

Biowaiver Monographs for Immediate-Release Solid Oral Dosage Forms: Quinine Sulfate

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ABSTRACT: The biowaiver approach permits evaluation of bioequivalence (BE) using a set of laboratory tests, obviating the need for expensive and time-consuming pharmacokinetic BE studies provided that both the active pharmaceutical ingredient and the formulations can meet the specified criteria. In the present monograph, the biowaiver-relevant data including solubility and permeability data, therapeutic use and therapeutic index, pharmacokinetic properties, reported excipient interactions, and BE/bioavailability studies of quinine sulfate are itemized and discussed. Quinine sulfate has borderline solubility characteristics and, on the whole, is highly permeable. Thus, depending on the jurisdiction, it is assigned to Biopharmaceutics Classification System class I or II. Although these characteristics would suggest a low risk of bioinequivalence among oral quinine products, a recent pharmacokinetic study showed bioinequivalence of two products. Even though quinine does not, strictly speaking, fit the definition of a narrow therapeutic index drug, it shows dose-related and, in some cases, irreversible side effects and toxicities at concentrations not far above the therapeutic concentration range. Taking all relevant aspects into consideration, a biowaiver cannot be recommended for new quinine immediate-release multisource products or major post-approval changes of already marketed quinine products, and in such cases, BE should be evaluated using an *in vivo* BE study. © 2011 Wiley Periodicals, Inc. and the American Pharmacists Association J Pharm Sci 101:499–508, 2012

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INTRODUCTION

The present biowaiver monograph addresses the active pharmaceutical ingredient (API) quinine sulfate. This monograph is a part of the biowaiver monograph series by the International Pharmaceutical Federation¹ (FIP), which aims at evaluating the risks

associated with bioequivalence (BE) assessment *in vitro* for the approval of new immediate-release (IR) solid oral dosage forms by waiving *in vivo* pharmacokinetic BE studies for a given API. This evaluation applies only to single-API drug products containing quinine sulfate and not to combination products.

Detailed information on the scope and purpose of this series of monographs has been discussed previously.² In a nutshell, each monograph is based on a comprehensive literature review, which forms the basis of the risk–benefit analysis of applying a biowaiver-based approval to new or extensively revised formulations of the given API. Some of the properties discussed include the solubility of the API, pharmacokinetics and permeability data,

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the therapeutic use and therapeutic index, dissolution data of already marketed drug products, data on excipient interactions, and any problems that have been reported with bioavailability (BA) and/or BE. Although the biowaiver monographs take the various guidelines on establishing BE into consideration, for example, those of the European Medicines Agency (EMA),³ the US Food and Drug Administration (FDA),⁴ and the World Health Organization (WHO),⁵ the decision to recommend or advise against biowaivers for the given API is based on scientific assessment of the risk–benefit analysis. Biowaiver monographs for more than 25 APIs have already been published and are freely accessible via the website of FIP.¹

GENERAL CHARACTERISTICS

Scope

Although the current 16th edition of the WHO Model List of Essential Medicines (EML)⁶ includes two different salt forms for solid oral quinine formulations, its sulfate and bisulfate, the latter is not the focus of this monograph. This decision was based on the following rationale: (a) The sulfate is the salt form used in most solid oral dosage forms of quinine,^{7,8} (b) the “Guidelines for Treatment of Malaria in the United States” from the Centers for Disease Control and Prevention (CDC)⁹ recommend only the sulfate salt of quinine for treating malaria, and (c) neither the physicochemical properties of quinine bisulfate nor its *in vivo* behavior are well characterized in the literature.

Name

Quinine (BAN), the L-stereoisomer of the antiarrhythmic API quinidine, is an alkaloid obtained from the bark of the cinchona tree.⁷ Quinine contains a quinoline group with a methoxy side chain, attached through a secondary alcohol linkage to a vinylquinuclidine ring.¹⁰ The chemical description of the sulfate salt form is (8 α ,9R)-6'-methoxycinchonan-9-ol sulfate dihydrate (2:1) (salt),¹¹ with the molecular formula (C₂₀H₂₄N₂O₂)₂·H₂SO₄·2H₂O, a molecular weight of 783.0 g/mol,^{12,13} and a melting point of approximately 225°C.¹⁴ The structure of quinine sulfate is given in Figure 1.

Therapeutic Indication and Dose

Quinine is an antimalarial agent, which is still widely used in many countries for treating uncomplicated malaria.^{15,16} It is a rapidly acting blood schizontocidal drug with activity against *Plasmodium falciparum*, *Plasmodium vivax*, *Plasmodium ovale*, and *Plasmod-*

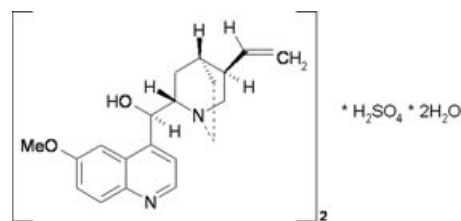


Figure 1. Structure of quinine sulfate.

ium malariae, and gametocytocidal effects on *P. vivax* and *P. malariae*, but not on *P. falciparum*.⁷

For the treatment of uncomplicated malaria, the CDC⁹ recommends taking 650 mg quinine sulfate [equivalent to two tablets of Qualaquin[®] (AR Scientific, Inc.; Philadelphia, Pennsylvania, USA)] three times per day for 3 or 7 days, whereas the WHO¹⁷ suggests taking 8 mg/kg quinine sulfate three times a day for 3 or 7 days. Various studies have concluded that a 7-day oral quinine course can cure malaria, if used correctly.^{18–21} On the contrary, numerous other references indicate that a 7-day quinine treatment schedule might be ineffective for treating uncomplicated malaria due to high rates of relapse.^{15,16,20,22} The question remains as to whether relapses are due to low sensitivity of the plasmodia to quinine, lack of patient compliance, or substandard drug products.

Since 2006, quinine is no longer recommended as first-line treatment for malarial infection by the WHO. However, in view of the fact that quinine in therapeutic doses is considered to be safe in any trimester of pregnancy,^{21–24} the WHO still highly recommends its use for treating uncomplicated malaria in pregnant women, preferably in combination with clindamycin.^{9,25} The efficacy of the combination of quinine with antibiotics in malaria treatment has been frequently reported in the literature.^{26–30}

Therapeutic Index and Toxicity

The most common adverse effects associated with quinine treatment include headache, vasodilatation, nausea, tinnitus, hearing impairment, vertigo or dizziness, blurred vision, and disturbance in colour perception.³¹ This cluster of symptoms is recognized as a mild form of cinchonism, which occurs to some degree in almost all patients taking quinine.³¹ Its more severe manifestation is characterized by vomiting, diarrhoea, abdominal pain, deafness, blindness, and disturbance in cardiac rhythm or conduction.³¹ Other adverse effects associated with quinine use include hypoglycaemia,^{7,31–34} hypothermia,^{7,31} renal failure,^{7,31,35} and granulomatous hepatitis.^{31,36} The adverse events of quinine are usually more severe at higher doses.³⁷ However, some adverse effects may be idiosyncratic because of the variable sensitivity of patients to the toxic effects of quinine.³¹ Furthermore,

even though most of quinine's adverse effects are reversible, recovery from blindness after an overdose is uncertain.³⁸

Overdosing of quinine has evoked some fatal cases.^{38–40} The quinine-associated fatalities are often related to cardiotoxicity in the form of arrhythmias and myocardial depression, characteristic of severe quinine poisoning.^{37,39} Numerous studies have demonstrated that severe adverse events of quinine can occur in patients with plasma concentrations above 10 mg/L.^{8,38–40} On the contrary, a study of White et al.⁴¹ showed only minor changes in the electrocardiograms of 31 patients with quinine plasma concentrations up to 20 mg/L and found no evidence of serious cardiotoxic events under therapeutic quinine concentrations. A lethal dose or lethal quinine plasma concentration has not yet been established,^{7,12} but fatal cases have been observed in adults after ingestion of 2–8 g quinine.³¹ However, the standard reference book "Clarke's Analysis of Drugs and Poisons" reports an estimated minimum lethal dose of 8 g.¹²

Although quinine is often designated as a narrow therapeutic index (NTI) drug in the literature,^{19,42,43} it does not appear on the official list of NTI drugs published by the National Institute of Health Sciences in Japan.⁴⁴ Further, the NTI drug list of the FDA⁴⁵ published in 1988 does not include quinine, even though it had been used therapeutically long before this list was generated. Quinine has a minimum therapeutic concentration of 3 mg/L and a minimum toxic concentration of 10 mg/L as reported by Clarke's Analysis of Drugs and Poisons.¹² Therefore, quinine does not quite meet the FDA⁴⁶ criteria for an NTI drug.

Summarizing, cinchonism is common and may occur in its mild manifestation even at therapeutic concentrations. Furthermore, as some studies have reported severe toxicity at concentrations that exceed 10 mg/L,^{8,47} a level not much above the concentration associated with therapeutic use of quinine, this drug approaches the criteria at which an API is considered an NTI drug.

CHEMICAL PROPERTIES

Polymorphism

No information on whether quinine exhibits polymorphism could be identified in the literature.

Solubility

The aqueous solubility of quinine sulfate is reported by the Merck Index as "one part in 820 parts water," and by Clarke's Analysis of Drugs and Poisons as "one part in 32 parts of boiling water."^{12,48} Another standard reference book, the Martindale,⁷ cites the solubility of quinine sulfate from the United States Pharmacopeia (USP⁴⁹; one part quinine sulfate to be soluble in 500 parts of water, sparing solubility in water at 100°C) and the European Pharmacopeia⁵⁰ (slightly soluble in water, sparingly soluble in boiling water).

Because the solubility data for quinine sulfate available in the literature do not cover the pH range of 1.0–7.5 at the required temperature of 37°C, additional solubility investigations were performed to classify its solubility properties according to the Biopharmaceutics Classification System (BCS). For these experiments, a standard shake-flask method was applied using six different aqueous media within the pH range of 1.0–7.5 at 37°C. [Solubility studies were performed at the Institute of Pharmaceutical Technology, Goethe University, Frankfurt am Main, Germany, using quinine sulfate ≥99% pure (lot #038K1517; Sigma–Aldrich, Steinheim, Germany).] The results are given in Table 1.

Partition Coefficient

Quinine is a moderately lipophilic compound and has a log *p* value of 3.4 (octanol–water).¹²

pKa

Quinine is a diprotic weak base. It possesses pKa values of 8.5 and 4.1 at 20°C,^{12,51} appearing as free base

Table 1. Solubility of Quinine Sulfate at 37°C in Different Media and Their Corresponding Dose/Solubility (*D/S*) Ratios Based on 300 mg*, 600 mg[†], or 648 mg[‡] Dose Strength

Medium	pH	Solubility (mg/mL)	<i>D/S</i> ^a (mL) Based on 300 mg API	<i>D/S</i> ^a (mL) Based on 600 mg API	<i>D/S</i> ^a (mL) Based on 648 mg API
SGF _{sp} ^b	1.0	10.5	28.7	57.1	62.0
SGF _{sp}	1.2	12.0	25.2	50.0	54.4
Acetate buffer	4.5	5.4	55.5	111.1	119.8
SIF _{sp}	6.8	1.3	240.4	461.5	519.3
SIF _{sp} ^c	7.5	0.3	1010.2	2000.0	2182.0

*Maximum available strength on the WHO Model List of Essential Medicines.⁶

[†]Maximum single orally administered dose in the SmPC.⁷⁵

[‡]Maximum single orally administered dose given by the CDC.⁷⁴

^aCriterion for highly soluble: *D/S* ≤ 250 mL.

^bSame composition as SGF_{sp} with pH adjusted to 1.0.

^cSame composition as SIF_{sp} with pH adjusted to 7.5.

SGF_{sp}, simulated gastric fluid without pepsin; SIF_{sp}, simulated intestinal fluid without pancreatin.

Table 2. Excipients* Present in Quinine Sulfate IR Solid Oral Drug Products with a Marketing Authorization (MA)[†] in Germany⁵² (DE), France⁵³ (FR), Ireland⁵⁴ (IE), Iceland⁵⁵ (IS), the Netherlands⁵⁶ (NL), Portugal⁵⁷ (PT), United Kingdom⁵⁸ (UK), and the United States⁵⁹ (US), and the Minimal and Maximal Amount of That Excipient Present Pro Dosage Unit in Solid Oral Drug Products with a MA in the US[‡]

Excipient	Drug Products Containing an Excipient with an MA Granted by the Named Country	Range Present in Solid Oral Dosage Forms with a MA in the US (mg)
Acacia	FR(1)	5–156 ^a
Alginic acid	NL(2)	32–80
Calcium hydrogen phosphate	PT(3)	104–850
Carmellose sodium	DE(4), FR(1)	2.2–160
Cellulose, microcrystalline	DE(4), IE(5), IS(6), UK(7–9)	4.6–1385 ^a
Croscarmellose sodium	IE(5), IS(6), UK(7,8)	2–180
Gelatin	DE(4)	1–756 ^a
Glucose	PT(3)	157–904
Lactose	NL(2), UK(9)	23–1020 ^a
Magnesium stearate	DE(4), FR(1), IE(5), IS(6), NL(2), PT(3), UK(7–9), US(10,11)	0.15–401 ^a
Povidone	IE(5), IS(6), NL(2), PT(3), UK(7–9)	0.17–80
Silica	DE(4)	0.50–100
Sodium laurilsulfate	IE(5), IS(6), UK(7,8)	0.65–52
Sodium starch glycolate	NL(2), PT(3), UK(9)	2–876 ^a
Starch	FR(1), NL(2), PT(3), UK(9), US(10,11)	0.44–1135 ^a
Talc	PT(3), US(10,11)	0.10–220 ^a
Vegetable oil, hydrogenated	IE(5), IS(6), UK(7,8)	2–261

(1) Quinine Sulfate Lafran 217.2/434.4 mg cp (2) Chinini sulfas 200, dragees 200 mg (3) Quinina Labesfal 300 mg comprimidos (4) Limptar[®] N Filmtabletten 200 mg (5) Quinine Sulfate 300 mg Coated Tablets

(6) Quinine Sulfate Actavis 200 mg filmhúðadar töflur (7) Quinine Sulfate Tablets 200/300 mg (Actavis UK Ltd.) (8) Quinine Sulfate Tablets BP 200 mg (Actavis UK Ltd.) (9) Quinine Sulfate 300mg Coated Tablets (Wockhardt UK Ltd.) (10) Quinine Sulfate (quinine sulfate) capsule 324 mg (AR Scientific, Inc.) (11) Quinine Sulfate (quinine sulfate) capsule 324 mg [Stat RX USA LLC]

*Colorants, water, and ingredients present in the printing ink are not included; excipients were also excluded if it could be assumed that they were present in the coating/polish only.

[†]The approval of a drug product by the local regulatory authority. Also the terms drug approval and registration are used.

[‡]FDA's inactive ingredient database, <http://www.fda.gov/Drugs/InformationOnDrugs/ucm113978.htm> (version date 31-12-2010).

^aThe upper range value reported is unusually high for solid oral dosage forms and the authors doubt its correctness.

at high pHs and as one of its ionized forms (quinine-H⁺ or quinine-2H⁺) at lower pHs.

Dosage Form Strengths and Dose

Globally, several single-API dosage form strengths of quinine sulfate are available in the market. The qualitative composition of single-API products identified in Europe^{52–58} and the United States,⁵⁹ most of which contain 200 or 300 mg of quinine sulfate, are given in Table 2. The WHO EML registers a dosage strength of 300 mg quinine sulfate, equivalent to approximately 246 mg base.⁶ The only product approved by the FDA, Quinine Sulfate (AR Scientific, Inc.; Philadelphia, Pennsylvania, USA), contains 324 mg quinine sulfate, which is equivalent to approximately 266 mg base.⁶⁰

PHARMACOKINETIC PROPERTIES

It has been frequently reported in the literature that the pharmacokinetic properties of quinine are altered by malarial infection.^{7,8,25,61} Further, its pharmacokinetic properties as well as its therapeutic response vary significantly with age and pregnancy.^{8,19,62}

Absorption and BA

Quinine has been demonstrated to be rapidly and almost completely absorbed,^{7,63–65} even in patients with marked diarrhoea.¹⁰ After oral administration,

less than 5% of the API can be recovered from the faeces.^{12,64} Fuder et al.⁶⁶ reported absorption rates of nearly 90% for oral tablets when compared with intravenous (i.v.) dose.

Various studies have been performed to analyze the pharmacokinetic properties of quinine sulfate in healthy individuals or patients with malarial infection. Most of them have been discussed and compared in previous review articles.^{8,61}

Studies investigating the pharmacokinetics of oral quinine sulfate have reported maximum plasma concentrations (C_{max}) ranging from 1.45⁶⁷ to 12.70 mg/L⁶⁷ (mean 2.41 ± 0.76 to 6.68 ± 3.00 mg/L)⁶⁷ in volunteers (single dose application of approximately 600 mg quinine sulfate), and from 5.54¹⁹ to 17.62 mg/L¹⁹ (mean 8.4 mg/L⁶⁸ to 12.7 mg/L⁶⁹) in patients with malarial infection (threefold application of approximately 10 mg/kg quinine sulfate for 1 week), respectively. In children suffering from malaria, mean C_{max} was found to be 7.3 ± 1.1 mg/L as compared with 3.4 ± 1.1 mg/L after convalescence.⁷⁰ Generally, the time to reach C_{max} was within 1–3 h (T_{max}).⁷ The absolute BA after oral quinine intake has been demonstrated to lie normally between 76%⁷¹ and 88%⁶⁵. However, a small study performed by Babalola et al.⁶⁷ investigated the absolute BA of two Nigerian oral quinine formulations (one capsule and one tablet formulation vs. an i.v. formulation) in two groups of six healthy individuals (parallel design) and found significantly

different absolute BA values of 73% for the capsule and 39% for the tablet formulation.

Permeability

No data on the permeability of quinine, for example, obtained from human mass-balance studies or CaCo-2 cell studies, could be identified in the literature.

Distribution, Metabolism, and Elimination

Quinine is widely distributed throughout the body.⁷ Its plasma protein binding is reported to be approximately 70% in healthy individuals, increasing up to 90% or more in patients with malarial infection.¹² The clearance of quinine is predominantly by hepatic metabolism,⁸ which is known to be inhibited by malarial infection.¹² The plasma elimination half-life ($t_{1/2}$) of quinine, which is increased during malarial infection, ranges from 4–15 h (mean 9 h).¹² The volume of distribution (V_d), which is about 2 L/kg in healthy volunteers, is significantly reduced in patients with malaria.¹² Sabchareon et al.⁷⁰ studied the pharmacokinetics of quinine in children and reported a more rapid elimination, but a smaller V_d as compared with adults. The pharmacokinetics obtained from pregnant women in comparison with normal adults showed significant differences in the same direction: shorter $t_{1/2}$, smaller V_d values, and reduced total clearance.⁸

DOSAGE FORM PERFORMANCE

Excipients

The excipients of 11 marketed IR solid oral drug products containing quinine sulfate as single API are given in Table 2. However, no studies about the likelihood of these excipients interacting with quinine release and absorption have been reported to date.

Bioequivalence

Hall et al.⁷² observed no significant differences in quinine plasma concentrations between a sugar-coated tablet product (containing quinine sulfate equivalent to 270 mg base; Strong Cobb Arner, Inc., Cleveland, Ohio, USA) and a gelatin capsule product (containing quinine sulfate equivalent to 270 mg base; Eli Lilly and Company, Indianapolis, Indiana, USA), leading the authors to conclude that these two formulations are bioequivalent. Babalola et al.⁶⁷ compared the absolute BA of two 600 mg quinine sulfate formulations, a capsule (Eli Lilly and Company) and a tablet (ACF Chemiafarma, Maarssen, the Netherlands), with an i.v. formulation, reporting values of 73% for the capsule and 39% for the tablet formulation and concluded that the two dosage forms were bioinequivalent. The excipients present in these two drug products were not reported, nor were their *in vitro* dissolution. Al-

though this study was carried out in parallel design with only six healthy volunteers per group,⁶⁷ the results cannot be ignored because the effect of formulation on quinine absorption were pronounced.

Dissolution

Dissolution test conditions for drug products containing quinine sulfate are given in the current version of the USP (FDA)⁴⁹ and the International Pharmacopoeia (WHO).¹¹ Because BCS-conforming dissolution tests have to be applied to reach the biowaiver decision,^{3–5} two marketed products as well as pure API were tested according to the BCS dissolution methods. [Dissolution studies were performed at the Institute of Pharmaceutical Technology, Goethe University. The investigated drug products were Qualaquin[®] (USA; only FDA-approved quinine product; AR Scientific, Inc.; Philadelphia, Pennsylvania, USA) and Obd Chininii Sulfatis Dragees 250 mg[®] (Hänseler AG, Herisau, Switzerland), as well as hard gelatine capsules filled with 300 mg quinine sulfate (Sigma-Aldrich). WHO⁵ biowaiver dissolution test conditions were applied because EMA³ and FDA⁴ exclude quinine sulfate from the biowaiver procedure due to its unfavorable dose/solubility (D/S) ratios according to their definitions. Quinine was analyzed at 250 nm (pH 1.2 and 4.5) and 238 nm (pH 6.8), respectively.) The results are depicted in Figure 2. None of the products or the pure quinine sulfate reference substance met the biowaiver dissolution criteria by the WHO⁵ for rapidly dissolving, that is, they were unable to release 85% or more within 30 min at all three pH values. Notably, no recommended comparator is given for quinine drug products by the WHO⁷³ list of “Recommended Comparator Products: Antimalarial Medicines.”

DISCUSSION

Solubility

The results from the BCS-conforming solubility measurements are shown in Table 1.

According to the FDA⁴ requirements, the D/S ratio must be less than or equal to 250 mL at 37°C over a pH range of 1.0–7.5 to meet the criterion for highly soluble. The highest single dose recommended in the Summary of Product Characteristics (SmPC) is used as D for the calculations. In the United States, the marketed product is Qualaquin[®] (AR Scientific, Inc.; Philadelphia, Pennsylvania, USA), which contains 324 mg quinine sulfate and is administered as 1–2 tablets/dose.⁷⁴ On the basis of this dosage regimen, which results in a maximum single dose of 648 mg API, quinine sulfate does not meet the criterion for highly soluble.

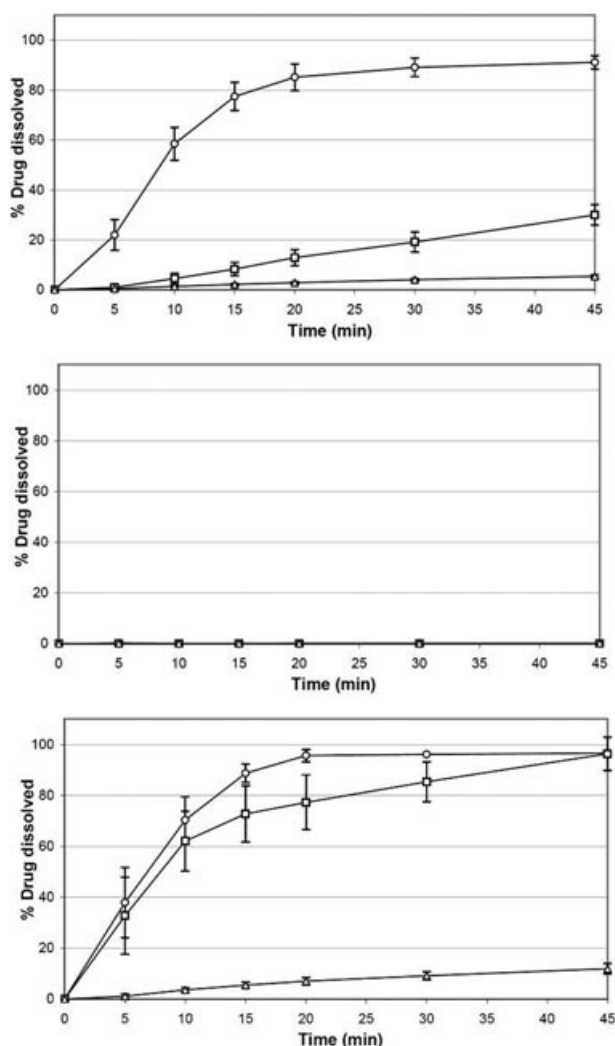


Figure 2. BCS-conforming dissolution of quinine sulfate drug substance and two quinine sulfate drug products according to EMA³/WHO⁵ test conditions [paddle apparatus; 75 rpm; three different media: simulated gastric fluid without pepsin (SGF_{sp}), pH 1.2; acetate buffer, pH 4.5; and simulated intestinal fluid without pancreatin (SIF_{sp}), pH 6.8; 37°C]. Top, Qualaquin®; middle, Obd Chininii Sulfatis 250 mg®; bottom, quinine sulfate pure reference substance filled in hard gelatine capsules. The dissolution data represent mean \pm SD of the percentage of quinine dissolved at each sampling time point. \circ , SGF_{sp}; \square , acetate buffer; \triangle , SIF_{sp}.

According to the EMA³ biowaiver requirements, the D/S ratios must be less than or equal to 250 mL at 37°C over a pH range of 1.0–6.8, whereby D is specified as the highest single oral dose recommended in the SmPC. Applying the appropriate dose of two tablets, which is equivalent to 600 mg of quinine sulfate,⁷⁵ the API clearly fails to meet the highly soluble criterion.

According to the WHO⁵ biowaiver criteria the D/S ratios must be less than or equal to 250 mL in

aqueous media, covering a pH range of 1.2–6.8 at 37°C to demonstrate high solubility. In this case, D is the highest dose strength listed in the WHO EML⁶ (300 mg quinine sulfate). At that dose, quinine sulfate meets the criterion for highly soluble, noting that its D/S value at pH 6.8 is close to the permissible limit.

In summary, quinine sulfate can or cannot meet the definition of high solubility depending on the locally applied criteria and should, therefore, be considered a borderline case.

Permeability and Absorption

Quinine sulfate is often reported to be highly permeable^{5,76} or borderline high-to-low permeable.⁷⁷ The absolute BA after oral quinine intake was reported to be 76% or 88%,^{65,71} indicating that quinine has good permeability. It should be noted that because quinine is extensively hepatically metabolised,⁸ the absolute BA represents a minimum estimate of the fraction absorbed. The observation that less than 5% of an oral dose of quinine is recovered in the faeces provides supporting evidence of high permeability.^{10,12,64} Thus, quinine can be tentatively classified as highly permeable according to the guidance of EMA,³ FDA,⁴ or WHO.⁵

BCS and Biopharmaceutical Drug Disposition Classification System

On the basis of a 300 mg dose, Lindenberg et al.⁷⁷ and Kasim et al.⁷⁶ classified quinine as BCS class I/III (borderline) and I, respectively. Wu and Benet⁷⁸ classified quinine as class I drug using their Biopharmaceutical Drug Disposition Classification System approach, that is, as highly soluble and extensively metabolized.

Taking all relevant data into consideration, for Europe and the United States, quinine is assigned to BCS class II, failing to meet the criteria for high solubility, but probably meeting the criterion for high permeability. It should be noted that drug products containing BCS class II APIs cannot qualify for the biowaiver in these jurisdictions. For countries following the WHO guidelines, quinine can be classified as BCS class I at the dose given in the EML, which would open the way for a biowaiver-based approval, provided the risk-benefit analysis is positive.

Risks of Bioinequivalence Caused by Excipients and/or Manufacturing Parameters

Babalola et al.⁶⁷ reported that quinine sulfate is poorly absorbed from a Nigerian tablet formulation (absolute BA = 39%), compared with a Nigerian capsule product (absolute BA = 73%). Because no information about the excipients present in these

formulations is given and no dissolution experiments were performed, the origin of this negative influence cannot be addressed. The BCS-conforming dissolution studies on two other products as well as the pure substance in our laboratories suggest that the use of different excipients and/or different manufacturing parameters can be expected to have an influence on the dissolution behavior of the dosage form and thus on BE.

Surrogate Techniques for *In Vivo* BE Testing

BCS-conforming dissolution tests, as specified by the EMA,³ FDA,⁴ or WHO,⁵ show slow and incomplete dissolution (Fig. 2) of both the pure drug and the two oral quinine drug products tested, with the result that in none of the three cases were the requirements for rapidly dissolving fulfilled. From these results it appears that it is unlikely that the biowaiver procedure for the approval of products containing quinine sulfate could be applied, as they would not be able to meet the dissolution criteria. Comparing the profiles, the slow dissolution appears to be mainly substance related rather than formulation related.

Patient's Risks Associated with Bioinequivalence

Quinine is classified by the Pan American Health Organization⁷⁹ as a drug with intermediate health risks. However, quinine shows quite some dose-related serious side effects, including fatalities at concentrations not far above those required for therapy. It has been reported that the ranges of therapeutic and toxic plasma concentrations are not well separated and can, in fact, overlap.⁸⁰ Therefore, supratherapeutic plasma concentrations of quinine are likely to be associated with high patient risk, for example, cardiotoxicities, which can even be life-threatening for the patient. It is of note that, in general, adult patients are especially at risk to exposure to toxic plasma concentrations because clearance of quinine is lower in these patients (with the exception of pregnant women) than in healthy volunteers.

On the contrary, subtherapeutic quinine plasma levels are associated with a high risk of therapy failure. As annually around 881,000 patients die of malaria,⁸¹ poor quality drug products in this therapeutic area can have a major impact on the public health status in the countries where this disease is prevalent. It is of note that children and pregnant women are especially at risk of exposure to subtherapeutic levels because clearance of quinine is higher in these patients than in healthy volunteers.

Thus, there is strong evidence that bioinequivalent drug products can, on the one hand, harm or, on the other hand, not adequately treat patients receiving quinine, and thus be detrimental to public health.

CONCLUSIONS

There are several concerns with applying the biowaiver to quinine products. First, the API does not or barely fulfills the solubility requirements for biowaiver-based approval. Second, the demonstrated dissolution characteristics of the pure substance and quinine drug products tested, including the innovator Qualaquin® (AR Scientific, Inc.; Philadelphia, Pennsylvania, USA), fail by far to meet the criteria for rapidly dissolving by EMA,³ FDA,⁴ or WHO.⁵ Quinine sulfate products are unlikely to be able to comply with the BCS-based dissolution specifications because the API itself has poor dissolution properties. Third, the patient risk associated with bioinequivalent quinine drug products outweighs the potential benefit of a quinine biowaiver. Taking all relevant aspects into consideration, the dissolution-based biowaiver is not justified for new quinine sulfate drug products or the reapproval of existing drug products after extensive variations like scale-up and postapproval changes level 3⁸² or European Union (EU) type II variations.⁸³ Hence, the BE decision of two different quinine formulations should be based on *in vivo* BE studies to be carried out in accordance with the guidelines of the relevant registration authority, for example, for registration in European countries, the "Guideline on the Investigation of Bioequivalence" by the EMA.³

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