



# Antimalarial Drug Quality in Mekong Countries

A. Smine,\* S. Phanouvong,\* L. Chanthap,\* R. Tsuyuoka,† N. Nivana,^ and N. Blum\*

\*United States Pharmacopeia Drug Quality and Information Program (USP DQI) 12601 Twinbrook Parkway, Rockville, MD 20852. ays@usp.org \*Malaria Control Center, †World Health Organization, and ^National Laboratory for Drug Quality Control, Phnom Penh Cambodia

## 1. INTRODUCTION

Southeast Asia has a long history of malaria, cycling from epidemics brought under control with antimalarial drugs only to have new, drug-resistant strains emerge. During the past decade, however, new strains of the particularly virulent form of *P. falciparum* have developed resistance to most first- and second-line antimalarial drugs in circulation. The Mekong RBM identified this as a major concern in the high mortality rate and growing costs of treatment. This situation presents an added threat to the population of the Mekong region for whom malaria continues to be a major health problem.

Poor drug quality has been determined to be one of the factors contributing to the growing resistance to antimalarial drugs. In recent studies conducted in the Mekong countries, 2-3 over 30% of drug samples marked "artesunate," collected from Mekong countries, actually contained no active ingredient; other preparations contained less than 25% of their stated ingredient. Use of fake or substandard antimalarial drugs is apparently widespread, primarily along Mekong countries' borders.

The United States Pharmacopeia Drug Quality and Information Program (USP DQI) embarked on a project to improve the quality of medicines used in priority disease programs in the Mekong region with the support of USAID. In close collaboration with WHO, Mekong RBM, and National Malaria Control Programs, USP DQI has been working to strengthen drug quality control systems in Cambodia, Laos, Thailand, Vietnam, and Yunnan Province of China. Recent data suggest that trade in counterfeit antimalarial drugs is widespread in South East Asia and presents a great threat to the lives of malaria patients.

### ANTIMALARIAL DRUGS QUALITY CAMBODIA

#### BACKGROUND:

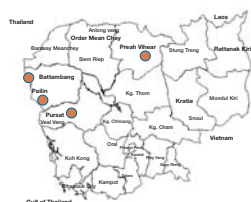
The kingdom of Cambodia is situated in the southwest portion of the Indochina Peninsula, bordered by Thailand, Laos, and Vietnam. The country is 181,232 km<sup>2</sup> with a population of 11 million inhabitants, a density of about 58 Cambodians/km<sup>2</sup>. Sixty percent of the Cambodian landmass is thinly populated forest and hilly areas, characteristic of malaria vector habitats with high malaria transmission, but with little or no access to the public health system. The health system is organized into provinces and operational districts (OD), with each OD composed of many health centers and health posts.



In April 2002, USP DQI conducted an assessment of drug quality control capabilities of Cambodia. It was found that antimalarial drug quality was still a major problem for malaria control in the country. Illegal drug shops and fake antimalarial drugs were widespread, especially in the border provinces. Many previous reports on drug quality have shown that counterfeit and sub-standard drugs are widespread in Cambodia. In March 2003, USP DQI organized a training workshop on drug sampling and basic tests for provincial health workers, and started a drug quality control program in collaboration with WHO, Malaria Control Center, and National Laboratory for Drug Quality Control.

## 2.

### ANTIMALARIAL DRUG QUALITY AT THE PROVINCIAL LEVEL



#### PROVINCE SELECTED:

**Battambang, Pailin, Pursat, and Preah Vihear**

- ✓ Border provinces: Cambodia-Thai
- ✓ High malaria incidence
- ✓ History of illegal drug trade and abundance of counterfeit drugs

#### DRUG OUTLETS IN THE FOUR SELECTED PROVINCES:

- ✓ 23 Pharmacies (run by a pharmacist)
- ✓ 12 Depot A (run by assistant pharmacist)
- ✓ 72 Depot B (run by a retired nurse)
- ✓ 391 Illegal drug shop

Drugs were collected from both legal and illegal drug outlets, from capital towns in each province.

#### ANTIMALARIAL DRUGS COLLECTED:

- ✓ Mefloquine
- ✓ Artesunate, Artemether, Arteether and Dihydroartemisinin
- ✓ Quinine
- ✓ Tetracycline
- ✓ Chloroquine

## 3.

### DRUG QUALITY SURVEY

- Random and convenience sampling: Collection of solid dosage forms only, at least 20 units per sample.
- Samples are collected based on lot/batch numbers and manufacturers in each province.
- Antimalarial drugs are tested every 2-3 month period.

#### BASIC TESTS:

**Step 1:** Collected samples are subjected to visual/physical inspection. A data report with the below information is completed for each tested sample.

- ✓ Trade Name, generic name
- ✓ Dosage form and strength
- ✓ Batch/lot number
- ✓ Expiry/manufacturing date
- ✓ Manufacturer name/address
- ✓ Location of collection address
- ✓ Number of drug and storage conditions
- ✓ Appearance
- ✓ Uniformity of Color/shape/size
- ✓ Cracks and breaks
- ✓ Any foreign contaminant and others

**Step 2:** A simple disintegration test is conducted

**Step 3:** Thin Layer Chromatography (TLC) test is done using GPHF mini-lab

**Step 4:** Report test results to Malaria Control Center and National Laboratory for Drug Quality Control (NLDOC).

**Step 5:** Confirmatory testing for selected samples:

- ✓ TLC in NLDQC
- ✓ HPLC, dissolution and others in USP DQI and Bureau of Drugs and Narcotics in Thailand

## 5. RESULTS

TABLE 3: Results of TLC testing using GPHF mini-lab

SAMPLES	Samples were collected from 13 different legal drug shops		Samples were collected from 41 different illegal drug shops	
	Pass	Fail	Pass	Fail
A+M4 (Artesunate 50 mg and Mefloquine 250 mg)	4	0	4	0
Malarian (Artesunate 200 mg Mefloquine 250 mg)	2	0	8	0
Artemether 50 mg	2	0	0	0
Artesunate 50 mg	6	3 (NAI)	17	4 (NAI)
Chloroquine 100 mg	2	0	0	1* (SSTD)
Chloroquine 150 mg	1	0	1	0
Chloroquine 241.9 mg	1	0	0	0
Chloroquine 250 mg	5	0	17	2* (SSTD)
Chloroquine 325 mg	0	0	0	1 (NAI)
Dihydroartemisinin 32 mg	0	0	5	0
Dihydroartemisinin 20 mg	0	0	1	0
Mefloquine 250 mg	5	0	11	2 (1 WAI & 1 NAI)
Quinine Sulfate 300 mg	2	6 (WAI)	7	24 (23 WAI & 1 SSTD)
Tetracycline 250 mg	4	2 (1 NAI & 1 SSTD)	11	6 (4 NAI & 2 SSTD)
Tetracycline 500 mg	6	0	10	0
<b>TOTAL</b>	<b>40</b>	<b>11 (22%)</b>	<b>92</b>	<b>39 (30%)</b>

\* Number of samples that failed the disintegration test  
NAI—No Active Ingredient WAI—Wrong Active Ingredient SSTD—Substandard (contains less than 80% API)

**NOTE:** From a total of 39 samples of Quinine Sulfate tablets, only 7 passed the basic test for quality. 30 samples have the wrong active ingredient and one sample was subpotent. This represents an average failure rate of 77% of all quinine samples collected between the four provinces. This is the highest rate of counterfeit quinine ever reported. To confirm these findings, samples of Quinine Sulfate were selected based on manufacturers and lot/batch numbers and sent to USP DQI laboratory for testing according to USP 26-NF 22 monograph for Quinine Sulfate tablets.

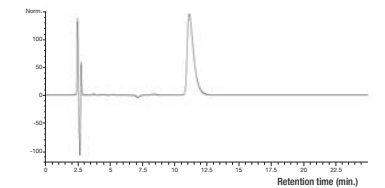
#### Methods:

- The identity of the Active Pharmaceutical Ingredient (API) was verified with HPLC using USP Quinine Sulfate RS.
- The content of the API was also determined by HPLC method.
- The samples that passed the HPLC test were subjected to dissolution according to USP monograph.

## 7. RESULTS

FIGURE 3: Chromatogram of a counterfeit sample (e.g., 006/03 BTB)

Same conditions as Figure 1



A typical chromatogram of the samples containing the wrong ingredient. The substance present in these samples is not quinine sulfate as shown by the retention times of samples and standard. There is no quinine peak around 9.3 min. and no Hydroquinone peak around 12.8 min. retention time.

TABLE 4: Summary of data of Quinine Sulfate tablets analysis

Sample ID	Average weight per tablet (mg)	ID test HPLC	Content of quinine (90-100%)	Dissolution: Not less than 80%
006/03 BTB	618.43	WAI	NA	NA
007/03 BTB	373.73	authentic	94.7% - conform	106% - conform
015/03 BTB	622.78	WAI	NA	NA
024/03 BTB	457.61	authentic	92.1% - conform	108% - conform
016/03 PL	618.74	WAI	NA	NA
021/03 PL	684.71	WAI	--	--
029/03 PL	602.96	WAI	--	--
008/03 PS	632.96	WAI	--	--
031/03 PS	752.04	WAI	--	--
054/03 PS	698.85	WAI	--	--
003/03 PVH	796.96	WAI	--	--
012/03 PVH	648.17	WAI	--	--

NA—Not applicable WAI—Wrong Active Ingredient

## 4. RESULTS

### Summary results of the situation of each province and sampling

TABLE 1: Origin of collected samples

Provinces	Total no. of samples collected	Samples from legal shops	Samples from illegal shops
BTB	43	33	10
Preah Vihear	39	1	38
Pailin	48	0	48
Pursat	57	17	40
<b>TOTAL</b>	<b>187</b>	<b>57</b>	<b>136</b>

TABLE 2: Results of laboratory testing

Provinces	Result											
	Quinine		Artesunate		Mefloquine		Chloroquine		DHA		Artemether	
Samples	Failed (%)	Samples	Failed (%)	Samples	Failed (%)	Samples	Failed (%)	Samples	Failed (%)	Samples	Failed (%)	
BTB	9	8 (89)	11	3 (27.2)	7	0	8	0	8	0	NF	NF
Preah Vihear	9	5 (56)	10	2 (20)	8	0	5	1 (20)	5	1 (20)	2	0
Pailin	10	9 (90)	9	0	4	1 (25.5)	9	0	12	3 (25)	2	0
Pursat	11	8 (73)	11	2 (18)	6	1 (17)	9	3 (33)	14	4 (29)	2	0
<b>TOTAL</b>	<b>39</b>	<b>30 (77)</b>	<b>41</b>	<b>7 (17)</b>	<b>25</b>	<b>2 (8)</b>	<b>31</b>	<b>4 (13)</b>	<b>39</b>	<b>8 (21)</b>	<b>6</b>	<b>0</b>

NF—Not found in the market  
DHA—Dihydroartemisinin

## 6. RESULTS

FIGURE 1: Chromatogram of the Standard Preparation: USP Quinine Sulfate RS, lot H

Concentration: 20.14 ug/mL Solvent: Mobile phase  
Flow rate: 1.2 mL/min Detection: 235 nm Injection volume: 50 uL  
Column: Waters uBondapak C18, 30 cm x 3.9 mm, 10 um particle size  
Mobile phase: water: acetonitrile, Methanesulfonic acid solution, and Diethylamine solution (860:100:20:20, v/v), pH adjusted to 2.6 with Diethylamine solution  
Methanesulfonic acid solution: 7 mL of Methanesulfonic acid was added to 4 mL of glacial acetic acid, and diluted with water to 100 mL.  
Diethylamine solution: 10 mL diethylamine diluted with water to 100 mL.

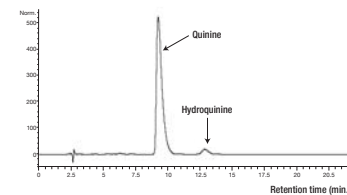
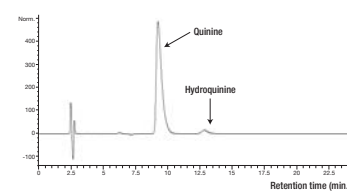


FIGURE 2: Chromatogram of a genuine sample (e.g., 007/03 BTB)

Same conditions as Figure 1



## 8. CONCLUSION

- The quality control program of antimalarial drugs in four selected provinces has proven to be an excellent way to survey the quality of drugs.
- Basic tests, such as visual inspection, disintegration and TLC are excellent tools to monitor the quality of pharmaceuticals at a non-laboratory setting and with a low cost.



- The German Pharma Health Fund—Mini-lab is a powerful and complete system for running basic tests.
- Counterfeit drugs are still widespread in Cambodia. In this survey, most of the failed samples contained no API or contained the wrong API, which means that these drugs were deliberately fraudulent.
- 77% of Quinine Sulfate tablets were counterfeit; this is alarming because Quinine Sulfate is given to severe malaria cases.

- Illegal pharmacies and unregistered drugs seem to contribute to the abundance of and the free trade in counterfeit drugs.

- In addition to Cambodia, the USP DQI control program is now set up and operating in four provinces in Thailand, four provinces in Vietnam, three provinces in Laos, and two sentinel sites in Yunnan Province of China.
- This regional program will help improve the quality of antimalarial drugs in the Mekong region.
- Trade in counterfeit drugs, such as Quinine Sulfate tablets, may cause death of patients and should be considered a very serious criminal activity.
- Serious investigations into the sources of counterfeit drugs should be done and law enforcement is the only deterrent that can stop these crimes.

## 9. REFERENCES

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