

We are IntechOpen, the world's leading publisher of Open Access books Built by scientists, for scientists

6,900

Open access books available

186,000

International authors and editors

200M

Downloads

Our authors are among the

154

Countries delivered to

TOP 1%

most cited scientists

12.2%

Contributors from top 500 universities



WEB OF SCIENCE™

Selection of our books indexed in the Book Citation Index
in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?
Contact book.department@intechopen.com

Numbers displayed above are based on latest data collected.
For more information visit www.intechopen.com



Tackling the Problems Associated with Antimalarial Medicines of Poor Quality

Kamal Hamed and Kirstin Stricker

Additional information is available at the end of the chapter

<http://dx.doi.org/10.5772/64671>

Abstract

The use of poor-quality antimalarials has devastating consequences, including increased morbidity, mortality, and drug resistance. Unfortunately, this issue appears to be widespread, especially in parts of Africa and Asia, jeopardizing the progress and investments already made in global malaria control in these regions. In developing countries, inadequate laws and regulatory oversight, along with the lack of human, technical, and financial resources, do not encourage the manufacture and distribution of high-quality medicines. The problem of poor-quality medicines can only be addressed by a multipronged approach that includes tackling poor regulation and ineffective/poorly implemented laws at national and international levels. In addition, pharmaceutical companies must be responsible for ensuring that the quality of antimalarials meets the stringent guidelines established by regulatory authorities, for testing their medicines accordingly and for releasing to market only medicines that pass these requirements. The chapter also discusses how the implementation of strategies such as the WHO Prequalification Program, the African Medicine Registration Harmonization initiative, and the ethical production of medicines by pharmaceutical companies help to ensure that antimalarial therapies marketed in low-income, malaria-endemic countries are quality assured.

Keywords: antimalarial medicines, malaria, quality, Africa, Asia

1. Introduction

Safe, effective, high-quality, and affordable medicines are essential for the achievement of positive, equitable health outcomes [1]. They are necessary for the prevention and treatment of serious public health threats, and for the achievement of the global health goals [2]. However,

there is growing concern regarding the increasing availability and use of poor-quality medicines, particularly in developing countries in Africa, Asia, and South America [3–7].

Poor-quality medicines include those that have been falsified (i.e., deliberately and fraudulently mislabeled with respect to identity and/or source) and substandard medicines (i.e., products resulting from poor manufacturing with no intent to deceive and usually with inadequate or too much active pharmaceutical ingredient) [2].

Falsified medicines have resulted in billions of dollars in illegal annual revenues going to criminals and have caused prolonged, severe illness and deaths. Falsified drugs particularly affect the most disadvantaged people in poor countries [5].

In particular, the use of substandard antimalarial agents has been reported [3, 4, 7–18]. A World Health Organization (WHO) survey of antimalarial medicine quality in six countries from sub-Saharan Africa discovered that nearly 30% of the fully tested samples of medications failed to comply with internationally recognized quality specifications [8]. Similarly, a review reported that approximately one third of antimalarial medication samples from sub-Saharan Africa, as well as from Southeast Asia, failed chemical assay analysis [3].

Factors contributing to poor-quality medicines are numerous [3]. In many developing countries, for example, first-line artemisinin-based combination therapy (ACT) cannot be afforded by many patients [4, 5]. Consequently, patients tend to procure cheaper alternatives that may be falsified or substandard and that may contain subtherapeutic amounts of the active pharmaceutical ingredients (APIs) or only one of the two active ingredients of the ACT [2, 12]. Thus, the use of such poor-quality antimalarial agents leads to increases in morbidity and mortality [19]. In addition, subtherapeutic concentrations of drugs *in vivo* may be contributing to the selection of resistant parasites [3, 20, 21]. In the face of seemingly ineffective agents, societies are at risk of losing confidence in antimalarial medicines, their doctors and the healthcare system, and thus jeopardizing years of global public health success and investment [2].

In many countries, inadequate laws and regulatory oversight, along with the lack of human, technical, and financial resources, do not encourage the manufacture and distribution of high-quality medicines [2, 22]. The WHO has estimated that nearly a third of countries lack the ability to oversee medicine manufacture, importation, or distribution [23]. With this in mind, the WHO is playing an important role in establishing quality standards for registration and quality control of antimalarials by a prequalification program [24]. Initiatives such as the African Medicine Registration Harmonization (AMRH), in which partners collaborate with the WHO, have also been started in an attempt to improve quality standards of medicines at local and regional levels [25]. In addition, pharmaceutical companies must be responsible for ensuring that the quality of antimalarials meets the stringent guidelines established by regulatory authorities, for testing their medicines accordingly and for releasing to market only medicines that pass these requirements [2, 22].

This chapter will discuss the extent and consequences of poor-quality antimalarial medicines. In addition, the ways in which this issue might be tackled are also discussed, with a focus on the role of pharmaceutical companies, the WHO, and local and regional initiatives.

2. Defining poor-quality antimalarials

A variety of definitions have been used to classify the different types of poor-quality medicines [3, 26, 27]. The WHO has attempted to develop a consensus on definitions of poor-quality medicines, and has outlined two classes of drugs, namely those that are falsified, and those that are substandard [26].

Falsified medicines have been fraudulently manufactured with fake packaging, and contain little or no active ingredient (and often other potentially harmful substances) [3, 26]. Falsified antimalarial tablets and ampoules containing little or no API are a major problem in some areas [25]. They may be impossible to distinguish from the genuine product and may lead to under-dosing and high levels of treatment failure. In some extreme cases, the falsified antimalarials may contain toxic ingredients [26].

Substandard medicines have been poorly manufactured by a legitimate producer with no intent to deceive, but they usually have inadequate or excessive amounts of active ingredient(s) and/or excipients [3, 26]. The WHO also includes degraded drugs within this class [26]. The degraded drugs were originally of good quality, but become poor quality as a result of unsuitable or extended storage after manufacturing, or through interaction with inadequate excipients [3, 26].

3. The growing problem of poor-quality antimalarials

The problem of poor-quality antimalarial agents, particularly those containing artemisinins, is widespread and varies among countries. There are numerous reports of falsified and substandard antimalarial agents in particular in Africa and Asia [8–18].

One WHO survey evaluated the quality of selected antimalarials in six countries in sub-Saharan Africa (Cameroon, Ethiopia, Ghana, Kenya, Nigeria, and United Republic of Tanzania) [8]. Samples were collected and tested for quality by reliable quality control laboratories according to specifications set up in recognized pharmacopeias. The researchers found that 28.7% of the 267 fully tested samples collected between April and June 2008 failed to comply with prespecified internationally acceptable quality criteria. A similar proportion of ACTs and sulfadoxine-pyrimethamine (SP) were subject to quality defects (29% for ACTs and 28% for SP; **Figure 1**). Prevailing problems associated with ACTs were related to the content of the APIs and the presence of impurities. For SP, it was mainly problems related to dissolution. Interestingly, only 4% of the drugs with the WHO prequalification status failed quality analysis, compared with 60% of drugs not prequalified by the WHO. Therefore, control of the quality of antimalarial medicines throughout the distribution system, according to proper specifications, is an important prerequisite for ensuring optimal treatment outcomes [8].

In Southeast Asia, a similar problem with poor-quality medicines has been reported in a review of published and unpublished data from studies evaluating samples of antimalarials [3]. In seven Southeast Asian countries, 497 (35%) of 1437 samples failed chemical analysis, 423 (46%)

of 919 samples failed packaging analysis, and 450 (36%) of 1260 samples were falsified [3]. The same review also found that, in sub-Saharan Africa (21 countries), 796 (35%) of 2297 samples failed chemical analysis, 28 (36%) of 77 samples failed packaging analysis, and 79 (20%) of 389 samples were falsified [3].

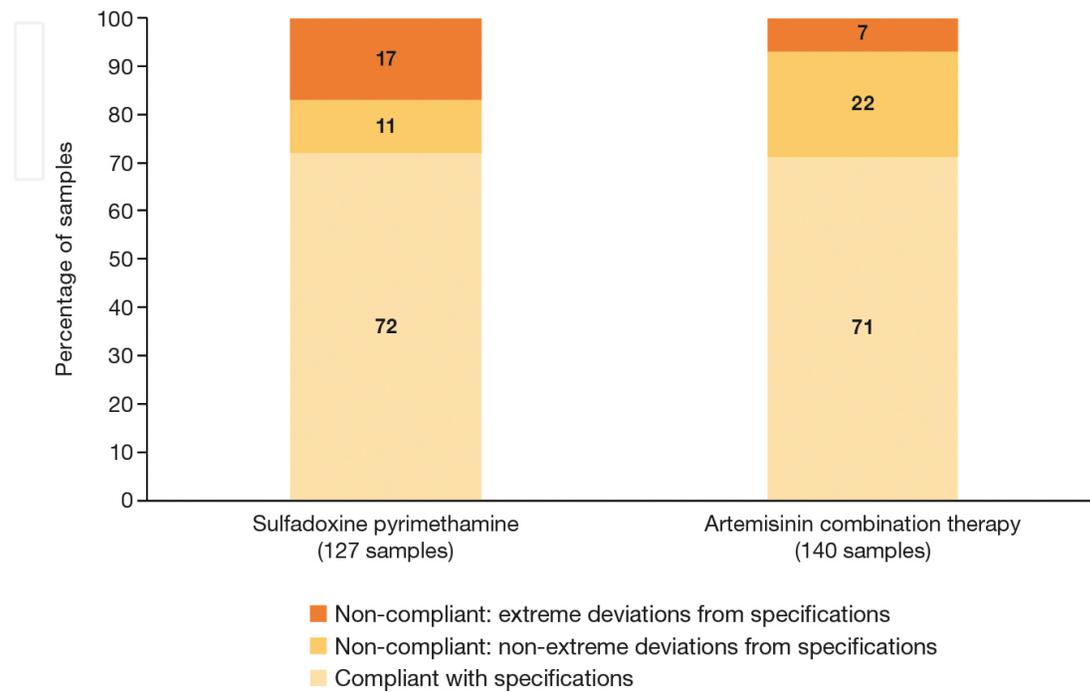


Figure 1. Proportions of compliant, moderately noncompliant and extremely noncompliant samples of artemisinin-based combination therapies (ACTs) and sulfadoxine-pyrimethamine (SP) in sub-Saharan Africa [8]. Extreme deviations were defined as a deviation by at least 20% from the declared content to one or more active ingredients, and/or dissolved percentage of one or more active ingredients less than the pharmacopoeial limit (Q) minus 25%.

The World-Wide Antimalarial Resistance Network (WWARN) has developed a comprehensive, open-access, global database, with a linked Antimalarial Quality Surveyor (an online visualization tool) in order to more fully understand the evidence relating to poor-quality antimalarials [15]. A systematic literature search from 1946 to March 2013 identified 251 published antimalarial reports, of which 130 had sufficient information to estimate the frequency of poor-quality antimalarials [15]. Out of 9348 antimalarials sampled, 30.1% (2813) failed chemical or packaging quality tests. Of the 2813 failed samples, 39.3% were classified as falsified, 2.3% as substandard, and 58.3% as poor quality without evidence available to categorize them as either falsified or substandard. Oral artesunate was the medicine most commonly reported as falsified (with 61.9% failing). The survey found that 60.6% (63) of the 104 malaria-endemic countries had no publicly available reports on antimalarial drug quality. Further investigation of the quality of antimalarials is required in the Americas, and in central and southern African regions, as there have been very few studies conducted in these malarious areas [15].

Studies from individual countries have also reported the existence of poor-quality antimalarials. One recent study used mystery shoppers and overt surveys to identify the quality of

antimalarials in Cambodia [12]. Of 291 samples tested, 31.3% did not contain an appropriate amount of the API, i.e., the API content was not within the 85–115% range when measured by high performance liquid chromatography, and the samples were therefore considered to be of poor quality.

A recent study of the quality of artemisinin-based antimalarials from Tanzania's private sector found that, while none of the 1737 antimalarial samples were falsified, 4.1% were outside the 85–115% artemisinin API range [17]. WHO prequalified drugs (25.7% of the total) were more likely to be of higher quality, with only 0.5% WHO prequalified drugs being of poor quality, compared with 5.4% of those not WHO prequalified.

4. Consequences of poor-quality antimalarials

The use of poor-quality antimalarials has serious consequences (see **Table 1**) [3, 19, 28–36].

Increases in morbidity and mortality

Financial loss for patients, healthcare system, pharmaceutical companies

Loss of public confidence in pharmaceutical brand, medicines, pharmacies, and healthcare providers

Increased drug resistance

Table 1. Consequences of poor-quality antimalarials.

4.1. Morbidity and mortality

Exposure to low-quality antimalarials results in poor treatment outcomes, with increased morbidity and mortality. The literature contains several case reports of patients placed at risk or dying as a result of poor-quality antimalarials [28–30]. A study in 39 sub-Saharan African countries estimated that approximately 122,350 (4%) of the deaths in children aged <5 years that occurred in 2013 were associated with poor-quality antimalarial agents [19].

The impact of falsified and substandard medicines is likely to extend beyond such increases in morbidity and mortality. The continued use of poor-quality antimalarials that carry subtherapeutic levels of active ingredient will most likely lead to drug resistance [26, 31–36]. Partial artemisinin-resistant *Plasmodium falciparum* malaria has been reported in several Asian countries in the Greater Mekong Subregion [31–35]. The change in parasite sensitivity is manifest in the form of delayed parasite clearance, and has been associated with mutations in the Kelch 13 (K13) propeller region [37]. Indeed, the Greater Mekong Subregion is a major source from which drug-resistant malaria, including artemisinin-resistant *P. falciparum*, is known to emanate [38]. This occurs for multiple reasons, among which the local prevalence of falsified or substandard artemisinins is an important exacerbatory factor [38]. Based on the new WHO Global Technical Strategy for malaria 2016–2030, countries in the Greater Mekong Subregion have established a Strategy for Malaria Elimination in the Greater Mekong (2015–

2030) in response to the threat of multidrug resistance in this region [36, 39]. The goals of the strategy are to eliminate *P. falciparum* malaria by 2025, and all malaria by 2030, in all countries in the Greater Mekong.

4.2. Resistance

Resistance can be prevented or its outset slowed by the use of combination antimalarials, with different mechanisms of action [26]. Consequently, the standard of care for uncomplicated *P. falciparum* (i.e. move P. from previous page to page 6, line 1 so as not to break *P. falciparum* (*P. [space] falciparum*) malaria is treatment with ACTs [26]. The use of artemisinin monotherapies in subtherapeutic doses for over 30 years and the availability of substandard artemisinins are thought to be a major driving force in the selection of the resistant phenotype in these regions [9, 10, 33]. Moreover, some therapies declared as combinations in effect have been proven to be artemisinin monotherapies [9]. Resistance to artemisinin compromises the efficacy of the ACT and adds pressure on the partner drug [26].

Resistance to chloroquine has also been confirmed in *Plasmodium vivax* in 10 countries [36]. ACTs are now recommended for the treatment of chloroquine-resistant *P. vivax*, with the exception of treatment with artesunate and SP, where resistance to the partner drug may compromise the efficacy of the combination therapy.

4.3. Economic burden

The use of poor-quality antimalarials can have a negative financial impact on patients and their families [3, 16, 40]. Replacement or additional drugs, repeated courses of poor-quality antimalarials, repeated consultations at health facilities, and lost work days can all impose an unwanted economic burden [3, 16, 40]. Indeed, recent modeling assuming current incidence rates of malaria indicates that widespread artemisinin resistance can be expected to lead to 116,000 excess deaths annually [41]. This burden may be particularly severe in some developing countries, where the majority of the population has to pay for their medicines and the cost of the medication represents a substantial proportion of the household income [40].

Poor-quality antimalarials also have negative financial consequences for healthcare systems, pharmaceutical companies, governments and societies, and their use may potentially jeopardize the investments made in the past decades to control and eliminate malaria [3, 16, 40]. The lost productivity and increased healthcare costs associated with the use of poor-quality antimalarials generally occur in resource-constrained countries that are already disproportionately bearing the global cost of malaria [36, 40]. These countries generally lack the increased financial resources needed to inspect, analyze and police the antimalarial supply chain [7].

In particular, the development and spread of resistance to antimalarial medicines has increased the cost of controlling malaria [36, 40, 41]. A decision-tree model estimated the direct medical costs for the effective treatment of malaria using ACT in nonresistant areas to be \$US114 million (2013 costs). In comparison, it was estimated that these costs would increase by 28% if ACT was failing at a rate of 30%, and treatment of severe malaria reverted to quinine [41]. Productivity losses were estimated to be \$US385 million for each year during which failing ACT was

used as first-line therapy [41]. Most of this cost was associated with the lost productivity associated with excess morbidity after treatment had failed.

The development of resistance to all current antimalarials would necessitate the development of new, and potentially more expensive, alternatives by pharmaceutical companies, further adding to the economic burden they incur when a poor-quality alternative is used instead of their legitimate high-quality product [40].

If clinical trials use poor-quality medicines, not only are resources wasted, but patients may be harmed [42]. In addition, the erroneous conclusions reached in these trials may inappropriately inform public health policy [42].

5. Tackling the problem of poor-quality antimalarials

A wide variety of issues have contributed to the proliferation of poor-quality medicines in developing countries (**Table 2**) [2, 3]. In order for the quality of antimalarials to be assured, these issues need to be addressed.

Inadequate testing of quality

- Lack of inexpensive surveillance testing systems
- Lack of prequalified laboratories

Poor consumer and healthcare worker knowledge about product authenticity

Inadequate standardization of procedures within quality surveys

Self-prescription of drugs

Availability of products via the Internet

Expensive drugs with large profit margins

Trading in free-trade zones or free ports with minimum regulation

Poor or inadequate national, regional and global legislation, with few legal penalties

Absence of drug regulatory authorities

Unethical practices by manufacturers of antimalarials

Lack of political will and cooperation from stakeholders

Stockouts, thefts, and the erratic supply of antimalarials

Table 2. Factors contributing to the manufacture and distribution of poor-quality antimalarials [2, 3, 16].

It is essential that antimalarial medications be produced according to good manufacturing practice, contain the correct drug(s) and excipients in appropriate doses, and have bioavailability that is similar to the reference product; in addition, the drugs must be stored under appropriate conditions, and be dispensed before their expiry date [26].

Some of the factors that contribute to the availability of poor-quality medicines can only be addressed by collaborative action between law enforcement bodies, regulatory authorities, and customs and excise agencies [26]. Encouragingly, some initiatives and mechanisms are already in place to help ensure that quality assured antimalarials are available for use in malaria-endemic countries.

5.1. Detection methods and technology

Tests capable of accurately detecting and classifying poor-quality medicines at the point of entry into countries and at public and private pharmacies are essential for understanding the types, names, extent, and amount of poor-quality medicines being dispensed both nationally and globally [2, 7].

Such tests can be conducted using quick, inexpensive methods in the field with the aim of examining packaging and detecting drug contents [7]. These tools would also empower those inspecting the medicines throughout the supply chain [7]. Rather than having to wait for the samples to be sent to national or international laboratories, results would be available more or less immediately [7]. Current methods for testing the quality of drugs in the field include visual packaging inspection, lot number reporting via mobile phones, thin-layer chromatography, colorimetric tests, and simplified spectroscopic methods [2, 7]. Portable instruments used to screen for the quality of antimalarial agents include Raman spectrometers and the Global Pharma Health Fund GPHF-Minilab® [40]. Other simple, technologies for testing the quality of antimalarials in the field are in development [43, 44].

More accurate methods of testing the quality of medicines involve laboratories that are equipped for exhaustive chemical analysis [2]. Such investigations can be difficult in developing countries, given the sophisticated and expensive equipment, the type of reagents, and the level of technical expertise that are required. For example, Kenya, Tanzania, South Africa, and Uganda are currently the only countries in Africa with WHO prequalified laboratories for drug quality testing [19, 45].

5.2. Field reports

Quality surveys can serve as an important source of information about the quality of medicines available. Data on the quality of antimalarials, if properly collected, interpreted and used, are essential for the planning of effective interventions [46]. However, reports that have not employed rigorous scientific techniques will potentially bias results [47]. To ensure consistency and accuracy, the WHO has recently produced draft guidelines for the conduct of surveys of quality medicines [46].

5.3. Legislation and regulation

Existing laws in many countries are insufficiently strict to deter the manufacturing and distribution of poor-quality medicines; where this legislation exists, it may not be implemented [22]. Such absence of legislation prohibiting the manufacture and distribution of poor-

quality medicines encourages their continued manufacturer, since there is no fear of being apprehended and prosecuted [2, 22].

Appropriate national medicine regulatory authorities would help to ensure that all pharmaceutical products on the market were safe, effective and meet approved quality standards [48]. Such regulation would control registration and postmarketing surveillance (quality monitoring and pharmacovigilance) of medicines, as well as the licensing and inspection of manufacturers, importers, exporters, wholesalers, distributors, pharmacies and retail outlets, control of clinical trials, and control of the promotion (Figure 2) [48]. It has also been suggested that an international legal convention against poor-quality medicines would address both regulatory and criminal international governance challenges [7].

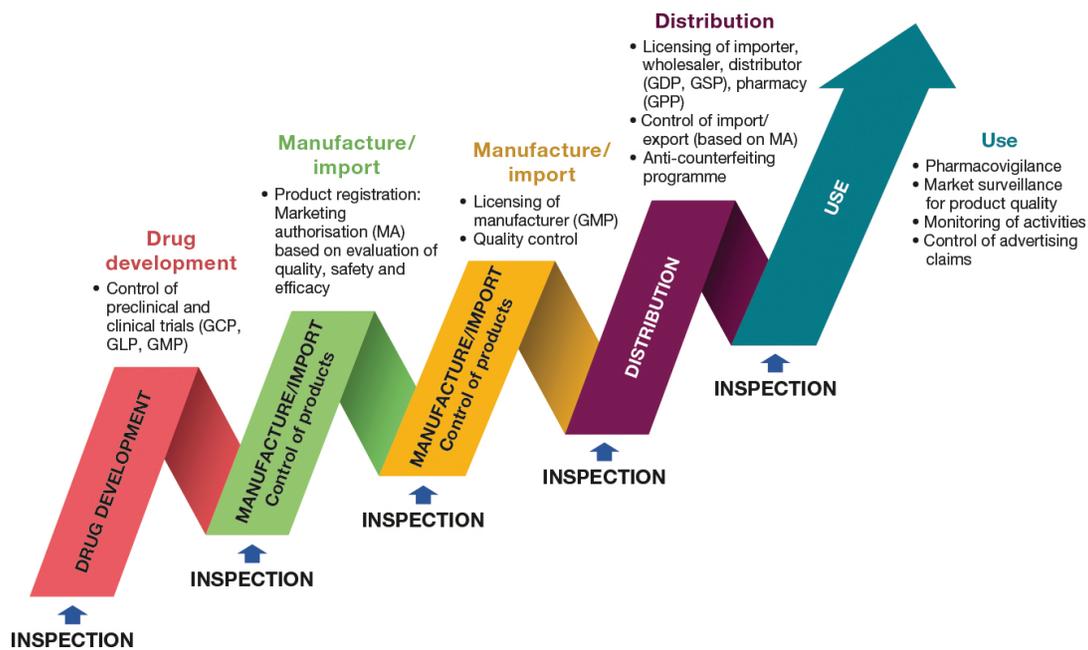


Figure 2. Regulatory system for medicines [48]. GCP, good clinical practices; GDP, good distribution practices; GLP, good laboratory practices; GMP, good manufacturing practices; GPP, good pharmaceutical practices; GSP, good storage practices.

However, the WHO has estimated that 30% of member countries lack any capacity to oversee medicine manufacture, importation, or distribution [23]. At present, only about 20% of member countries have well-developed medicine regulation at varying levels of development and operational capacity.

In particular, the lack of global harmonization of drug registration processes is contributing to the increased availability of poor-quality antimalarials. Regulatory authorities such as the European Medicines Agency (EMA) and the United States Food and Drug Administration (FDA) provide guidelines for the registration of new drugs for the pharmaceutical industry. Such guidelines include steps for assuring drug quality [49, 50]. For example, the FDA regulates and controls new drugs according to the new drug application process and the

review and ultimate approval of generic drugs is controlled by regulations for abbreviated new drug applications.

However, similar rigorous standards are not applied universally, and particularly in sub-Saharan Africa. Africa currently has more than 50 independent local regulatory health authority agencies, with different administrative and technical requirements, processes and timelines for medicine registration and regulatory review, and with variable transparency of the registration process. A recent WHO assessment in 26 sub-Saharan African countries found that drug approval regulation was not carried out to the extent required to ensure the quality, efficacy, and safety of medicines [48]. Few countries in sub-Saharan Africa relied on the decisions made by other regulators, such as those stringently applied by the EMA or FDA, or by the WHO through its Prequalification of Medicines Program [48].

5.4. The role of the WHO

Many look to the WHO for leadership in regulating the quality of medicines, especially in light of its successful implementation of the public health treaty on tobacco control [7].

Due to the association of oral artemisinin monotherapies with the development of resistance, the WHO urges regulatory authorities in malaria-endemic countries *“to take measures to halt the production and marketing of these oral monotherapies, and promote access to quality-assured artemisinin-based combination therapies”* [51]. The number of countries that allow the marketing of oral artemisinin monotherapies has dropped markedly since the World Health Assembly adopted a resolution supporting the ban in 2007. As of November 2015, marketing of artemisinin monotherapies was still allowed by seven countries: Angola, Cape Verde, Colombia, Gambia, Sao Tome and Principe, Somalia, and Swaziland [51]. However, a continued strengthening of pharmaceutical regulation and the enforcement of existing regulations will be required for the complete withdrawal of oral artemisinin monotherapies from all countries.

In an attempt to standardize the quality of medicines that reach the market, in terms of their efficacy, safety, and method of manufacture, the WHO are managing the Prequalification of Medicines Program [24]. This program’s quality evaluation criteria are based on international pharmaceutical standards and a mix of the best practices applied by the world’s leading regulatory authorities [52]. Products that meet all of the criteria of the WHO Prequalification of Medicines Program are considered to be quality assured and are added to a WHO list of prequalified medicinal products [53]. This list is used by international procurement agencies and by countries to guide bulk purchasing of medicines. Currently, over 40 of the prequalified medicinal products on this list are antimalarial agents [53]. This program has validated the entry of a number of generic products into markets and procurement pools [52]. Such validation has provided an incentive for other manufacturers of generic products to raise their quality standards and increase the availability of affordable medicines.

In addition to prequalifying medicines, this program also prequalifies pharmaceutical quality control laboratories and active pharmaceutical ingredients, as well as advocating for medicines of guaranteed quality [24].

5.5. The AMRH initiative

One of the means of improving quality standards is to engage regional networks in developing countries with larger, more powerful and better resourced organizations such as the WHO. One example of such a network is the African Medicine Registration Harmonization Initiative (AMRH) [25, 54]. This program aims to harmonize the registration of medicinal products in Africa across regional economic communities (RECs) [25, 54]. In Africa, the RECs range in size from five to more than twenty-five member states—and all have been invited to participate in the AMRH program.

Partners involved in the AMRH program include the WHO, the New Partnership for Africa's Development, the African Union Commission, the Pan-African Parliament, the World Bank, the Bill and Melinda Gates Foundation, the UK Department for International Development, and the Clinton Health Access Initiative [25]. The WHO is to provide leadership for the development of common technical standards, documents, tools, and processes in line with international standards. The WHO also provides technical assistance for capacity-building and organizes joint assessment and inspection activities [25].

The first REC to secure funding from the AMRH initiative trust fund was the East African Community (EAC). The EAC Medicines Registration Harmonization (MRH) project was formally launched in 2012 in Tanzania and aims to achieve a harmonized medicines registration process in its member countries (Uganda, Kenya, the United Republic of Tanzania, Rwanda, and Burundi) based on common documents, processes, and shared information [25]. Given the progress made in the EAC MRH project, the AMRH initiative plans to expand to other RECs in Africa. It is hoped that five or six groupings will eventually cover the entire African continent. Continued support by concerned governments and international partners will be crucial for its success [25].

5.6. The role of pharmaceutical companies

Poor manufacturing and quality-control practices in the production of genuine drugs (either branded or generic) have considerable impact on the quality of medicines [40]. Pharmaceutical companies are responsible for ensuring that quality meets the guidelines of stringent health authorities, for testing their medicines accordingly and for releasing only medicines that pass these requirements [55]. Chinese and Indian manufacturers are commonly cited as sources of poor-quality antimalarials, but manufacturers in other countries may also be involved [7, 40]. It is essential that pharmaceutical companies behave ethically at all times and follow relevant guidelines and codes of conduct provided by regulatory authorities if the quality of medicines is to be assured.

Reputable pharmaceutical companies must ensure that medicines are under strict surveillance, and with quality control measures in place at all stages of the drug supply chain. Novartis, for example, ensures the quality control of medicines in a three-step process that involves verification, authentication, and pharmaceutical forensic investigations. Verification occurs at the local level to attest to the genuineness of the packaging materials and the plausibility of the manufacturing data (batch number, manufacturing, and expiry date). Authentication, done

in the field, involves analyzing the product (tablets, liquids) with vibrational spectrometers. In the case of substantiation of falsification of medicines, a pharmaceutical forensic investigation then occurs, and any substantiated falsification incidents are escalated to the key stakeholders and national health authorities and the WHO are notified.

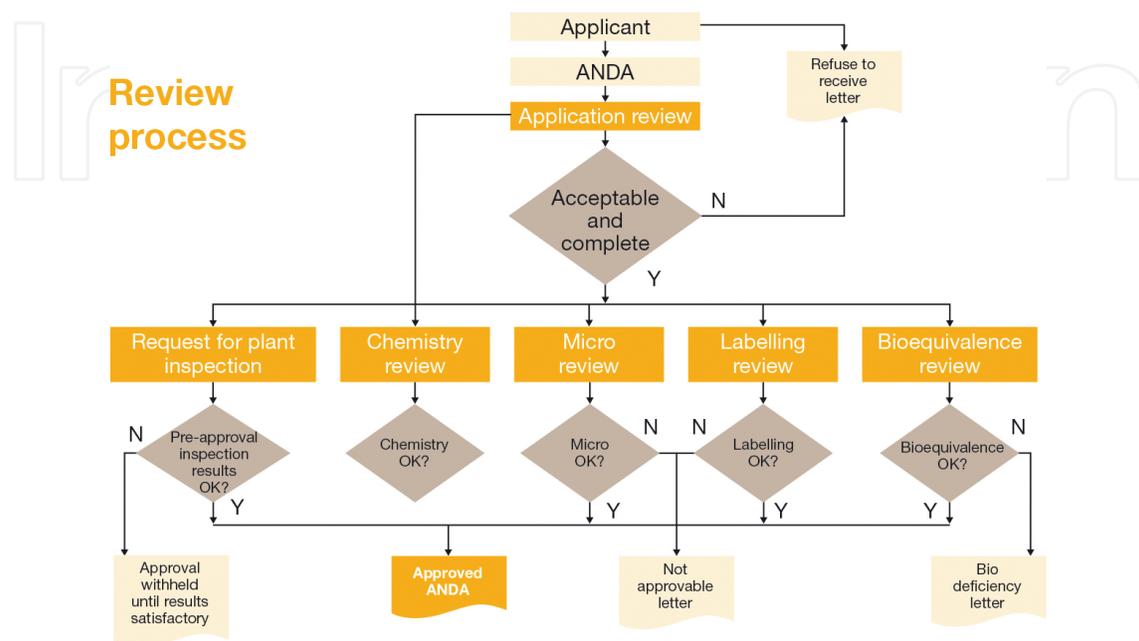


Figure 3. Process for review and approval of generic drugs (ANDA) [58]. Source: US Food and Drug Administration (public domain).

In countries where stringent regulatory authorities exist, pharmaceutical companies developing new drugs must follow a new drug application process that requires both preclinical and clinical studies [50]. In contrast, the approval of generic drugs or new formulations of existing drugs occurs via an abbreviated process that does not require clinical efficacy and safety studies (**Figure 3**) [56]. One of the dangers with some generic products is that they may contain the correct amounts of the drug, but, because of their formulation, they are not adequately absorbed, resulting in lower efficacy. Consequently, this abbreviated process requires proof that the generic product (or new formulation of a reference product) and the reference product have comparable bioavailability. If this is established, the products are said to be bioequivalent [56, 57].

Different types of evidence may be used to establish bioequivalence for pharmaceutically equivalent drug products, including *in vivo* or *in vitro* testing, or both [56]. If a generic product or new formulation shows equivalent exposure to the original marketed compound, it is assumed that its efficacy and safety will also be equivalent [56]. To this end, the WHO recommended that not only must all antimalarial medicines be manufactured according to good manufacturing practice and have the correct drug and excipient content, but they must also be proven to have bioavailability that is comparable to that of the reference listed product [26].

An example of a study that was conducted in line with these bioequivalence guidelines involves the antimalarial artemether-lumefantrine [58]. Because development of this compound adhered to these guidelines, this formulation received the WHO prequalification status in June 2014 [53]. The novel fixed-dose tablet formulation of the antimalarial artemether-lumefantrine 80/480 mg was developed in order to reduce the pill burden at each dose and potentially enhance adherence. It was then tested in a bioequivalence study in healthy volunteers against four standard tablets of artemether-lumefantrine 20/120 [59]. Bioequivalence between the two formulations was established, with the prespecified criteria for bioequivalence being met. These prespecified criteria were that the 90% confidence intervals for the geometric mean ratio (novel formulation versus four standard tablets) of the primary pharmacokinetic endpoints (AUC and C_{max}) for artemether and lumefantrine were contained within the acceptance interval of 0.80–1.25. These outcomes established that the rate and extent of absorption of both components of the ACT in the novel formulation of artemether-lumefantrine are comparable to those in the standard tablets.

6. Conclusion

There is a pressing need to reduce the use of poor-quality antimalarial medicines, especially in Africa and Asia. The problem is driven by several factors, including a lack of national and international drug legislation, and inadequate quality assurance by some pharmaceutical companies. This chapter has reviewed the steps and studies needed to ensure development of high-quality medicines based on health authority regulations (including WHO prequalification). The problem of poor-quality medicines can only be addressed by a multipronged approach that includes tackling poor regulation and ineffective/poorly implemented laws at national and international levels. Sustained national and international financing must underpin any such future approach. A legal framework or treaty that protects all countries against poor-quality medicines is also urgently required. Such a framework would facilitate the production of high-quality antimalarials and protect all countries against those who produce, distribute, and sell poor-quality products. In addition, pharmaceutical companies must be responsible for ensuring that the quality of antimalarials meets the stringent guidelines established by regulatory authorities, for testing their medicines accordingly and for releasing only medicines that pass these requirements into the market. The harmonization of the registration process across all nations would help ensure that patients throughout the world obtain access to high-quality antimalarials.

Surveillance of the quality of antimalarials is an essential component of the global fight against malaria. The establishment of a highly qualified, well-resourced international organization that works in collaboration with national medical regulatory bodies, pharmaceutical companies, and international agencies may help to ensure access to high-quality antimalarials on a global level. The implementation of strategies such as the WHO Prequalification Program, the AMRH initiative, and the ethical production of medicines by pharmaceutical companies will help to ensure that antimalarial therapies marketed in low-income, malaria-endemic countries are quality assured. Future research must focus on innovative technologies that accurately and

affordably support the detection of poor-quality medicines at all levels of the supply chain, including prequalified reference laboratories. It is to be hoped that the implementation of such a multipronged approach by policy makers and leaders at the international and national levels will ensure the continued global availability of affordable, high-quality drugs to patients with malaria.

Acknowledgements

KH is an employee of Novartis Pharmaceuticals Corporation and KS is an employee of Novartis Pharma AG.

Author details

Kamal Hamed^{1*} and Kirstin Stricker²

*Address all correspondence to: kamal.hamed@novartis.com

1 Novartis Pharmaceuticals Corporation, East Hanover, NJ, USA

2 Novartis Pharma AG, Basel, Switzerland

References

- [1] Hamburg M. Foreword to the global pandemic of falsified medicines: laboratory and field innovations and policy implications. *Am J Trop Med Hyg.* 2015;92(6 Suppl.):1.
- [2] Nayyar GM, Breman JG, Herrington JE. The global pandemic of falsified medicines: laboratory and field innovations and policy perspectives. *Am J Trop Med Hyg.* 2015;92(6 Suppl.):2–7.
- [3] Nayyar GM, Breman JG, Newton PN, Herrington JE. Poor-quality antimalarial drugs in southeast Asia and sub-Saharan Africa. *Lancet Infect Dis.* 2012;12(6):488–496.
- [4] Newton PN, Green MD, Mildenhall DC, Plancon A, Nettey H, Nyadong L, et al. Poor quality vital anti-malarials in Africa – an urgent neglected public health priority. *Malar J.* 2011;10:352.
- [5] Newton PN, Green MD, Fernandez FM, Day NP, White NJ. Counterfeit anti-infective drugs. *Lancet Infect Dis.* 2006;6(9):602–613.

- [6] Hajjou M, Krech L, Lane-Barlow C, Roth L, Pribluda VS, Phanouvong S. Monitoring the quality of medicines: results from Africa, Asia, and South America. *Am J Trop Med Hyg.* 2015;92 (6 Suppl.):68–74.
- [7] Nayyar GM, Attaran A, Clark JP, Culzoni MJ, Fernandez FM, Herrington JE, et al. Responding to the pandemic of falsified medicines. *Am J Trop Med Hyg.* 2015;92(6 Suppl.):113–118.
- [8] Sabartova J, Toumi A. WHO report: survey of the quality of selected antimalarial medicines circulating in six countries of sub-Saharan Africa. 2015. Available from: <http://www.who.int/medicines/publications/qamsareport/en/> [Accessed: July 7, 2016].
- [9] El-Duah M, Ofori-Kwakye K. Substandard artemisinin-based antimalarial medicines in licensed retail pharmaceutical outlets in Ghana. *J Vector Borne Dis.* 2012;49(3):131–139.
- [10] Bate R, Coticelli P, Tren R, Attaran A. Antimalarial drug quality in the most severely malarious parts of Africa—a six country study. *PLoS One.* 2008;3(5):e2132.
- [11] Dondorp AM, Newton PN, Mayxay M, Van Damme W, Smithuis FM, Yeung S, et al. Fake antimalarials in Southeast Asia are a major impediment to malaria control: multinational cross-sectional survey on the prevalence of fake antimalarials. *Trop Med Int Health.* 2004;9(12):1241.
- [12] Yeung S, Lawford HL, Taberner P, Nguon C, van Wyk A, Malik N, et al. Quality of antimalarials at the epicenter of antimalarial drug resistance: results from an overt and mystery client survey in Cambodia. *Am J Trop Med Hyg.* 2015;92(6 Suppl.):39–50.
- [13] Chikowe I, Osei-Safo D, Harrison JJ, Konadu DY, Addae-Mensah I. Post-marketing surveillance of anti-malarial medicines used in Malawi. *Malar J.* 2015;14:127.
- [14] Osei-Safo D, Agbonon A, Konadu DY, Harrison JJ, Edoh M, Gordon A, et al. Evaluation of the quality of artemisinin-based antimalarial medicines distributed in Ghana and Togo. *Malar Res Treat.* 2014;2014:806416.
- [15] Taberner P, Fernandez FM, Green M, Guerin PJ, Newton PN. Mind the gaps—the epidemiology of poor-quality anti-malarials in the malarious world—analysis of the WorldWide Antimalarial Resistance Network database. *Malar J.* 2014;13:139.
- [16] Karunamoorthi K. The counterfeit anti-malarial is a crime against humanity: a systematic review of the scientific evidence. *Malar J.* 2014;13:209.
- [17] ACT Consortium Drug Quality Project Team and the IMPACT2 Study Team. Quality of artemisinin-containing antimalarials in Tanzania's private sector—results from a nationally representative outlet survey. *Am J Trop Med Hyg.* 2015;92(6 Suppl.):75.
- [18] Ravinetto R, Ngeleka Mutolo D, de Spiegeleere B, Marini R, Hasker E, Schiavetti B. The quality of paediatric medicines supplied by private wholesalers in Kinshasa, DRC. *Trop Med Int Health.* 2015;20(1 Suppl.):136.

- [19] Renschler JP, Walters KM, Newton PN, Laxminarayan R. Estimated under-five deaths associated with poor-quality antimalarials in sub-Saharan Africa. *Am J Trop Med Hyg.* 2015;92(6 Suppl.):119–126.
- [20] Dondorp AM, Nosten F, Yi P, Das D, Phyo AP, Tarning J, et al. Artemisinin resistance in *Plasmodium falciparum* malaria. *N Engl J Med.* 2009;361(5):455.
- [21] White NJ, Pongtavornpinyo W, Maude RJ, Saralamba S, Aguas R, Stepniewska K, et al. Hyperparasitaemia and low dosing are an important source of anti-malarial drug resistance. *Malar J.* 2009;8:253.
- [22] Attaran A. Stopping murder by medicine: introducing the Model Law on Medicine Crime. *Am J Trop Med Hyg.* 2015;92(6 Suppl.):127.
- [23] World Health Organization. What encourages counterfeiting of medicines? 2013. Available from: <https://www.wiltonpark.org.uk/wp-content/uploads/WP1185-WHO-What-encourages-counterfeiting-of-medicines.pdf>. [Accessed: July 7, 2016].
- [24] World Health Organization. Prequalification of medicines by WHO. Factsheet No. 278. 2013. Available from: <http://www.who.int/mediacentre/factsheets/fs278/en/>. [Accessed: July 7, 2016].
- [25] African Medicine Registration Harmonization Programme. AMRH Programme. 2014. Available from: <http://amrh.org/>. [Accessed: July 7, 2016].
- [26] World Health Organization. Guidelines for the treatment of malaria. 2015. Available from: www.who.int/malaria/publications/atoz/9789241549127/en/. [Accessed: July 7, 2016].
- [27] Attaran A, Barry D, Basheer S, Bate R, Benton D, Chauvin J, et al. How to achieve international action on falsified and substandard medicines. *BMJ.* 2012;345:e7381.
- [28] Newton PN, McGready R, Fernandez F, Green MD, Sunjio M, Bruneton C, et al. Manslaughter by fake artesunate in Asia-will Africa be next? *PLoS Med.* 2006;3(6):e197.
- [29] Keoluangkhot V, Green MD, Nyadong L, Fernandez FM, Mayxay M, Newton PN. Impaired clinical response in a patient with uncomplicated *falciparum* malaria who received poor-quality and underdosed intramuscular artemether. *Am J Trop Med Hyg.* 2008;78(4):552–555.
- [30] Chaccour CJ, Kaur H, Mabey D, Del Pozo JL. Travel and fake artesunate: a risky business. *Lancet.* 2012;380(9847):1120.
- [31] Ye R, Hu D, Zhang Y, Huang Y, Sun X, Wang J, et al. Distinctive origin of artemisinin-resistant *Plasmodium falciparum* on the China-Myanmar border. *Sci Rep.* 2016;6:20100.
- [32] Tun KM, Imwong M, Lwin KM, Win AA, Hlaing TM, Hlaing T, et al. Spread of artemisinin-resistant *Plasmodium falciparum* in Myanmar: a cross-sectional survey of the K13 molecular marker. *Lancet Infect Dis.* 2015;15(4):415.

- [33] Dondorp AM, Yeung S, White L, Nguon C, Day NP, Socheat D, et al. Artemisinin resistance: current status and scenarios for containment. *Nat Rev Microbiol.* 2010;8(4):272.
- [34] Noedl H, Se Y, Schaecher K, Smith BL, Socheat D, Fukuda MM. Evidence of artemisinin-resistant malaria in western Cambodia. *N Engl J Med.* 2008;359(24):2619.
- [35] Phyo AP, Nkhoma S, Stepniewska K, Ashley EA, Nair S, McGready R, et al. Emergence of artemisinin-resistant malaria on the western border of Thailand: a longitudinal study. *Lancet.* 2012;379(9830):1960.
- [36] World Health Organization. World Malaria Report. 2015. Available from: <http://www.who.int/malaria/publications/world-malaria-report-2015/report/en/> [Accessed: July 7, 2016].
- [37] Mita T, Tachibana S, Hashimoto M, Hirai M. Plasmodium falciparum kelch 13: a potential molecular marker for tackling artemisinin-resistant malaria parasites. *Expert Rev Anti Infect Ther.* 2016;14(1):125–135.
- [38] Cui L, Yan G, Sattabongkot J, Chen B, Cao Y, Fan Q, Parker D, Sirichaisinthop J, Su XZ, Yang H, Yang Z, Wang B, Zhou G. Challenges and prospects for malaria elimination in the Greater Mekong Subregion. *Acta Trop.* 2012;121(3):240–245.
- [39] World Health Organization. Strategy for malaria elimination in the Greater Mekong Subregion: 2015–2030. 2015. Available from: http://www.wpro.who.int/mvp/documents/strat_mal_elim_gms/en/. [Accessed: July 7, 2016].
- [40] Johnston A, Holt DW. Substandard drugs: a potential crisis for public health. *Br J Clin Pharmacol.* 2014;78(2):218.
- [41] Lubell Y, Dondorp A, Guérin PJ, Drake T, Meek S, Ashley E, Day NPJ, White NJ, White LJ. Artemisinin resistance—modelling the potential human and economic costs. *Malar J.* 2014;13:452.
- [42] Newton PN, Schellenberg D, Ashley EA, Ravinetto R, Green MD, ter Kuile FO, et al. Quality assurance of drugs used in clinical trials: proposal for adapting guidelines. *BMJ.* 2015;350:h602.
- [43] Weaver AA, Lieberman M. Paper test cards for presumptive testing of very low quality antimalarial medications. *Am J Trop Med Hyg.* 2015;92(6 Suppl.):17.
- [44] Ho NT, Desai D, Zaman MH. Rapid and specific drug quality testing assay for artemisinin and its derivatives using a luminescent reaction and novel microfluidic technology. *Am J Trop Med Hyg.* 2015;92(6 Suppl.):24.
- [45] World Health Organization. WHO list of prequalified quality control laboratories. 38th edition, 2016. Available from: www.who.int/prequal/lists/PQ_QCLabsList.pdf [Accessed: February 22, 2016].
- [46] World Health Organization. Guidelines on the conduct of surveys of the quality of medicines: draft for comment. 2016. Available from: <http://www.who.int/medicines/>

areas/quality_safety/quality_assurance/Guidelines-on-medicines-quality-surveys-QAS15-630_30062015.pdf. [Accessed: July 7, 2016].

- [47] Newton PN, Lee SJ, Goodman C, Fernandez FM, Yeung S, Phanouvong S, et al. Guidelines for field surveys of the quality of medicines: a proposal. *PLoS Med.* 2009;6(3):e52.
- [48] World Health Organization. Assessment of medicines regulatory systems in sub-Saharan African countries. 2010. Available from: www.who.int/healthsystems/Assessment26African_countries.pdf?ua=1. [Accessed: July 7, 2016].
- [49] European Medicines Agency. EMA Scientific Guidelines. 2015. Available from: http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000043.jsp&mid=WC0b01ac05800240cb [Accessed: July 7, 2016].
- [50] United States Food and Drug Administration. FDA drug development guidelines. 2015. Available from: <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/InvestigationalNewDrugINDApplication/ucm176522.htm>. [Accessed: July 7, 2016].
- [51] World Health Organization. Withdrawal of oral artemisin-based monotherapies. 2016. Available from: http://www.who.int/malaria/areas/treatment/withdrawal_of_oral_artemisinin_based_monotherapies/en/. [Accessed: July 7, 2016].
- [52] World Health Organization. Improving quality for better treatment and greater access: prequalifications of medicine programme. 2012. Available from: http://apps.who.int/prequal/info_general/documents/advocacy/Advocacy_booklet_2012.pdf. [Accessed: July 7, 2016].
- [53] World Health Organization. WHO list of prequalified medicinal products. 2016. Available from: <http://apps.who.int/prequal/>. [Accessed: July 7, 2016].
- [54] World Health Organization. WHO support for medicines regulatory harmonization in Africa: focus on East African Community. 2014. Available from: http://www.who.int/medicines/publications/druginformation/DI_28-1_Africa.pdf. [Accessed: July 7, 2016].
- [55] World Medical Association. WMA Declaration of Helsinki—Ethical Principles for Medical Research Involving Human Subjects. 2016. Available from: <http://www.wma.net/en/30publications/10policies/b3/>. [Accessed: July 7, 2016].
- [56] United States Food and Drug Administration. Product-specific recommendations for generic drug development. 2016. Available from: <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm075207.htm>. [Accessed: July 7, 2016].
- [57] European Medicines Agency. Guideline on the investigation of bioequivalence. 2015. Available from: www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2010/01/WC500070039.pdf. [Accessed: July 7, 2016].

- [58] United States Food and Drug Administration. The FDA Process for Approving Generic Drugs. 2007. Available from: <http://www.fda.gov/Training/ForHealthProfessionals/ucm090320.htm>. [Accessed: July 7, 2016].
- [59] Lefevre G, Bhad P, Jain JP, Kalluri S, Cheng Y, Dave H, et al. Evaluation of two novel tablet formulations of artemether-lumefantrine (Coartem) for bioequivalence in a randomized, open-label, two-period study. *Malar J.* 2013;12:312.

IntechOpen

IntechOpen

