chloroquine-resistant malaria has since disappeared and studies using chloroquine for malaria in prophylaxis in populations such as pregnant women and people with HIV infection have shown that chloroquine works well. Other places, particularly in eastern Africa and some parts of western Africa, are finding similar results. However, for southeast Asia and South America, chloroquine resistance has not disappeared.

One SME expressed that malaria is "exclusively in the research setting" and "so most of the time ... It's very, very rare that somebody is treated with chloroquine in the United States." Around twice a year, the hospital may have someone admitted for malaria. Oral chloroquine was previously used for treatment and prevention of malaria; now artemisinin-based combination therapy is used. Unlike chloroquine which is only recommended for *P. vivax* malaria, artemisinin-based therapy is guaranteed to work. Most cases are *P. falciparum*, which is likely to kill the patient. When seeing a patient with malaria, practitioners often do not know which *Plasmodium* species it is, so people will treat for the species that would kill the patient. For prevention of malaria, the previous chloroquine dose was 1 tablet a week because chloroquine has a very long half-life. The current option for prevention of malaria for traveling is a daily atovaquone and proguanil tablet. Chloroquine is not prescribed because it causes resistance as well as side effects like hallucinations and psychosis. Chloroquine is always on the "newly out of stock list" because currently there is not a huge need for it.

There is no official recommendation for chloroquine in the treatment or prevention of malaria in sub-Saharan Africa. One SME suggested that a potential future use of chloroquine could utilize intermittent full curative doses for better patient adherence as compared to the previous 1 pill weekly dosing. There is also interest in using chloroquine as an alternative for the prevention of malaria during pregnancy because of resistance to the current drug, sulfadoxine/pyrimethamine. Other potential uses for chloroquine are in combination with another anti-malarial or for different vulnerable populations.

When asked about the need for compounding parenteral chloroquine, the SMEs had differing views. One SME was confused about why chloroquine would need to be compounded and did not see the need for another parenteral therapy. For the pediatric/neonatal population and patients who are unable to swallow tablets, the tablets can be crushed. This SME quoted a 1987 paper from "one of the most famous malaria researchers," saying "although widely considered dangerous, parenteral chloroquine is extensively used," and remembered chloroquine injection was possibly associated with arrhythmias. For patients with severe disease or those who could not tolerate taking medicine by mouth, this SME would use the parenteral therapy options available. This used to be quinine and is now artesunate, which works well

and does not require monitoring. Another SME stated that they would not prescribe chloroquine injection. On the other hand, a different SME stated that they have never personally used intramuscular or intravenous chloroquine, but "see no reason to object to it." Another SME commented that they would be interested in a suitable long-acting injection for prevention of malaria while traveling to replace the current daily Malarone tablet, which is "tiresome".

Results of survey

One professional medical and specialty association was contacted to request distribution of the survey; 0 associations distributed the survey and 1 association failed to respond (refer to Appendix 3 for complete list of associations). Zero people responded to the survey.

Table 11. Characteristics of survey respondents

No survey respondents provided this information

Table 12. Conditions for which chloroquine phosphate prescribed or administered

No survey respondents provided this information

Table 13. Reasons for using compounded chloroquine phosphate

No survey respondents provided this information

Table 14. Use of non-patient-specific compounded chloroquine phosphate

No survey respondents provided this information

CONCLUSION

Chloroquine phosphate was nominated for inclusion on the 503B Bulks List as a 64.5 mg/mL IM or IV injection for the prophylaxis and treatment of malaria. Chloroquine phosphate is not approved in any of the national medical registries searched, however, chloroquine sulfate is available as a 40 mg/mL injectable solution in Abu Dhabi.

From the literature review and interviews conducted, chloroquine phosphate was used for prophylaxis and/or treatment of malaria. However, due to rising resistance, many practitioners have stopped using chloroquine. More recently, there have been studies suggesting that chloroquine-resistant malaria has disappeared in parts of Africa. In the US, malaria is rare. Artemisinin-based therapy for treatment of malaria is preferred over chloroquine because chloroquine only works if the malaria caused by *P. vivax* and most cases are caused by *P. falciparum*. For prophylaxis of malaria, the current option is a daily atovaquone and proguanil tablet.

Parenteral chloroquine's safety has been questioned due to arrhythmias and sudden death in children. Therefore, bolus IV infusion of chloroquine should not be used. Instead, parenteral chloroquine given by IV, IM, and/or SC routes should be closely monitored and/or given in smaller and more frequent doses.

When asked about the need for compounding parenteral chloroquine, the SMEs had differing views. One SME was confused why someone would want to compound chloroquine and did not see the need for another parenteral therapy. Another SME stated they would not prescribe the chloroquine injection. On the other hand, a different SME stated that they have never personally used IM or IV chloroquine, but "see no reason to object to it." An SME commented that they would be interested in a suitable long-acting injection for prevention of malaria while traveling.

No survey responses were received.

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APPENDICES

Appendix 1. Search strategies for bibliographic databases

MEDLINE search strategy

- Platform: Ovid
- Years searched: Ovid MEDLINE and epub ahead of print, in-process and other non-indexed citations and daily 1946 to March 3, 2020
- Date last searched: March 4, 2020
- Limits: Humans (search hedge); English language
- Number of results: 247

1	chloroquine/	14094
2	chlor#quin$.tw.	17597
3	chlor#chin$.tw.	20
4	chlorquin$.tw.	69
5	cho#oquin$.tw.	24
6	clor#quin$.tw.	29
7	clor#chin$.tw.	1
8	klorokin$.tw.	1
9	or/1-8	21908
10	exp administration, intravenous/	141842
11	infusions, parenteral/	26195
12	injections/	42187
13	injections, intramuscular/	30789
14	inject$.tw.	727452
15	infusion$.tw.	241610
16	(parenteral$ adj2 (administ$ or therap$ or treat$ or deliver$)).tw.	11993
17	intravenous$.tw.	334634
18	intra venous$.tw.	566
19	intravascular$.tw.	46913
20	intra vascular$.tw.	296

21	intramuscular$.tw.	51478
22	intra muscular$.tw.	706
23	or/10-22	1288710
24	antimalarials/	25410
25	pre-exposure prophylaxis/	1937
26	de.fs.	2948872
27	dt.fs.	2183728
28	ad.fs.	1393168
29	tu.fs.	2190901
30	pc.fs.	1263942
31	antimalaria$.tw.	17456
32	therap$.tw.	2697918
33	treat$.tw.	5344998
34	prevent$.tw.	1376437
35	prophyla$.tw.	160900
36	or/24-35	10693217
37	malaria/	44613
38	malaria, cerebral/	1979
39	exp malaria, falciparum/	17638
40	malaria, vivax/	4381
41	malaria$.tw.	81121
42	falciparum.tw.	35871
43	plasmodi$.tw.	49643
44	((blackwater or march or remittent) adj3 fever$).tw.	386
45	or/37-44	104395
46	and/9,23,36,45	379

47	exp animals/ not humans/	4674491
48	46 not 47	298
49	limit 48 to english language	247

Embase search strategy

- Platform: Elsevier
- Years searched: 1947 to present
- Date last searched: March 4, 2020
- Limits: Humans (search hedge); English language
- Number of results: 613

1	chloroquine'/de	39202
2	chloraquin*':ti,ab,tn	15
3	chlorachin*':ti,ab,tn	0
4	chloroquin*':ti,ab,tn	23525
5	chlorochin*':ti,ab,tn	61
6	chlorquin*':ti,ab,tn	146
7	choloquin*':ti,ab,tn	12
8	cholochin*':ti,ab,tn	0
9	choroquin*':ti,ab,tn	48
10	chorochin*':ti,ab,tn	0
11	cloriquin*':ti,ab,tn	0
12	clorichin*':ti,ab,tn	0
13	cloroquin*':ti,ab,tn	92
14	clorochin*':ti,ab,tn	4
15	klorokin*':ti,ab,tn	11
16	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15	43370
17	parenteral drug administration'/de	2103
18	intramuscular drug administration'/de	71554
19	intravascular drug administration'/exp	417233
20	inject*':ti,ab	1081672
21	infusion*':ti,ab	352385
22	(parenteral* NEAR/2 (administ* OR therap* OR treat* OR deliver*)):ti,ab	18102

23	intravenous*':ti,ab	482382
24	intra venous*':ti,ab	1433
25	intravascular*':ti,ab	67425
26	intra vascular*':ti,ab	675
27	intramuscular*':ti,ab	74319
28	intra muscular*':ti,ab	1269
29	#17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28	2042248
30	antimalarial agent'/de	25817
31	pre-exposure prophylaxis'/de	3891
32	infection prevention'/de	59380
33	drug dose':lnk	621716
34	drug administration':lnk	1717677
35	drug therapy':lnk	3841536
36	prevention':lnk	1159372
37	antimalaria*':ti,ab	28417
38	therap*':ti,ab	4072661
39	treat*':ti,ab	7765275
40	prevent*':ti,ab	1876511
41	prophyla*':ti,ab	257381
42	#30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41	12841358
43	malaria'/de	83669
44	cerebral malaria'/de	3968
45	malaria falciparum'/de	16771
46	placenta malaria'/de	513
47	plasmodium knowlesi malaria'/de	291
48	plasmodium malariae infection'/de	493

49	plasmodium ovale malaria'/de	411
50	plasmodium vivax malaria'/de	3966
51	malaria*':ti,ab	103690
52	falciparum*':ti,ab	44401
53	plasmodi*':ti,ab	59497
54	((blackwater OR march OR remittent) NEAR/3 fever*):ti,ab	507
55	#43 OR #44 OR #45 OR #46 OR #47 OR #48 OR #49 OR #50 OR #51 OR #52 OR #53 OR #54	140636
56	#16 AND #29 AND #42 AND #55	916
57	[animals]/lim NOT [humans]/lim	5999949
58	#56 NOT #57	757
59	#56 NOT #57 AND [english]/lim	613

Appendix 2. Survey instrument

Welcome. We want to understand your clinical use of compounded chloroquine phosphate. Your feedback will help the Food and Drug Administration (FDA) develop a list of drugs that can be used in compounding by 503B outsourcing facilities. Your anonymous responses will be shared with the FDA. The time required to complete this survey is approximately 10-15 minutes.

If you have additional questions or concerns about this study, please email: compounding@rx.umaryland.edu.

If you have questions about your rights as a research subject, please contact HRPO at 410-760-5037 or hrpo@umaryland.edu.
Thank you,

Dr. Ashlee Mattingly,
Principal Investigator
The University of Maryland School of Pharmacy

An agency may not conduct or sponsor, and a person is not required to respond to a collection of information unless it displays a currently valid OMB control number.

OMB Control No. 0910-0871
Expiration date: June 30, 2022

1. How familiar are you with the following terms?

	Very familiar	Somewhat familiar	Not familiar
Compounded drugs (medications prepared to meet a patient-specific need)	o	o	o
503A Compounding pharmacy (a pharmacy that prepares compounded medications prescribed by practitioners to meet a patient-specific need)	o	o	o
503B Outsourcing facility (a facility that compounds larger quantities without the receipt of a patient-specific prescription)	o	o	o

2. Do you prescribe or administer chloroquine phosphate to your patients?

- o Yes
- o No

3. Do you prescribe or administer chloroquine phosphate by any of the following dosage forms and/or routes of administration? (check all that apply)

- o Intramuscular injection
- o Intravenous injection
- o None of the above

4. I prescribe or administer chloroquine phosphate for the following conditions or diseases: (check all that apply)

- o Malaria
- o Other (please explain) _____

5. I use compounded chloroquine phosphate because: (check all that apply)

- o Commercial products are not available in the dosage form, strength, or combination I need. (please explain) _____
- o Patient allergies prevent me from using commercially available products. (please explain)_____
- o Patient conditions prevent me from using commercially available products. (please explain) _____
- o There are no commercially available products containing chloroquine phosphate.
- o Other (please explain) _____

6. Do you stock non-patient-specific compounded chloroquine phosphate at your practice?

- o Yes
- o No
- o I'm not sure

7. I obtain compounded chloroquine phosphate from the following: (check all that apply)

- o Compound myself at my practice
- o Have the product compounded by an in-house pharmacy
- o Purchase, or have a patient purchase, from a compounding pharmacy
- o Purchase, or have a patient purchase, from an outsourcing facility
- o Other (please explain) _____

8. What is your practice setting? (check all that apply)

- o Physician office/private practice
- o Outpatient clinic
- o Hospital/health system
- o Academic medical center
- o Emergency room
- o Operating room
- o Other (please describe) _____

9. What degree do you hold? (check all that apply)

- o Doctor of Medicine (MD)
- o Doctor of Osteopathic Medicine (DO)
- o Doctor of Medicine in Dentistry (DMD/DDS)
- o Doctor of Pharmacy (PharmD) or Bachelor of Science in Pharmacy (BS Pharm)
- o Naturopathic Doctor (ND)
- o Nurse Practitioner (NP)
- o Physician Assistant (PA)
- o Other (please describe) _____

Appendix 3. Survey distribution to professional associations

Specialty	Association[a]	Agreed/Declined, Reason for Declining
Allergy/Immunology	American Academy of Allergy, Asthma and Immunology (AAAI)	Declined – survey not approved
Anesthesia	American Society of Regional Anesthesia and Pain Medicine (ASRA)	Declined – failed to respond
	Society for Ambulatory Anesthesia (SAMBA)	Declined – failed to respond
	Society for Neuroscience in Anesthesiology and Critical Care	Declined – failed to respond
Cardiology	American College of Cardiology (ACC)	Declined – failed to respond
	American College of Chest Physicians	Declined – failed to respond
	The American Society for Preventive Cardiology	Declined – failed to respond
	Heart Failure Society of America	Declined – failed to respond
Critical Care	Critical Care Societies Collaborative	Declined – failed to respond
	Society of Critical Care Medicine (SCCM)	Declined – failed to respond
Dentistry & Oral Medicine	Academy of General Dentistry (AGD)	Declined – provided interview referrals
	American Dental Association (ADA)	Declined – failed to respond
Dermatology	American Academy of Dermatology (AAD)	Agreed
	American Osteopathic College of Dermatology (AOCD)	Declined – not interested
Endocrinology	The Endocrine Society (ENDO)	Agreed
	Pediatric Endocrine Society	Agreed

Gastroenterology	American College of Gastroenterology	Declined – failed to respond
	American Gastroenterological Association (AGA)	Declined – failed to respond
	Obesity Medicine Association (OMA)	Declined – did not have anyone to contribute to research
Hematology	American Society of Hematology (ASH)	Declined – does not distribute surveys
Infectious Disease	American Academy of HIV Medicine (AAHIVM)	Declined – failed to respond
Medicine	American Medical Association (AMA)	Declined – failed to respond
	American Osteopathic Association (AOA)	Declined – failed to respond
Naturopathy	American Association of Naturopathic Physicians (AANP)	Agreed
	The Oncology Association of Naturopathic Physicians (OncANP)	Agreed
Nephrology	American College of Clinical Pharmacists: Nephrology Practice Network	Agreed
	American Society of Nephrology	Declined – provided interview referrals
Nutrition	American Society for Parenteral and Enteral Nutrition (ASPEN)	Declined – provided interview referrals
Obstetrics and Gynecology	American Gynecological and Obstetrical Society (AGOS)	Declined – failed to respond
	Nurse Practitioners in Women's Health	Agreed
Ophthalmology	American Academy of Ophthalmology (AAO)	Agreed
Otolaryngology	American Academy of Otolaryngology-Head and Neck Surgery (AAO-HNS)	Declined – survey not approved
Pain Management	American Academy of Pain Medicine (AAPM)	Declined – survey not approved
	American Academy of Physical Medicine and Rehabilitation	Declined – failed to respond

Pediatrics and Neonatology	American Academy of Pediatrics (AAP)	Agreed
Primary Care	American College of Physicians (ACP)	Declined – failed to respond
Psychiatry	American Academy of Clinical Psychiatrists	Declined – failed to respond
	American Association for Geriatric Psychiatry	Declined – failed to respond
Rheumatology	American College of Rheumatology (ACR)	Agreed
Surgery	Ambulatory Surgery Center Association (ASCA)	Agreed
	American Academy of Orthopaedic Surgeons (AAOS)	Declined – no interest in participation from members
	American Association of Hip and Knee Surgeons (AAHKS)	Declined – only send surveys from members
	American College of Surgeons (ACS)	Agreed
	American Society for Metabolic and Bariatric Surgery (AMBS)	Declined – only send surveys from members
	The Association of Bone and Joint Surgeons	Declined – failed to respond
	Physician Assistants in Orthopaedic Surgery	Declined – failed to respond
	Society of American Gastrointestinal and Endoscopic Surgeons (SAGES)	Declined – failed to respond
	Society of Gynecologic Surgeons (SGS)	Declined – policy limits number of surveys per year and do not have a method to identify if any of the SGS members are using ipamorelin
Toxicology	American Academy of Environmental Medicine (AAEM)	Declined – failed to respond
Urology	Sexual Medicine Society of North America (SMSNA)	Agreed

[a]Associations who declined in Year 1 were not contacted in Year 2.