OCCASIONAL PAPER
Observatory Series 07

The State of Medicine Quality in the Mekong Sub-Region

Sauwakon Ratanawijitrasin
and Souly Phanouvong

MEKONG ANTI TRAFICS
Observatoire des trafics illicites

IRASEC

THE STATE OF MEDICINE QUALITY IN THE MEKONG SUBREGION

Editing: Alicia Hartmann and Linh-Anh Moreau
Cover: Mikael Brodu
Layout: Muriel Nguyen and Linda Fraikin
Photos: © the authors

ISBN 978-616-7571-19-5

A collection directed by Alicia Hartmann and François Robinne

THE STATE OF MEDICINE QUALITY IN THE MEKONG SUBREGION IN THE 2000s AND THE CHALLENGES AHEAD

By
Sauwakon Ratanawijitrasin, PhD
Souly Phanouvong, PharmD, PhD

MEKONG ANTI TRAFICS
Observatoire des trafics illicites
IRASEC
Mahidol University
Wisdom of the Land
USAID FROM THE AMERICAN PEOPLE
USP
PROMOTING THE QUALITY OF MEDICINES

TABLE OF CONTENTS

LIST OF FIGURES

LIST OF TABLES

INTRODUCTION

As waves of emerging and re-emerging diseases send repercussions around the world time and again, the global community has come to realize the interconnectedness of our world, of its countries, peoples, and activities. Today, what happens in one place can have an impact far beyond the boundary of a geographical locale. The world community pulls together to examine the many interrelated factors causing epidemics that are difficult to contain, and to re-examine old issues in a new light. Medicine quality is one of such issues. Efficacy, safety, and quality are three essential attributes of a medicine. Without these, effective prevention, treatment and care cannot be achieved, and patient safety may be at risk. When a poor quality medicine is used to treat an infectious disease, the impacts of its use can be wide and serious, as ineffective anti-infectives may fail to help stop the spread of an epidemic, engender drug resistance, and erode public confidence in health care systems. Patients contribute to their own and their children's vulnerability to expensive-to-treat or even incurable infectious diseases if their over-use of anti-infectives leads to resistance (Eggleston et al. 2010). The potential societal ramifications of poor quality anti-infective medicines in the current rapidly globalized world have brought new focus and new urgency to the raising of awareness and the seeking of solutions to stem the spread of bad medicines, as nations and the global community work together to combat emerging and re-emerging diseases.

The Mekong Subregion has long been a key geographical area of global interest in regards to medicine quality and its implications on global health. The Mekong River originates in the highlands of China's Yunnan Province, crossing five countries—China, Myanmar, Lao PDR, Thailand, Cambodia—then opening to the sea in southern Vietnam. These riparian states linked by the Mekong form the Greater Mekong Subregion (GMS). After the Indochina War ended in the late 1970s, the countries in

this region forged close ties—economically, politically, and culturally—and brought rapid development to the region. Social transformation and economic development are both evident in the boom in trade, tourism and transportation links. With such ties and new demands for goods and services arising from development, the flow of people and goods has increased. One of the trades enhanced by these closer relations is that of medicine, genuine as well as counterfeit. The more rapid and frequent exchanges not only brought increased flows of people and goods, they also, inevitably, heightened the spread of infectious diseases (WHO 2009).

Malaria epitomizes the interactions among the many dynamics in population movement, trade, and infectious disease epidemiology in this region. The spread of malaria has long been a problem in the Mekong Region, especially along borders. Many of the border areas are characterized by forest and forest fringe areas with high malaria transmission, poor geographical accessibility, high population mobility, and low population density. Large-scale population movement from highly endemic areas to low endemic zones has contributed substantially to the spread of *P. falciparum*—a virulent species of protozoa causing malaria in humans—within and beyond the region. An example of extensive migration leading to the spread of malaria is the return of 100,000 to 200,000 gem miners from Borai Province in Cambodia to their home provinces in western Thailand following the Ruby Rush from 1988 to 1992, and the subsequent increase in *P. falciparum* cases. Estimates from clinics in Mae Sot District in Tak Province in western Thailand on the Thai-Myanmar border indicated that 80% of malaria infections were acquired in eastern Thailand on the Thai-Cambodian border (Delacollette et al. 2009).

These movements intensified the problem of multi-drug resistance historically found in the Mekong Region. Since the 1970s, the Thai-Cambodian border has been the global epicentre of emerging resistance to anti-malarial medicines. It is in this region that parasite resistance to chloroquine was first documented, followed by resistance to sulfadoxine -pyrimethamine, and finally to mefloquine. These resistance strains were later shown by molecular markers to have spread far outside the GMS. Concerns about anti-malarial drug resistance have increased with recent results from surveillance sites on the Thai-Cambodian border, which have shown prolonged parasite clearance of *P. falciparum* to artemisinin-combination therapies (Noedl et al. 2008, Delacollette et al. 2009, Phyo et al. 2012). The improved road, rail and other transportation facilities accelerate the

movement of populations across the borders, leading to conditions that can promote disease transmission. Yet, this greater interconnectedness in transportation and trade coexists with a difficult access to health facilities for people living in remote areas. Availability and affordability of good quality medicines remains a problem, especially for hill-tribe people and ethnic minorities living in remote areas, as well as for migrant populations. These disadvantaged groups are most likely to suffer from poor quality medicines.

Pharmaceutical products play an important role in the prevention and treatment of diseases, and thus help improve health. In order for a pharmaceutical product to achieve its therapeutic effects, it must meet three pre-requisite criteria, namely, efficacy, safety and quality. It must also be appropriately used. Almost all countries—developed as well as developing—have, with varying degrees, a system of pharmaceutical regulation, depending, in part, on their pharmaceutical industry and legal development status. However, in many developing countries, the quality of pharmaceutical products has often been found to be a problem. Reports, as reviewed below, indicate that substandard and counterfeit medicines are available in different distribution channels in the Mekong Subregion. The use of poor quality medicines[1] can produce serious health implications, including treatment failure, prolonged treatment duration, and hospitalization, even death, wasted resources, and some cases may lead to drug-resistance.

With the looming threat of epidemics in recent years, the quality of pharmaceuticals has been an increasing concern worldwide, and particularly within the Mekong Subregion. This region is a key area where avian influenza outbreaks took place, and where many resistant strains of malaria parasites were initially identified. The issue of medicine quality is in the interest of many parties as all have a stake in ensuring that patients have access to good quality medicines. Consumers/patients need quality drugs to alleviate their illness conditions. The use of substandard or counterfeit drugs not only fails intended treatment and prevention, but

[1] The term "poor-quality medicines" in this document refers to pharmaceutical products that do not meet quality standard specifications. They may be classified as counterfeit or substandard. Their definitions vary slightly from country to country depending on their legal framework. See ANNEX I for details.

might also causes harm. Health care providers need to enhance health outcomes to earn patient trust and confidence. Pharmaceutical companies' reputation and profits mainly depend on the trust in their products' quality, safety, and efficacy. Governments have a responsibility to protect and promote public health; they also have to spend public resources on effective care.

This study tries to discuss and provide some insightful information, with supporting data, on the quality of essential medicines in the Mekong Subregion. The majority of data discussed in this paper is derived from a United States Pharmacopeia (USP) Drug Quality and Information Program (DQI) project that took place between 2003 and 2006[2] , funded by the United States Agency for International Development (USAID) with some contribution from the World Health Organization (WHO), on selected anti-malarials, anti-tuberculosis agents, anti-retrovirals and antibiotics collected and tested from the Mekong Subregion countries through a regional medicine quality monitoring (MQM) mechanism.

This paper aims to contribute to increasing awareness and interest on the pharmaceutical quality and counterfeit medicines issues in the Mekong Subregion. It provides a review of existing empirical findings regarding the state of medicine quality in the region. It also analyzes data on quality testing of drug samples from the five countries in the region, in order to develop a conceptual framework for addressing the issue at the regional level, and to suggest areas for further study.

This study employs two main methodologies:

1. Archival study: Literature review of existing studies—both qualitative and quantitative—and reports on drug quality issues in the Mekong Subregion, including incidents and cases where information is publicly available.
2. Analysis of test results data from an international database—USP-PhaReD database. The database analysis will produce descriptive statistics of pass/fail test results by generic (International Nonproprietary Names—INN), drug group, country, province, distribution channel, etc., as well as counterfeit identified.

[2] The USP DQI is a predecessor of Promoting the Quality of Medicines (PQM), a programme that is based on a cooperative agreement between the USP and USAID.

1 - THE MEKONG SUBREGION AND MEDICINE QUALITY

1.1 - Legal Framework for Medicine Quality in the Five Countries

Substandard and counterfeit medicines exist in the Mekong Subregion despite the existence of legal frameworks and regulatory systems designed to control them. Although legal definitions and requirements of substandard and counterfeit medicines under the laws in each country might differ, these two categories of medicines both fall within the realm of regulation. The following sections provide brief reviews of the legal definitions and requirements related to medicine quality, with a special focus on substandard and counterfeit medicines, in the five countries—Cambodia, China, Lao PDR, Thailand and Vietnam.

In Cambodia, the 1996 Law on the Management of Pharmaceuticals provides a broad framework for pharmaceutical management matters. This law grants the Ministry of Health the authority to issue instructions and control activities concerning pharmaceuticals.

According to Cambodian law, a counterfeit drug is defined as a drug

(1) which is deliberately produced with incorrect quantity of or wrong active ingredients, or
(2) without active ingredients or unregistered product which amounts of active ingredients are deliberately outside the defined pharmacopoeias or accepted standard, or
(3) which is deliberately and fraudulently mislabelled with respect to identity source or with fake packaging,
(4) which is repacked or produced by an unauthorized person.

A substandard drug is then defined as a registered product which its specifications are out of defined pharmacopoeias or accepted standard.

In China, the Drug Administration Law of the People's Republic of China, revised in 2001, provides clear definitions and conditions for the regulation and management of pharmaceutical matters. Under Article 48,

the production (including dispensing) and distribution of counterfeit drugs are prohibited. The definition of counterfeit drug is clearly outlined for any of the following cases:

(1) the ingredients in the drug are different from those specified by the national drug standards; or
(2) a non-drug substance is simulated as a drug or one drug is simulated as another.

Also, a drug shall be treated as a counterfeit drug in any of the following cases:

(3) its use is prohibited by the regulations of the drug regulatory department under the State Council;
(4) it is produced or imported without approval, or marketed without being tested, as required by this Law;
(5) it is deteriorated;
(6) it is contaminated;
(7) it is produced by using drug substances without approval numbers as required by this Law; or
(8) the indications or functions indicated are beyond the specified scope.

Likewise, the production (including dispensing) and distribution of substandard drugs are also prohibited under Article 49. Any drug with content not up to the national drug standards is a substandard drug. In addition, the law also specifies that any drug shall be treated as a sub-standard drug in any of the following cases:

(1) the date of expiry is not indicated or is altered;
(2) the batch number is not indicated or is altered;
(3) it is beyond the date of expiry;
(4) no approval is obtained for the immediate packaging material or container;
(5) colourants, preservatives, spices, flavourings or other excipients are added without authorization; or
(6) other cases where the drug standards are not conformed. (Order of the President of the People's Republic of China 2001).

In Lao PDR, the Law on Drugs and Medical Products promulgated in 2000 defines counterfeit drug as any modern or traditional medicine that is a fake or is an imitation of a drug that is produced, distributed and legally registered (Article 11).

A substandard drug is termed in this law as a "non-standard" drug, and is defined as any modern or traditional medicine, the composition of which is inconsistent with the drug's registered formula (Article 12). In addition, the law also defines another category, a "deteriorated drug" as any modern or traditional medicine, the quality of which has deteriorated due to expiration or other impacts. (Article 13).

This law also stipulates that the retail sale of drugs and medical products can only be conducted through legally licensed pharmaceutical stores (Article 26).

In Thailand, the legal framework for drug regulation is currently provided by the long standing Drug Act of 1967 (BE 2510). Under this law, production, sale, and importation of fake drugs, substandard drugs, deteriorated drugs, unregistered drugs, drugs who had their license withdrawn for more than six months, are prohibited (Article 72). The definition of counterfeit or fake drug is clearly specified in the law (Article 73) as any drug or substance:

(1) which is wholly or partly an imitation of a genuine drug; or
(2) which shows the name of another drug, or an expiry date which is false; or
(3) which shows a name or mark of a producer, or the location of the producer which is false;
(4) which falsely shows that they are in accordance with a pharmaceutical preparation which has been registered; or
(5) which was not produced in accordance with standard such that the product contains the active ingredient in quantity or strength is lower than the minimum or higher than the maximum amount registered by more than twenty percent.

Article 74 defines a sub-standard drug as a drug:

(1) which was not produced in accordance with standards such that the product contains the active ingredient in quantity or strength is lower than the minimum or higher than the maximum amount registered, but to a degree less than that stated in Article 73 (5)—which is that of fake drug.
(2) Produced such that the purity and other characteristics which are deemed important to its quality deviate from the criteria specified

in the registered formula or the formula modified according to the Minister's order.

In addition, another category called "deteriorated drug" is also defined and regulated. A drug is considered deteriorated drug if:
(1) its expiry date as shown on the label has been reached;
(2) it has been denatured as to have the characteristics of a fake drug or differing from the standard under Article 74.

In Vietnam, the current Pharmaceutical Law was adopted in 2005. Article 2 of this law specifies the terms of a substandard drug as a drug that has failed to meet the quality standards registered with the competent authorities. The same article defines counterfeit drug as a product deliberately and fraudulently made in drug form, including the following:
(1) containing no pharmaceutical substances;
(2) containing pharmaceutical substances different from those stated on the label;
(3) counterfeiting product names, industrial designs of drugs which have been already registered by other manufacturers for industrial property protection.

Another article (Article 9) stipulates that trading in drugs of unclear origin, counterfeit drugs, substandard drugs, expired drugs, drugs in the banned list of import, drugs for clinical trials, drugs which are not permitted for marketing, sample drugs used for registration or for promotion to physicians is strictly forbidden by law. In addition, selling drugs at places that are not legally authorized to sell drugs is also a strictly forbidden act.

Because each country may have a different legal definition for substandard and counterfeit medicines, in multi-country studies the definition developed by the World Health Organization (WHO) is usually employed. Substandard medicines are genuine medicines produced by manufacturers authorized by the appropriate national medicine regulatory authority (NMRA) but do not meet quality specifications set for them by national standards (WHO 2011).

Substandard medicines are products whose composition and ingredients do not meet the correct scientific specifications, and which are consequently ineffective and often dangerous to the patient. Substandard

products may occur as a result of negligence, human error, insufficient human and financial resources or counterfeiting.

A counterfeit medicine, according to the World Health Organization, is one that is "deliberately and fraudulently mislabelled with respect to identity and/or sources." Counterfeiting can apply to both branded and generic products. These products may contain correct ingredients or wrong ingredients, without active ingredients, with insufficient active ingredients or with fake packaging. (WHO 2003)

1.2 - Assessing the Quality of Medicines in the Mekong Subregion: a Brief Review of Existing Empirical Studies

This section provides a review of existing empirical studies on medicine quality in the Mekong Region, covering Cambodia, Yunnan Province in China, Lao PDR, Thailand and Vietnam. This review is not meant to be exhaustive nor comprehensive, therefore it does not list the results of all studies. It is rather intended to highlight some of the issues and problems surrounding the quality of medicines, and when medicine quality becomes a matter of interest for intervention, e.g., monitoring their quality and taking enforcement action.

In addition to surveys of medicine quality conducted in a specific country, there have also been studies undertaken across many countries. A multi-country study focusing on artesunate was carried out between 1999 and 2000, in which 104 samples in blister packs purporting to contain artesunate were collected from shops, pharmacies, NGOs, and hospitals in Myanmar, Cambodia, Vietnam, Lao PDR and western Thailand. Test results showed that 29% of the blister packs collected contained no detectable artesunate. All were falsely labelled as having been manufactured by Guilin Pharmaceuticals Co.—a major producer of artesunate in Asia. Of the artesunate samples bought from pharmacies and shops, 39 (38%) were counterfeit. Fakes were found in all five countries. The proportion of fake artesunate in Cambodia was reported to be 25%, Lao PDR 38%, Myanmar 40%, Thailand 11%, and Vietnam 64% (Newton et al. 2001).

Figure 1: Example of counterfeit chloroquine phosphate tablets found in Cambodia in 2004

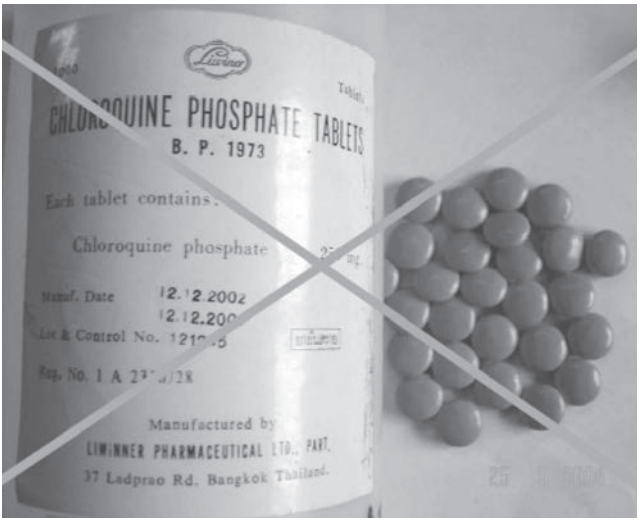


Photo: M. Boravann

Medicine quality in Cambodia has long been a concern for many parties. Since the late 1990s, many organizations monitored, using different methodologies, the quality of medicines collected from different areas of the country. Cambodia's Ministry of Health has received support from international organizations to conduct quality surveys. Key among them are the European Commission-Cambodia Malaria Control Project (EC-CMCP), World Health Organization, and United States Pharmacopeia. Results from many studies have revealed the extent of medicine quality problems in both public and private sectors. For example, the EC-CMCP surveys, conducted during 1998-1999, found that most of the mefloquine tablets and about half of the artesunate blister packs sampled were fake medicines.[3] A subsequent survey uncovered that fake artesunate was sold by 71% of 133 drug vendors and pharmacies in 12 market places, and fake mefloquine by 60% of those outlets (Rozendaal 2001). A WHO-funded

[3] In Cambodia, a fake medicine is a pharmaceutical product that does not contain the active pharmaceutical ingredient of that product as claimed on the label .

Ministry of Health survey in 2000 collected and tested 230 samples, the majority of which were anti-infectives, from Phnom Penh markets and five provinces (Kampong Cham, Kampong Chhnang, Takeo, Kampong Speu, and Kandal). Quality tests revealed that 13% failed to meet standard. Among these, 10.4% were considered counterfeit (failed the test and not registered) and 2.6% were considered substandard (failed the test but registered) (cited in USP-DQI 2004).

Figure 2: Example of counterfeit artesunate found in the Mekong Subregion in 2004

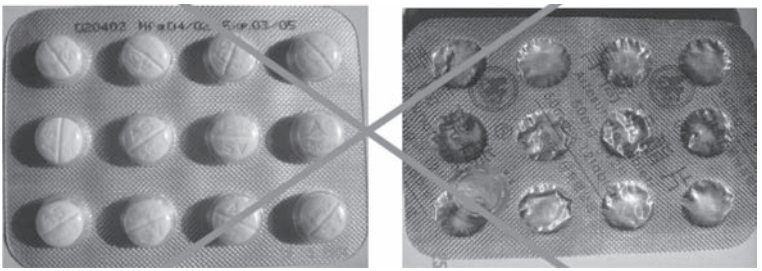


Photo: T. Sovannarith

Figure 3: Example of counterfeit amoxicillin capsules found in Cambodia, 2009

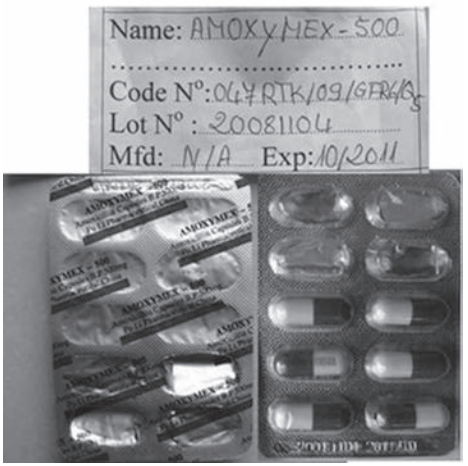


Photo: M. Boravann

Figure 4: Multi-colour medicine sachets of cocktail pills repacked by retail drug outlets are still available in some parts of the countries in the Mekong Subregion. This photo was taken in Cambodia in 2011.

Photo: T. Sovannarith

Poor quality medicines in Cambodia were distributed through public, private, as well as non-governmental facilities. In a study tracing 132 samples of 14 types of medicines, most of which were again anti-infectives, 13% of the samples from public facilities, 7.7% from non-governmental organizations (NGOs)/mission facilities and 9.6% from private retail outlets were substandard (cited in USP-DQI 2004). In 2003, a USP-DQI study collected 451 drug samples from 171 outlets in Pursat, Battambong, Pailin and Preah Vihear provinces bordering Thailand and Lao PDR. The results showed that the average failure rate of quinine was as high as 71.8%, artesunate 19.8%, and tetracycline 26.6%, followed by chloroquine 8.5% and mefloquine 7.7%. Counterfeit and substandard anti-malarials were available both in licensed and unlicensed drug outlets. Fifty-eight percent of the 38 licensed and 75% of 133 unlicensed drug outlets surveyed sold counterfeit medicines (Lon et al. 2006). Another study focusing on the quality of aspirin tablets sold in drugstores in Phnom Penh was conducted between 2002 and 2003. Aspirin tablets were purchased from 96 randomly selected drugstores, both legal and illegal, proportionally from the seven districts of Phnom Penh. Test results show that although 83.3% of the aspirin samples met the assay for content as claimed on the

label, most failed dissolution test. Overall, only 7.3% passed all the test criteria (Yang et al. 2004). More recently, in July 2008, inspections carried out by the Pharmacists Association of Cambodia discovered that approximately 20-40% of medicines sampled from pharmacies in Phnom Penh were unregistered (Sovan & Yin 2008). Another report in 2009 revealed that samples of chloroquine, artesunate, quinine, amoxicillin, ampicillin, and penicillin failed laboratory testing (USP-DQI 2009). The Cambodian medicine regulatory authority has stepped up law enforcement in recent years to curb the sale and smuggling of counterfeit and substandard drugs.

In a large country like China, findings from one geographical area can by no means represent the situation in the entire country. Documented studies in China, although few, involved larger numbers of samples in comparison to surveys conducted in other countries in the region. A 1997 report from an investigation conducted by the Ministry of Health of the People's Republic of China indicates that, of 1100 medicines, 138 products failed to meet national standards. Among these failed medicine samples, 48 were identified as fake medicines with pirated registration numbers. Another survey carried out in 1998 found that 13.1% of the 20,000 batches tested were either counterfeit or fell below standards (cited in USP-DQI 2004). Another study by the China Food and Drug Administration examining 110,426 batches of anti-malarial medicines from nine provinces during March–August 2006 found a total of 3,122 batches to contain counterfeit or substandard medicines.

Similar to Cambodia, attempts have been made to assess medicine quality in Lao PDR. Studies have been conducted by the Food and Drug Quality Control Center (FDQCC) in collaboration with external agencies since the early 1990s.

Various drug quality studies found varying percentages of substandard and fake medicines. For example, studies in the first half of the 1990s found 17% of the samples substandard in one survey, 33% substandard in another, and both substandard and counterfeit medicines were identified in two other studies (USP-DQI 2004). A survey of 106 private pharmacies in Savannakhet Province in 1997 uncovered that 46% of 366 samples of four different essential medicines were substandard, with 3.3% containing

no active ingredient. A follow-up survey on 92 pharmacies conducted in 1999 found a lower percentage of substandard medicines at 22%, though this is still a worrisome level (cited in USP-DQI 2004).

A study covering a large number of about 2,300 samples collected from districts, pharmacies, and shops, using stratified random sampling methods, found that 28 of the 29 (96%) artesunate tablets collected did not contain the active ingredient (Sengaloundeth et al. 2009).

Very limited information on medicine quality is available in Myanmar. This is not because of the absence of interest in the medicine quality situation in the country, but rather due to the political situation and international relations over the past decades. Of the few studies available, one was conducted by the World Health Organization (WHO) in 1999. This study found that 16% of the 212 samples tested for quality failed, with active ingredients below pharmacopoeial limits. Chloramphenicol preparations showed a high failure rate of 35%, followed by ranitidine at 20%, co-trimoxazole at 19%, and amoxicillin at 16% (Wondemagegnehu 1999). In another study reported in 2008, counterfeit artesunate was found in Kengtung, the capital of the Shan State, as well as along the border of Myanmar and Thailand (cited in McGinnis 2010).

Monitoring medicine quality in Thailand has long been routinely conducted by the Thai Ministry of Public Health according to its annual plan. In addition to the internal agencies' efforts, the Ministry also collaborates with international organizations. A 1997 study on a small number of samples (15) of anti-microbial medicines collected from pharmacies and other retailers found 40% of samples had active ingredients outside the pharmacopoeial limits, with roughly 50% of these obtained from non-pharmacy outlets (Shakoor et al. 1997). An analysis was performed on the internal test results data from the Ministry's routine monitoring between 1990 and 2003. The results from quality tests on samples on a wide variety of medicines collected revealed that percentages of substandard medicines during those years ranged from 8.8 to 17.0% (Ratanawijitrasin 2003).

Aside from anti-microbials, medicines for treating erectile dysfunction have been another key target of counterfeiting. A news report in 2008 indicated that of the 217 samples of Viagra purchased from Bangkok and

other provinces, test results found that 202 samples were counterfeit, with only 17%-48% of the active ingredient (Bangkok Post 2008).

In recent years, heightened law enforcement attempts have been made by the Ministry of Public Health. Crackdowns on illegal manufacturers and licensed pharmacies in Bangkok selling counterfeit medicines resulted in the confiscation of many illegal pharmaceutical products, many of them being expensive and lifestyle medicines. These included Viagra, Cialis, Levitra anabolic steroids, clindamycin, minoxidil, Nolvadex, and Finpecia (Matichon newspaper 2010, 2011a, 2011b).

Quality control of medicines in Vietnam is performed by the National Institute of Drug Quality Control in Hanoi, the Sub-Institute of Quality Control in Ho Chi Minh City, and drug quality control laboratories in provincial health departments.

In a 1995 post-marketing survey, 31,125 drug samples were collected from various parts of Vietnam and tested for quality. Around 5% (1,703 samples) did not meet the quality standards. Among these, 1,537 were substandard and the remaining 166 were counterfeit (USP DQI 2004). In a 1999 study conducted by WHO, 288 samples of anti-microbials (amoxicillin, ampicillin, chloramphenicol, chloroquine, metronidazole, rifampicin, and tetracycline) and other non-anti-microbial medicines were collected and tested. Results of laboratory testing showed that 22 samples did not meet the pharmacopoeial standards on active ingredients; the overall failure rate was 8% (Wondemagegnehu 1999).

More recently, the quality of anti-epileptic medicines was surveyed. Tablets of carbamazepine, phenytoin, and valproate collected from the city of Long Xuyen (An Giang Province) were tested. It was found that only 35% of the samples met quality standards (Mac et al. 2008). In its continuing efforts to estimate the risk, the drug regulatory authority in Vietnam reported that, of the 25,460 medicine samples tested in 2007, 3.3% failed quality standards (Thanh Nien News 2008).

As reviewed above, there have been numerous studies on medicine quality in the Mekong Region. A number of observations can be made from these existing efforts to summarize past situations and identify

potential future developments. Increased interest in monitoring medicine quality in the Mekong Region generally began in the 1990s, with enhanced monitoring efforts in various countries over the past decades. The types of medicines which received the greatest interest in quality monitoring are anti-infectives. Certain groups gained special attention, for example anti-malarials and antibiotics. Findings from existing studies clearly showed that substandard and counterfeit medicines exist in all the Mekong Subregion countries. The situation of certain types of medicines and in certain areas of the region should be a cause for great concern. However, findings of poor quality medicines did not necessarily lead directly to legal enforcement or other actions by the responsible parties.

From a methodological point of view, each of the existing studies covers a limited geographical area, and a limited number of medicines. The methodologies employed in these studies for sample collection and testing are varied. Furthermore, few attempts have been made to conduct follow-up monitoring in the areas previously studied, with the same methodologies, on the same set of medicines. With all these various findings from different methodologies, it is difficult to establish relationships between any causal factors and the quality of medicines found in a specific area or at a point in time.

Results from each of the studies were reported separately. Most of them can be seen as separate cross-sectional findings. Piecing together these findings can only provide a very limited picture, rather than an overall view, of the quality situation in a country or the region.

This led to attempts to "systematize" and "standardize" the methodologies for sample collection, testing, data analysis, and reporting. Examples of such efforts are documented in the following references: WHO 1999, Phanouvong et al. 2004, Newton et al. 2009, USP-PQM 2010. The efforts to monitor medicine quality and to standardize the methodologies to do so are essential in understanding and improving the quality of medicines.

Given the current practices and knowledge, a number of suggestions can be made to help better understand the state of medicine quality as well as to make better use of such efforts. First, the monitoring of medicines

quality is important to public health, as well as industry development. Such efforts should be continued and be supported. Second, systematized and standardized methodologies for medicine quality monitoring will eventually help make findings from different studies more comparable. Development of such protocols should be a collaborative effort by all the parties involved. Third, a web-based database should be developed to compile the quality findings from the different studies on the quality of medicines. This would help make better use of the findings, as well as enable cross-sectional and longitudinal analyses of the various data together, where feasible. In the sections below, framework and examples of analysis from a prototype of such database will be described. Both the standardization of methodologies and the development of database and framework for analysis will help make the costly endeavour of medicine quality monitoring more cost-effective.

Fourth, the ultimate intended effect of all the monitoring efforts should be the reduction of substandard and counterfeit medicines in the region. This can be fulfilled when the supplies of these bad medicines can be blocked, and demand can be decreased. Therefore, systematic efforts should be made to help better understand capacity limitations in regulatory systems and related factors in law enforcement in these countries. In addition, there should also be systematic efforts to help better understand health-seeking behaviour, as well as access to medicines, of people in the Mekong Region, particularly those in areas where substandard and counterfeit medicines are rampant.

2 - THE MEKONG SUBREGION MEDICINE QUALITY STUDY

The five-country Mekong Subregion study is a research project comprising multiple components and stages, including a series of medicine quality monitoring surveys, laboratory testing, database development, and multi-country comparative analysis. The surveys were conducted in the greater Mekong Subregion by the United States Pharmacopeial Convention—Promoting the Quality of Medicines programme (USP-PQM,

formerly USP DQI—Drug Quality and Information) in collaboration with drug regulatory agencies in five countries in the region—namely Cambodia, China (Yunnan Province), Lao PDR, Thailand, and Vietnam. Note that this study did not include medicine samples from Myanmar. Samples of pharmaceutical products were collected from various distribution channels and tested for their quality[4]. The test results of the samples collected between 2002 and 2008 were then compiled in a database developed in collaboration with the Pharmaceutical System Research and Development Foundation (PhaReD, formerly PSyRIC—Pharmaceutical System Research and Intelligence Center).

The development of this international medicine quality database and the analysis of the data illustrate an approach for more effective management and utilization of information gained from medicine quality monitoring surveys and quality tests. The following sections describe the survey and analysis methods, as well as database contents, and analyze the test results reflecting the state of the quality of medicines in the region.

2.1 - Methodologies

Three different designs were employed at the different stages of this study: first, the survey methodology for pharmaceutical product samples collection, which determines which medicines to collect, where from, how to collect, and how many; second, the methods for testing the medicine samples collected, which consist of three test levels—basic screening or field test, national quality control laboratory testing, and confirmatory testing (the requirements and methods of these tests follow the appropriate test procedures and specifications in, where appropriate, the relevant pharmacopoeias), and third, the methodology for data analysis, which applies descriptive statistics to examine results obtained from the tests described above.

A set of criteria was jointly established by the national health programmes and DQI (PQM) with inputs from other partners, including

[4] Testing for quality in this documents means testing key quality attributes of medicine samples including the appearance (visual/physical examination of the packaging and labelling), identification of the active pharmaceutical ingredient(s) (API), assay of content of the API(s), disintegration and dissolution for certain samples in solid dosage forms.

WHO, to select the anti-infective medicines to be collected. These criteria included:

a) products used in the national health programme,
b) products that have testing specifications, and
c) products with some historical information suggesting their quality problems.

The main focus was on anti-malarial, anti-tuberculosis and anti-retroviral medicines. The most commonly used antibiotics were also collected. Almost all the medicines collected in this project were those for infectious diseases. These include antibiotics, anti-malarial, anti-tuberculosis (anti-TB), and anti-retroviral (ARV) medicines. Table 1 lists the types of products contained in this database, collected and tested for quality, using generic names. While anti-malarial medicines were collected from all the countries, other medicines were selectively targeted. The range of anti-malarial medicines was perhaps the most comprehensive compared to other product groups. Twelve antibiotics were targeted. These include amoxicillin, ampicillin, benzylpenicillin, phenoxymeth, cefalexin, chloramphenicol, ciprofloxacin, cloxacillin, co-trimoxazole, erythromycin, metronidazole, and tetracycline. Not all the participating countries collected all these medicines.

The samples mostly came from the border provinces of the surveyed countries, from various types of distribution channels, including hospitals, clinics, health centres, malaria clinics, pharmacies, retail drug outlets, street vendors, distributors, and warehouses. Cambodia, which had the largest number of samples collected in this study, conducted the monitoring in seven border provinces, six of which border Thailand and one with Vietnam. For China, the study covered only two border counties, one with Myanmar and the other with Lao PDR in Yunnan Province. Six provinces in Lao PDR—bordering Cambodia, Thailand and China—were monitored. In Thailand, samples were collected from nine provinces. Among these, five provinces are located near the border with Myanmar to the west—ranging from the northern hilly region to the southern seaboard, one province at the border with Lao PDR, and the rest near the Thai-Cambodian border. Of the eight provinces and one city in Vietnam where samples were collected, seven are border provinces adjacent to Cambodia, Lao PDR, and/or China. Names and locations of the provinces from which samples were collected for testing are displayed in Figure 5.

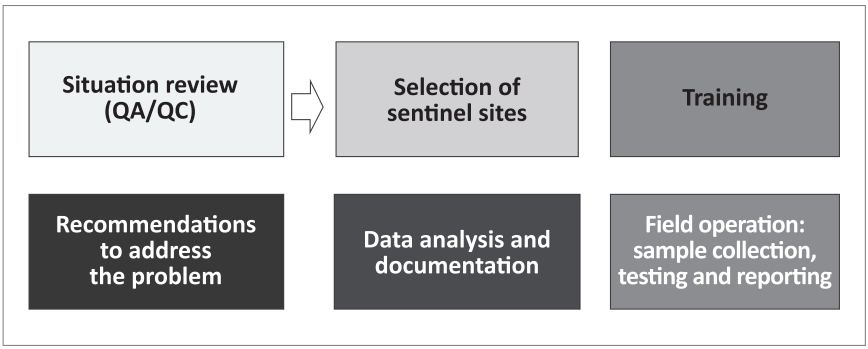
Figure 5: Map of countries of the Mekong Subregion with dots illustrating the locations of pharmaceutical sample collection sites

In each country, samples were collected using two techniques: formal inspection and 'mystery shopping'. The former was carried out by sampling team(s) that consisted of representatives from a medicines

regulatory agency, national QC lab, disease programme, and local health agencies; while the latter was performed by 'disguised' consumers and/or by the provincial or district health authority personnel who were not known by the sellers in the sampling area. Each country collected two rounds of samples per year.

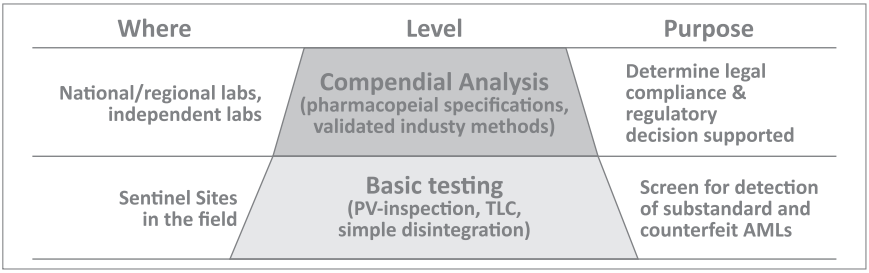
A sample consisted of a minimum of 20 units for tablet or capsule dosage forms of single API preparations; 30 units for two or more APIs formulations; and 10 units for injectables. If fewer units were found (i.e. in informal sector), samples with less than 20 units were also collected. Every effort was taken by the sample collectors to record necessary information about the samples in the standardized sampling form. Special precautions were taken to ensure sample integrity and quality and to protect them from physical damage during the sampling, transportation, and testing phases. Samples were kept and stored according to the manufacturer's recommended storage conditions. The source of a sample should be traceable, i.e., samples that had the 'identifiable' name of the drug product and its API(s) and the manufacturer's address on the label. Where possible, samples should have been in their original container or package.

Figure 6: Methodological framework on medicines quality monitoring applied in the GMS by the United States Pharmacopeia Promoting the Quality of Medicines Program



Source: United States Pharmacopeia Drug Quality and Information Program. Ensuring the Quality of Medicines in Resource-Limited Countries: An Operational Guide. Rockville, Md.: The United States Pharmacopeial Convention. Available online: www.usp.org/worldwide/dqi/resources/technicalReports

Figure 7: Three levels of testing for checking the quality of the samples



As described earlier, three levels of testing were designed for checking the quality of the samples collected: field, QC lab and confirmatory. For the field level testing, samples collected from the various distribution channels were first subjected to field testing using the Global Pharma-Health Fund (GPHF) Minilab® kit that can be carried out with a simple setup and without a laboratory.

The kit provides all necessary basic screening test tools and supplies which can help early detection of substandard and counterfeit drugs for some 50 essential medicines. The test procedures and techniques consist of a physical/visual inspection, a simple disintegration, and a thin-layer chromatography (TLC). A person with general scientific knowledge in analytical chemistry and pharmaceutical sciences who participated in a week-long proper training programme would be able to conduct such a test[5].

Physical/visual inspection of pharmaceutical products is the first step in any quality control activities, as it helps ensure the authenticity of the package. Visually inspecting the integrity of the packaging, the appearance of tablets, or other dosing forms may help to identify potentially poor quality products. An examination of remaining shelf-life and compliance with approved labelling, packaging, and shipping instructions is also important. The physical appearance of a medicine dosage form—shape, size, colour—can provide an important clue in identifying suspicious and

[5] The GPHF-Minilab® - Protection Against Counterfeit Medicines. Accessed Nov 20, 2011. http://www.gphf.org/web/en/minilab/index.htm

Figure 8: Basic tests used in the medicines quality monitoring programme in the Mekong Subregion

Visual Inspection

Disintegration Test

Thin Layer Chromotography

Source: GPHF Minilab® Manual, 2008 update

potentially counterfeit medicines. Visual inspection may also indicate substandard manufacturing, such as crumbling, chips, or cracks in solid dosage forms.

Simple disintegration is a test to determine whether a pharmaceutical solid dosage form (tablet or capsule) will disintegrate within the specified time when placed in a liquid medium at a temperature between 35° and 39°C. All immediate release tablets or capsules should disintegrate within 30 minutes. In the field, where the Minilab kit is used, disintegration can be performed using tap or distilled water in a 100–150 ml. wide-neck bottle.

Thin-layer chromatography (TLC) test technique in the GPHF-Minilab® kit comes with ready-to-use TLC plates with essential labware and chemicals, as well as authentic tablets and capsules for reference purposes. TLC is a simple and effective test for identification and semi-quantification of the API(s) contained in the formulations. The GPHF-Minilab® has been developed for rapid quality verification for counterfeit medicines.

A pre-determined subset of samples were then analysed using the so-called 'level two or QC lab test' at the respective national quality control laboratories whose analysts were trained by the USP PQM experts.

Samples from Lao PDR were tested at the Food and Drug Quality Control Center; those from Vietnam were tested at the National Institute of Drug Quality Control (NIDQC); those from Thailand were analysed at the laboratory of the Bureau of Drug and Narcotic; and those from Cambodia were tested at the National Quality Control Laboratory of Drug and Food (now know as National Health Product Control Laboratory). Due to logistical and technical reasons, samples from Yunnan were tested at the NIDQC.

Figure 9: Officers conduct a simple disintegration test of oseltamivir tablets in Cambodia

Photo: S. Phanouvong

The QC lab tests were used to determine whether the samples' quality conformed to pharmacopoeial specifications for appearance, identification of API(s), assay for content of API(s), and, in certain cases, dissolution property. High-performance liquid chromatographic (HPLC) and ultraviolet (UV) spectrophotometric methods were used for most identification and assay tests at the QC lab level. Dissolution serves as a quality control test by providing evidence of the product's physical consistency and manufacturing process. It is a critical regulatory and compendial requirement in the testing of solid dosage forms and quantitatively determines the in-vitro biological availability. If a product fails the dissolution property test, it is most likely that the product will not be absorbed by the body, thus it will not produce any therapeutic effect. The following pharmacopoeial methods and procedures were used in this project, namely: the International Pharmacopoeia, the United States Pharmacopeia, the Chinese Pharmacopoeia, and the Vietnamese Pharmacopoeia, of their

latest edition. Confirmatory tests were conducted on some samples at reference laboratories with ISO-IEC 17025 accreditation. These included the USP Research and Development Laboratory in Rockville, Maryland, USA; the NIDQC in Vietnam. These laboratories used pharmacopoeial specifications to test the samples.

Figure 10: Training on basic testing for field monitoring of anti-infective medicines in Thailand, 2009

Photo: BND staff

Figure 11: Training on quality control technique and procedures to detect counterfeit and substandard medicines to central and field laboratory staff in Vietnam

Photo: S. Phanouvong

Table 1: Types of medicine samples in USP-PhaReD database

Cambodia	China	Lao PDR	Thailand	Vietnam
Antibiotics				
Amoxicillin, Ampicillin, Benzylpenicillin, Phenoxymeth, Cefalexin, Chloramphenicol, Ciprofloxacin, Cloxacillin, Erythromycin, Metronidazole Tetracycline		Amoxicillin, Ampicillin, Benzylpenicillin, Phenoxymeth, Cefalexin, Chloramphenicol, Ciprofloxacin, Cloxacillin, Erythromycin, Metronidazole, Tetracycline	Tetracycline	Amoxicillin, Ampicillin, Benzylpenicillin, Phenoxymeth, Cefalexin, Chloramphenicol, Ciprofloxacin, Cloxacillin, Co-trimoxazole, Erythromycin, Metronidazole Tetracycline
Anti-malarials				
Artesunate, Chloroquine, Mefloquine, Quinine	Artesunate, Chloroquine, Pyrimethamine, Quinine	Artesunate, Chloroquine, Quinine	Artesunate, Chloroquine, Mefloquine, Pyrimethamine, Quinine	Artesunate, Chloroquine, Mefloquine, Primaquine, Pyrimethamine, Quinine
Anti-TB				
Ethambutol, Isoniazid, Pyrazinamide, Rifampicin		Isoniazid, Rifampicin		Ethambutol, Isoniazid, Pyrazinamide, Rifampicin
ARVs				
Lamivudine, Nevirapine, Stavudine, Zidovudine				Efavirenz, Indinavir, Lamivudine, Nevirapine, Stavudine, Zidovudine
Others				
Griseofulvin, Paracetamol, Furosemide				

2.2 - Medicine Quality Database and Analysis of Test Results

The *USP-PhaReD Medicine Quality Database*, which is the first international database on medicine quality, is a web-based searchable database of drug quality test results. The database was developed between 2007 and 2009. It contains information on the results of quality testing on more than 3,000 drug samples collected between 2002 and 2008 from the five countries.

Altogether, 3,669 samples of pharmaceutical products, covering 2,728 production batches, were collected from multiple survey rounds conducted over seven years. The numbers of samples collected from each of the five countries in different years are listed in Table 2.

Table 2: Number of Samples Collected by Country by Year

Year	2002	2003	2004	2005	2006	2007	2008	Total by country
Cambodia	180	177	135	150	50	215	253	**1,160**
Yunnan, China		39	76	11				**126**
Lao PDR		87	93		217	446	193	**1,036**
Thailand			369					**369**
Vietnam			193	90		284	411	**978**
Total	180	303	866	251	267	945	857	**3,669**

This data set is of great value for revealing the state of medicine quality in the Mekong Subregion due to a number of attributes, as described below:

Firstly, large numbers of samples in wide ranges of categories were included. A total of 31 types of medicines (by International Nonproprietary Names) in 3,669 samples covering 2,728 production batches were

monitored. The samples were in various dosage forms—the majority of which were tablets with a small number of capsules, injections, and syrups. Secondly, the large geographical distribution covered multiple countries with border area locales—33 provinces/counties in five countries. Thirdly, it was a multi-year study with a follow-up of one to seven years. And fourthly, all participating countries employed the same basic methods in sample collection and testing.

Even with these strengths, there are certain aspects that do not allow for generalization, and render some cross-country data within this set not entirely comparable, thus limiting the range of possible analyses. Since the pharmaceutical samples were collected on a non-random basis due to availability and feasibility, the surveys were not based on random sampling design. Therefore, the data cannot be generalized as country-level data. In terms of medicine types and time, because not all five countries collected the same types of medicine and conducted follow-up sample collections every year during the seven years of the survey period, analyses to compare the whole range of results could not be made. In addition, the legal definition of counterfeit pharmaceuticals and the methods to identify them in the survey vary from country to country (Annex I). As a consequence, some analyses may have to rely on data from fewer than five countries.

Descriptive statistics are used to examine the patterns of quality testing results. The following aspects of medicine quality are examined in the analysis, with a focus on substandard and counterfeit products, both at the regional and country levels, where existing data are amenable:

(1) overall picture,
(2) medicine quality trends by country,
(3) quality of medicines by group,
(4) counterfeit medicines,
(5) quality by distribution channels,
(6) risks to consumers.

3 - MEDICINE QUALITY AS REFLECTED IN THE FIVE COUNTRY STUDY

The analysis to be presented in the sections below covers two levels: country and region. The regional analysis relies on the combined data of test results from all five countries. Where aggregation of data is required in the examination and comparison of results from different countries, we take into account the comparability of the data. Furthermore, because the samples used for the tests were not collected randomly, and came from the border provinces of these countries, which were areas known to have deeper problems in medicine quality and were often targeted for investigation and enforcement, the degrees of the problem revealed in this analysis do not represent national or regional averages. In addition, because the quality testing takes time from sample collection to final analysis, the test results inevitably reflect quality of samples from previous times, rather than the current situation. In this case, the analysis generated from this study may serve as reference points to which data from new monitoring efforts can compare longitudinally to see if the quality situation has improved or deteriorated.

For any results from a monitoring study, the fact that quality problems exist at all should send a signal or sound an alarm on the need for intervention. This is because, ideally, no medicine should fail the scrutiny for quality.

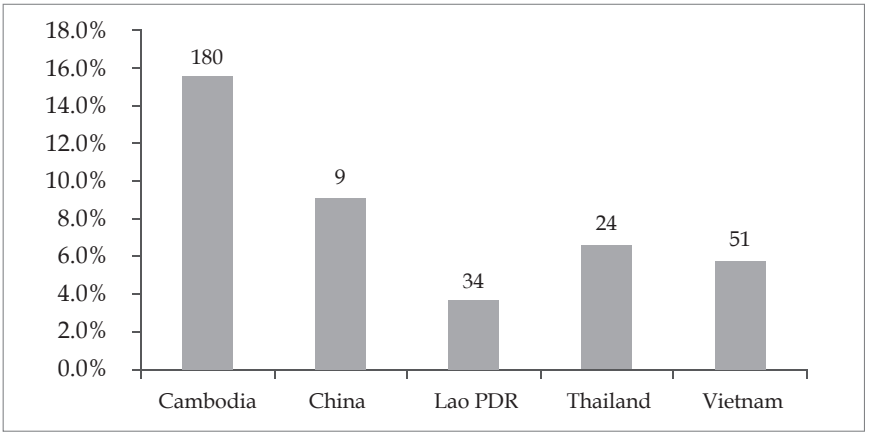
In this analysis, a medicine at any level of quality that fails to ensure patient safety is considered a failed product. Thus, the two categories—substandard and counterfeit medicines—are both failed products. Neither of them meets the legal requirements on quality.

3.1 - Medicine Quality: the Overall Picture

When the results of all the medicine samples collected from all the survey rounds from these five countries are combined, the percentage of samples that did not pass quality testing range from 3.3% in Lao PDR to 15.5% in Cambodia, with an average failure rate of 8.1% for the region.

Figure 12 presents the percentage of medicine quality failure from each of the countries.

Figure 12: Percentage of samples failing quality testing by country



Note: The number above each bar chart indicates the number of poor-quality (substandard as well as counterfeit) samples from each country. Note that the total number of samples collected from each country varies.

3.2 - Medicine Quality Trends at Country Level

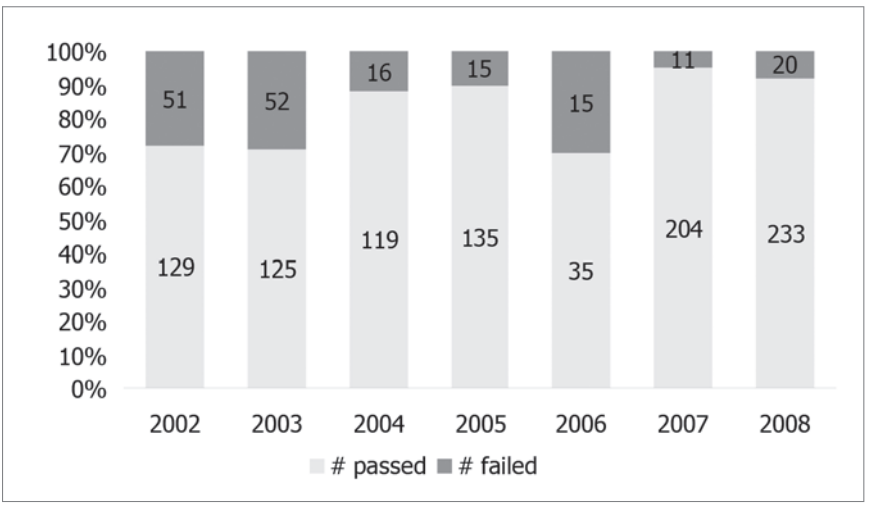
The quality failure rate found in each country represents the overall multi-year monitoring results. Three out of the five countries—Cambodia, Lao PDR and Vietnam—sampled in different years. Data from Thailand is only available for one year in this database. Furthermore, in regards to the samples collected from Yunnan Province in China for three years, the number of samples tested each year is too small to allow for any meaningful analysis in trends. Thus, we looked at changes over time only in Cambodia, Lao PDR, and Vietnam.

Among the countries surveyed, Cambodia has the most complete set of data. Figure 13 depicts the relative rates of samples that passed and failed quality testing over the years. The total number of samples per year is shown on each of the bar charts to allow the readers to judge the relative

weight of the data from different years. High failure rates occurred during 2002 and 2003, at 28.3% and 29.4%, respectively. There was then a general downward trend, except for a jump to 30% in 2006.

Products with relatively high failure rates were the anti-malarials —artesunate tablets and chloroquine tablets—with almost 60% of the samples failing quality tests. These high anti-malarial failure frequencies caused the rise in overall failures in 2006.

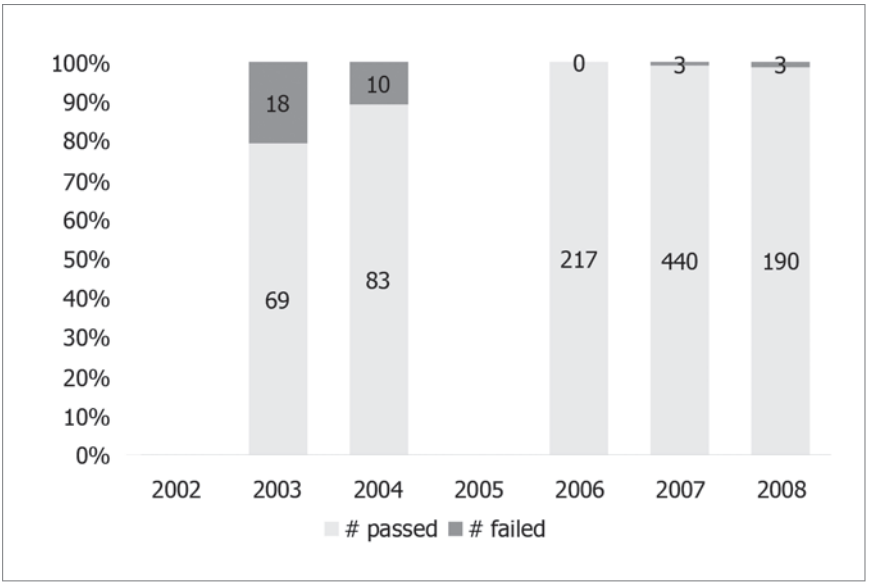
Figure 13: Quality of medicines samples collected in Cambodia between 2002-2008 showing the proportion of products that passed and failed quality testing



Note: The number in the dark grey section on each bar chart indicates the number of poor-quality (substandard as well as counterfeit) samples tested each year in Cambodia.

In Lao PDR, samples were collected between 2003 and 2008, except in 2005. Thus, the data is available for five years only. The findings from Lao PDR show a general improvement trend in quality. The highest failure rate among the surveys in Lao PDR was 20.7% in 2003, but this fell by half the following year, and subsequently tapered to 0-2%.

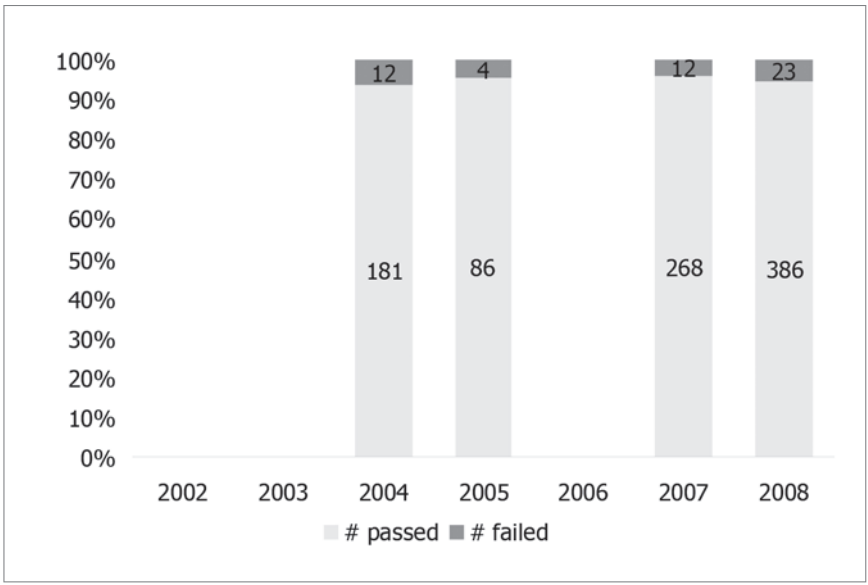
Figure 14: Quality of medicines samples collected in Lao PDR between 2003-2008 showing the proportion of products that passed and failed quality testing



Note: The number in the dark grey section on each bar chart indicates the number of poor-quality (substandard as well as counterfeit) samples tested by year in Lao PDR.

In contrast to the findings in Cambodia and Lao PDR, the frequency of medicines failing quality testing in Vietnam was relatively low and stable at 4-6% from 2004 to 2008.

Figure 15: Quality of medicines samples collected in Vietnam between 2004-2008 showing the proportion of products that passed and failed quality testing

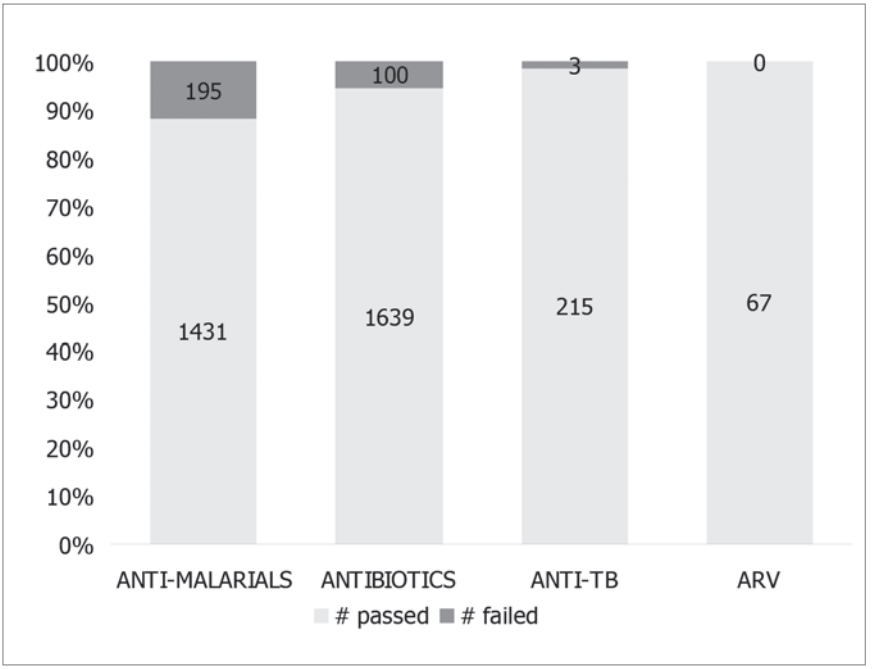


Note: The number in the dark grey section on each bar chart indicates the number of poor-quality (substandard as well as counterfeit) samples tested by year in Vietnam.

3.3 - Quality of Medicines by Therapeutic Group

In the many studies on medicine quality in the Mekong Subregion, the main medicines of interest have primarily been anti-microbials. This study follows the same focus. Of more than 3,000 samples collected, only six items belonged to categories that are not anti-microbials. Hence, the analysis here focuses only on anti-microbial medicines as they are the main targets. Medicines in four anti-microbial therapeutic categories were sampled and tested: anti-malarials, antibiotics, anti-tuberculosis medicines, and anti-retrovirals.

Figure 16: Quality of four categories of anti-microbial medicines samples collected and tested in the region (2003-2008)



Note: The number in the dark grey section on each bar chart indicates the number of poor-quality (substandard as well as counterfeit) samples by therapeutic group.

With a 12% failure rate, anti-malarial medicine is the most problematic group among the four. Antibiotics, of which 6% did not pass quality testing, came second. Failed anti-tuberculosis medicines rated at 1.4%, while all the anti-retroviral medicines for the treatment of HIV were found to meet quality standards.

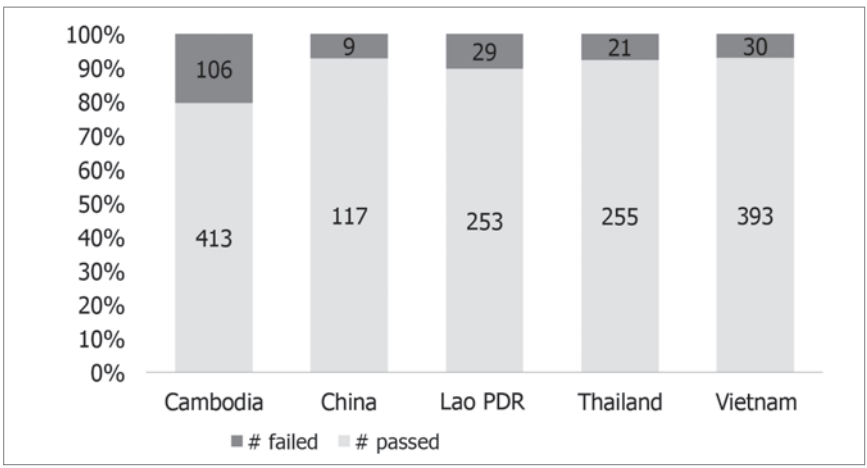
Because of such a wide variation among the quality of these different medicine groups, it is interesting to learn more about the explanations behind such differences. Except for antibiotics, many countries manage the other three groups of anti-microbials in vertical programmes. Theoretically, the government should be in a position to ensure that the medicines distributed and dispensed are of good quality. Otherwise, all

the efforts made to exert direct control of the treatment of these serious infectious diseases would be in vain. The fact that more than 10% of anti-malarial drugs that are circulating are of poor quality demands that investigations be made into the workings of drug distribution and its context in the region. Further analysis is made on each of the different medicine groups and country to identify problem areas.

3.3.1 - Anti-malarial medicines

This data suggests that the problem is most severe in Cambodia—where 20% of the anti-malarials failed to pass the tests, followed by Lao PDR at 10%. In the other three countries, the rates were around 7%.

Figure 17: Quality of anti-malarials collected by country



Note: The number in the dark grey section on each bar chart indicates the number of poor-quality (substandard as well as counterfeit) samples by country.

In Cambodia, the type of anti-malarial medicines that did not pass quality testing included artesunate, chloroquine, mefloquine, and quinine solid dosage forms. The most problematic drug was quinine with only 37% of the samples passing the tests. Of the rest of the samples, about 3% were substandard and as high as 60% were identified as counterfeits, based on the country's legal definition.

The failure rates of anti-malarials from Lao PDR were also alarming, with 17% of chloroquine and 13% of artesunate not passing. The failure rate for this whole group in Lao PDR was 10%.

Figure 18: Inspectors of the Food and Drug Department of Lao PDR inspect retail pharmacy outlets as part of the monotherapies ban policy implementation in Lao PDR

Photo: S. Phanouvong

Among the samples from Yunnan Province in China, the most problematic anti-malarial was artesunate (in tablet form) with a worrisome 17% failure rate, although the sample was small. The overall rate for this anti-infective group was 7%. Artesunate, a key component of artemisinin-based combination therapy (ACT), is one of the most efficacious medicines for treating *P. falciparum* malaria. In 2009-2010, due to the increasing concern of prolonged parasite clearance time and resistant malaria to artemesinin monotherapy in the region, especially in the 'hot spot' malaria zone along the Thai-Cambodian border areas, artesunate solid dosage form as monotherapy was banned by most countries in the Mekong Subregion[6].

[6] Despite the countries in Mekong subregion have banned the artesunate solid dosage form monotherapy, recent year sample collection rounds from the PQM-supported medicines quality monitoring activities suggested that artesunate tablets have been founds in private sector although in very limited frequency and quantity.

In Thailand, substandard artesunate, chloroquine, and quinine were found, with relatively, yet still problematic, lower failure rates of 4%, 17%, and 6%, respectively.

In Vietnam, the item with the highest failure rates was quinine (13%), followed by chloroquine and artesunate (9% and 3%).

That older, less effective, anti-malarial medicines are widely available throughout the border areas of these countries suggests that they are bought and used by people in these areas. Although it is not known which dosage regimens are actually used by those who buy medicines to treat themselves, the appropriateness of medicine use is questionable. With great efforts made at the global, regional and national levels to devise the best ACT treatment regimens for malaria, the reality in the field is significantly different from what policy-makers intended. To effectively control the spread of the malaria epidemic, policy implementation requires no less attention than policy formulation.

This study also suggests that many anti-malarial medicines were substandard and that the quality level is considerably lower than in other categories of anti-microbials that were monitored. The threats from poor quality medicines are multi-fold. First, they do not cure and might cause harm to the patients. Second, patients taking bad medicines are led to believe that treatment is being made and defer seeking appropriate care. Third, there is a great risk in the development of the parasite's resistance strains.

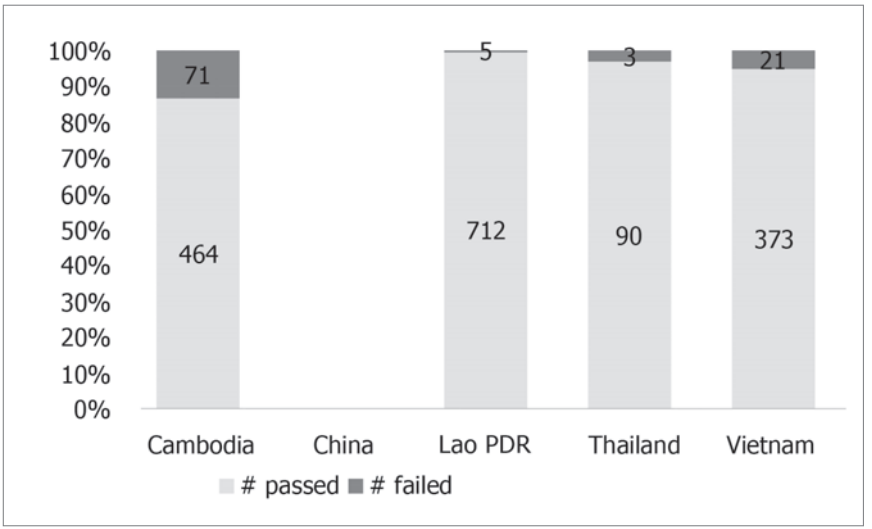
The incidence of malaria in the Mekong Subregion is still relatively high, and drug resistant strains of malarial parasites first arose in this area. High rates of poor quality medicines to treat the disease and the inappropriate treatment regimens used constitute a serious cause for concern to public health, and demands serious call for intervention.

3.3.2 - Antibiotics

The majority of the antibiotics tested were from Lao PDR (717 samples). No antibiotics were collected from China for this study; and only

tetracycline was collected from Thailand. Hence, the numbers presented in Figure 19 are not entirely amenable for cross-country comparison.

Figure 19: Quality of antibiotics collected and tested by country



Note: The number in the dark grey section on each bar chart indicates the number of poor-quality (substandard as well as counterfeit) antibiotic samples by country.

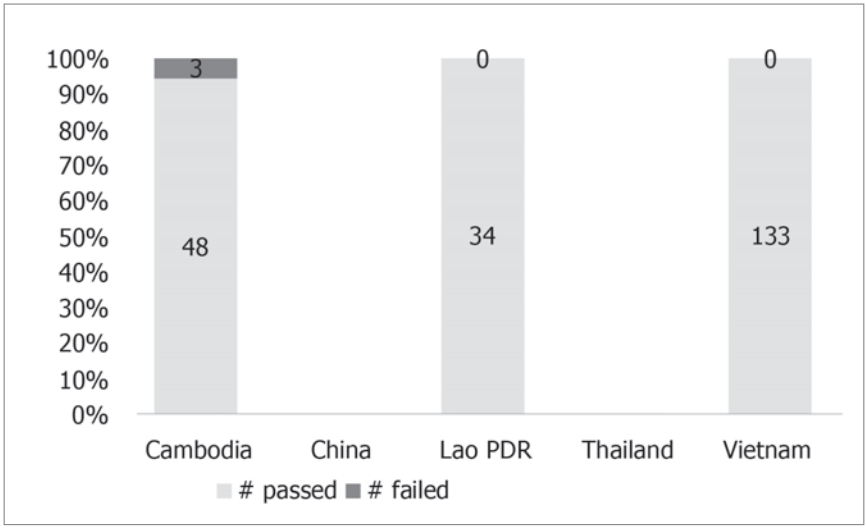
In Cambodia, the antibiotic with the highest failure rate was tetracycline—only 81% passed quality tests. About 11% were substandard and 7% were found to be counterfeit products. Another antibiotic with serious poor quality issues was ampicillin, of which 16% were substandard.

In Thailand, only tetracycline samples were collected, and 3% were substandard. For Lao PDR and Vietnam, tetracycline and ampicillin had the highest failure rates compared to other medicines.

3.3.3 - Anti-tuberculosis medicines

Of the three countries from which samples of anti-TB medicines were collected, it was found that some samples from Cambodia did not pass the test. They contained low doses of isonizid and rifampicin.

Figure 20: Quality of anti-TB medicines collected and tested by country

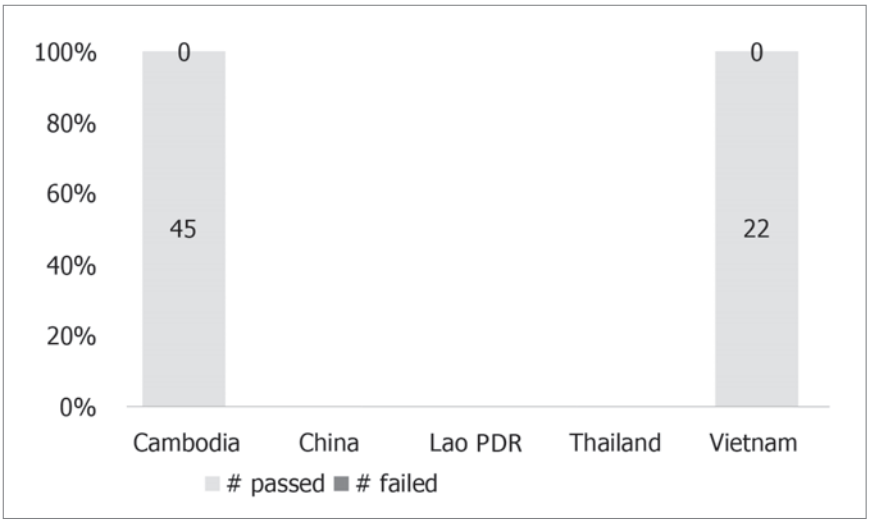


Note: The number in the dark grey section on each bar chart indicates the number of poor-quality (substandard as well as counterfeit) anti-TB samples by country.

3.3.4 - Anti-retroviral medicines (ARVs)

Anti-Retroviral medicines were collected only in Cambodia and Vietnam. All of the ARV samples passed the tests.

Figure 21: Quality of ARVs collected and tested by country

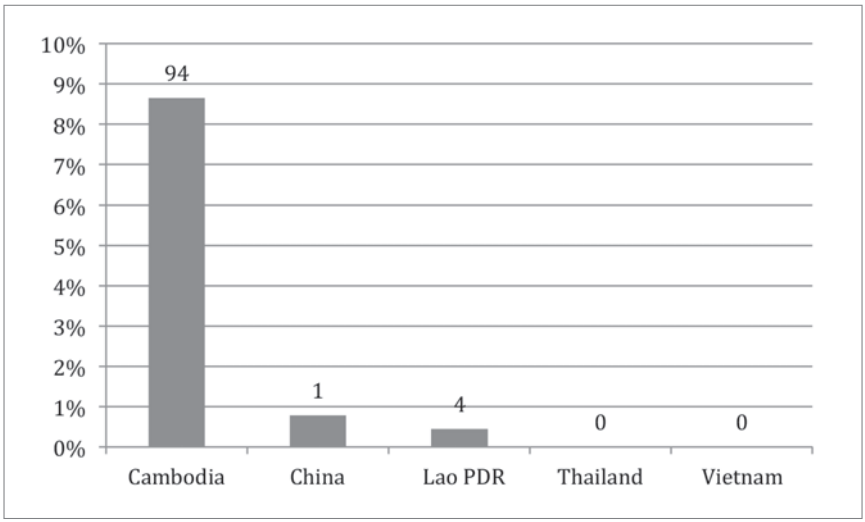


3.4 - Counterfeit Medicines[7]

Of the pharmaceutical products collected in the various rounds of surveys, 99 (2.7%) samples were identified as counterfeit medicines. The vast majority of the counterfeit products identified came from Cambodia; and all of them were detected between 2001 and 2004. Of the other relatively few counterfeit samples (5 out of 99), 4 came from Lao PDR, and 1 from Yunnan Province (China). The number is too small to allow any meaningful analysis. Therefore, we decided to focus on the situation in Cambodia.

[7] Refer to definitions of counterfeit medicines in Annex I

Figure 22: Counterfeit medicines by country



Note: The y-axis indicates the percentages of counterfeit medicines. The number above each bar chart indicates the number of counterfeit samples from each country. Note that the total number of samples collected from each country varies.

Figure 23: Counterfeit medicines found in Cambodia between 2005-2008

Photo: M. Boravann

Table 3: Counterfeit medicines identified in the five countries during 2002-2008

Year	Country	Number of counterfeit
2002	Cambodia	44
2003	Cambodia	36
	China	0
	Lao PDR	0
2004	Cambodia	14
	China	1
	Lao PDR	0
	Thailand	0
	Vietnam	0
2005	Cambodia	0
	China	0
	Vietnam	0
2006	Cambodia	0
	Lao PDR	0
2007	Cambodia	0
	Lao PDR	3
	Vietnam	0
2008	Cambodia	0
	Lao PDR	1
	Vietnam	0
Total		99

3.4.1 - Types of counterfeit medicines

A staggering 60 counterfeit samples were quinine, constituting 60% of the quinine samples collected and 64% of all the counterfeits identified. The second target with the largest percentage of fake medicines was artesunate, of which 9% of the samples were counterfeit. This was followed by 7% for tetracycline, 4% for mefloquine, and 0.6% (1 sample) for chloroquine.

Table 4: Counterfeit medicines identified in Cambodia

Medicine	Number of samples collected and tested	Number of counterfeit	Percentage of counterfeit
Quinine	100	60	60.0%
Artesunate	172	16	9.3%
Tetracycline	203	14	6.9%
Mefloquine	71	3	4.2%
Chloroquine	155	1	0.6%

Many of the counterfeit quinine tablets and tetracycline capsules were labelled as manufactured by a company named Brainy Pharmaceutical. Although the country of manufacturing was not shown, the label texts appeared in both English and Thai.

Table 5: Examples of counterfeit quinine identified in Cambodia with information regarding active ingredients, trade-name and manufacturer as stated on the packaging

Trade name	Stated manufacturer	Site	Number of samples
Quinine	Brainy Pharmaceutical	Clinic Street Vendor Retail Drug Outlets Unknown	2 1 1 9
Quinine	UNKNOWN	Retail Drug Outlets Unknown	2 3
Quinine sulfate	Brainy Pharmaceutical	Pharmacy Unknown	5 2

However, this name does not appear in the list of pharmaceutical businesses licensed by the Thai Food and Drug Administration. It is likely to be a counterfeiting company. Other counterfeit medicines were purported to be manufactured by companies in different countries, for example: Australia, Belgium and China.

Of the five counterfeit medicines detected, four were anti-malarials. With the increasing failure rates of artemisinin-based therapy, the findings of these counterfeit anti-malarials underline serious concerns over the increasing possibilities of drug resistance.

Table 6: Examples of counterfeit artesunate identified in Cambodia with information regarding active ingredients, trade name and manufacturer as stated on the packaging

Trade name	Manufacturer's name as claimed on label	Origin of sample	Number of samples
Artesunate	Guilin Pharmaceutical Works	Pharmacy Unknown	1 6
Arinate	[missing manufacturer name, labeled as made in Belgium]	Unknown	1
Artesunate	Central Pharmaceutical Factory No.2, Dopharma	Street Vendor	1

Table 7: Examples of counterfeit mefloquine identified in Cambodia with information regarding active ingredients, trade name and manufacturer as stated on the packaging

Trade-name	Manufacturer's name as claimed on label	Origin of sample	Number of samples
Mefloquine	Gateway Pharmaceuticals Panlaboratories Ply Ltd Australia	Pharmacy	1

Table 8: Examples of counterfeit tetracycline identified in Cambodia with information regarding active ingredients, trade name and manufacturer as stated on the packaging

Trade-name	Manufacturer's name as claimed on label	Origin of sample	Number of samples
Tetra-250	Brainy Pharmaceutical	Retail Drug Outlets Pharmacy	1 2
Tetracycline	Brainy Pharmaceutical	Clinic Pharmacy Street Vendor	1 1 4
Tetraclor	Chemephand Medical (Thailand)	Pharmacy	1

3.4.2 - Source as provincial sites

Counterfeit samples were detected in all the provinces from which medicine samples were collected between 2002 and 2004. In Cambodia, the monitored provinces include Battambang, Pailin, Preah Vihear, and Pursat.

Table 9: Number and percentage of counterfeit medicines in Cambodia identified by province and year

Year	Province	Number of samples collected	Number of counterfeit samples	Number of counterfeit samples by year	Percentage of counterfeit samples by year
2002	Battambang	43	10	44	24%
	Pailin	42	11		
	Preah Vihear	37	9		
	Pursat	55	14		
	unknown	3	0		
2003	Battambang	44	7	36	20%
	Pailin	52	13		
	Preah Vihear	28	7		
	Pursat	43	8		
	unknown	10	1		
2004	Battambang	36	2	14	10%
	Pailin	26	3		
	Preah Vihear	23	2		
	Pursat	37	5		
	unknown	13	2		
2002-04		**492**	**94**		**19%**

The number of counterfeits found appeared to decrease each year, and no counterfeit samples were reported from 2005 to 2008. When surveys expanded after 2004 to a number of additional provinces, such as Kampong Cham, Koh Kong, Ratanakiri, and Stung Treng, no counterfeits were reported from these provinces.

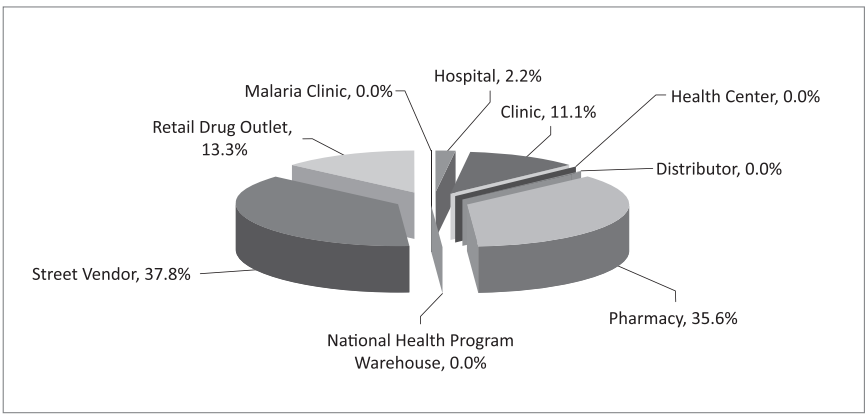
3.4.3 - Distribution channels: mainly street vendors and pharmacies?

Because the distribution channels from which 54 out of the 99 samples identified as counterfeits were not recorded, the data in this analysis should not be considered definitive. However, this data, as incomplete as

it is, remains useful in suggesting potential problematic areas for counterfeit products. In addition, the analysis here serves to provide an analytical framework for investigating problems at the final stage of flow through which counterfeit medicines reach the hands of consumers.

Of the counterfeits with 'known' sources, the majority were collected from street vendors (37.8%) and pharmacies (35.6%). Retail drug outlets and clinics were the other two types of distribution channels with a share greater than 10%. No counterfeits were found among the samples collected from health centres, distributors, national health programme warehouses, and malaria clinics.

Figure 24: Percentage of counterfeit medicines from each distribution channel out of total counterfeit samples found in the countries surveyed



3.5 - Quality of Medicines and Consumer' Risk

Because counterfeit and substandard medicines constitute real threats to the consumer health, the chance of buying a pharmaceutical product that does not meet quality standards can be considered as the 'risk' that a consumer faces in a place where a medicine is dispensed. Therefore, any distribution channel where counterfeit and substandard medicines are found is not performing its role in providing quality-assured medicines, and is a place where patient safety might be at risk.

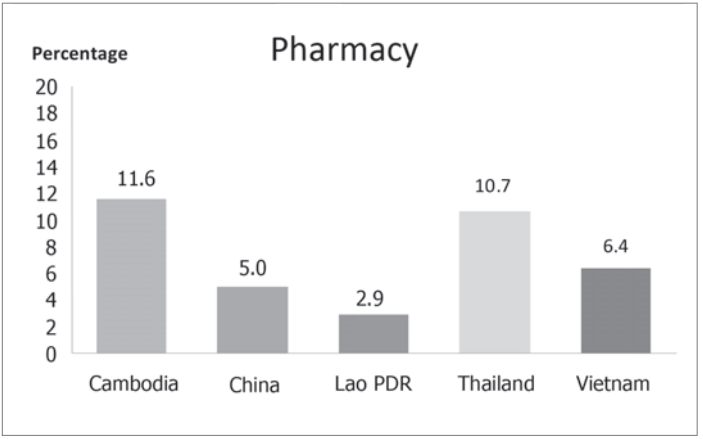
In the analysis below, the data is analysed in light of the risk to consumers when they acquire medicine from different distribution settings. The data include all the medicine samples that did not pass the quality scrutiny. The percentages were calculated based on the number of samples collected from each respective channel.

3.5.1 - What is the risk a consumer may face when acquiring a medicine from various sources?

Pharmacies are the channel from which all the countries surveyed had samples collected. The risks to consumer when acquiring medicines from a pharmacy at a border province in Cambodia and Thailand are 12% and 11% respectively. In Lao PDR, such risk, which was found to be 3% in this study, was the lowest in the group.

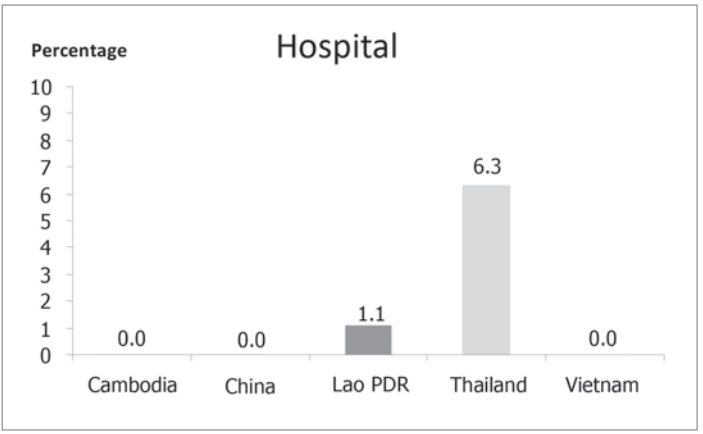
From this dataset, the risks of getting low quality medicines from hospitals in the border area stand at 6% for Thailand, and 1% for Lao PDR. No substandard or counterfeit medicines were identified in hospitals in the other three countries. Among the clinics in the three countries (Cambodia, Lao PDR, and Yunnan Province in China) where medicines were collected, the risks were high in both Cambodia (17%) and Yunnan Province in China (15%). Even in the government sector, a medicine quality problem was still identified. Substandard medicines were discovered in malaria clinics in Thailand and Yunnan, China. In addition, they were also found in a national programme warehouse in Yunnan.

Figure 25: Consumers' risk of receiving bad medicines from pharmacies at the border provinces in each of the countries



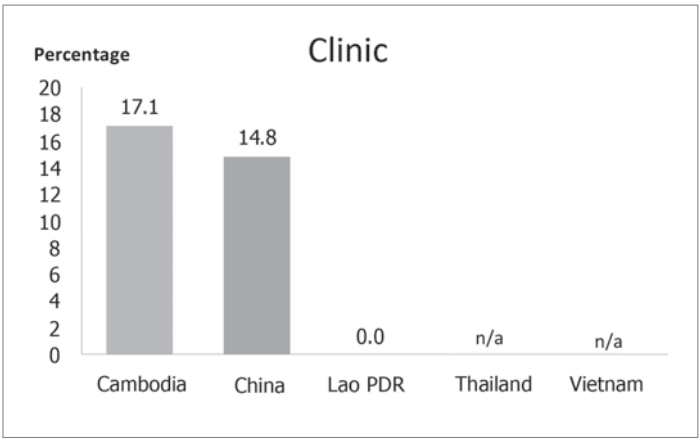
Note: Number above on each bar chart indicates the percentage of poor-quality (substandard as well as counterfeit) samples from each country. Note that the total number of samples collected from each country varies.

Figure 26: Consumers' risk of receiving bad medicines from hospitals in the border provinces in each of the countries



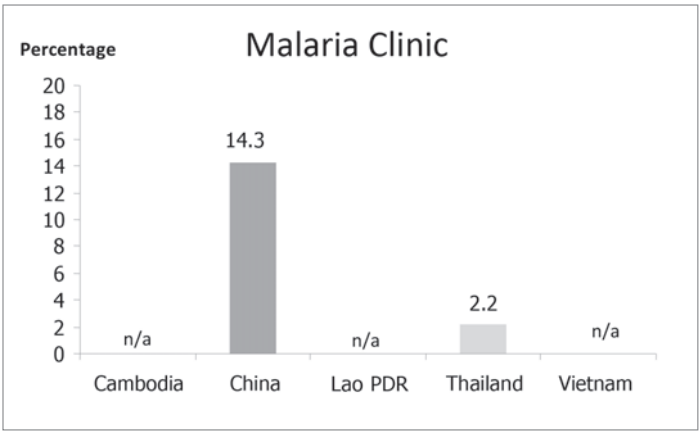
Note: The number above on each bar chart indicates the percentage of poor-quality (substandard as well as counterfeit) samples from each country. Note that the total number of samples collected from each country varies.

Figure 27: Consumers' risk of receiving bad medicines from clinics in the border provinces in each of the countries



Note: The number above on each bar chart indicates the percentage of poor-quality (substandard as well as counterfeit) samples from each country. Note that the total number of samples collected from each country varies.

Figure 28: Consumers' risk of receiving bad medicines from malaria clinics in the border provinces in each of the countries



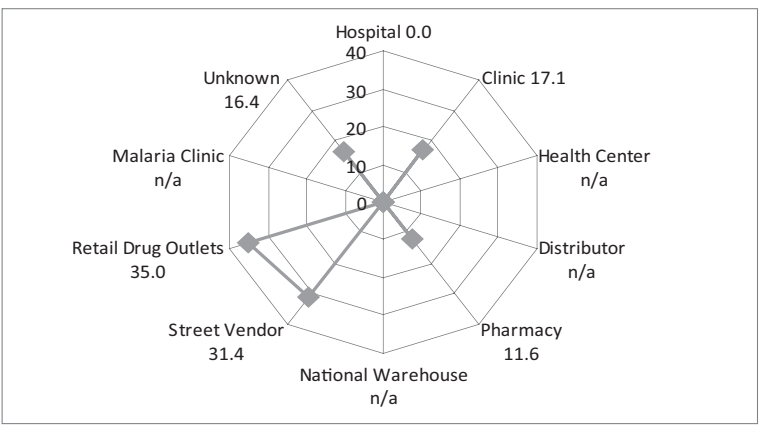
Note: The number above on each bar chart indicates the percentage of poor-quality (substandard as well as counterfeit) samples from each country. Note that the total number of samples collected from each country varies.

3.5.2 - Comparative consumer risks

From another angle, a consumer in the Mekong Subregion should have information regarding his or her own risk when acquiring medicine from different types of settings in each of the countries. Each of the following charts provides a graphical display of the percentages of medicines that did not meet quality standards—both substandard and counterfeit—from the various distribution channels in border areas. Because the charts for different countries are put on the same scale, the values from the different graphs are comparable.

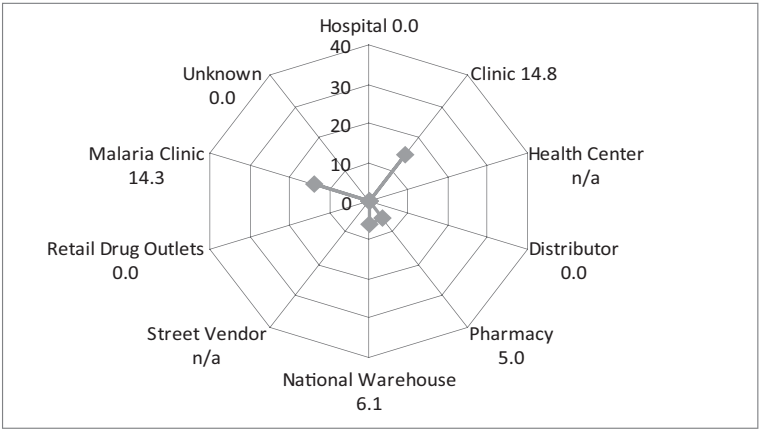
Among the five countries under this multiple-year study, the highest risk for a consumer to obtain poor quality medicines was in Cambodia. With the exception of the hospital, the risk that a consumer in Cambodia might receive medicine with questionable quality was high for all distribution channels as all were greater than 10%. Retail drug outlets and street vendors, with the percentages of problem medicines higher than 30%, were particularly troublesome. Comparatively, a consumer in Yunnan Province, China, was exposed to a lower risk of bad quality medicines. However, low quality medicines were still available from pharmacies, clinics, and malaria clinics. A consumer in Lao PDR might find him or herself relatively safer getting medicines from clinics than pharmacies in the border areas. Pharmacies were also a risk in the border provinces in Thailand and Vietnam.

Figure 29: Consumers' risk of receiving poor quality medicines from various distribution channels in the border provinces of Cambodia



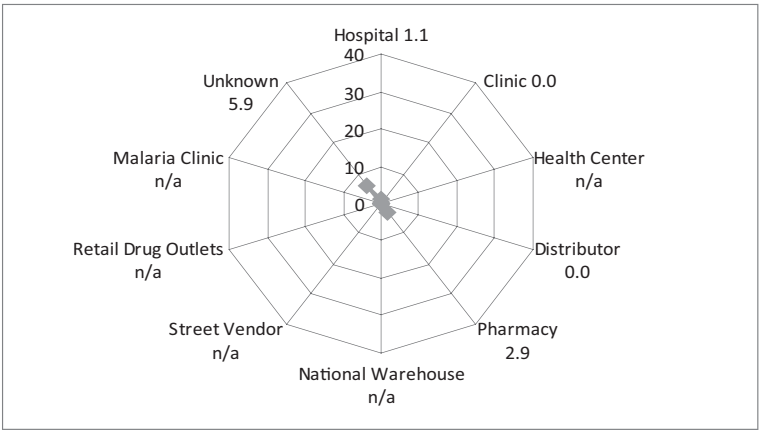
Note: The number indicates percentage

Figure 30: Consumers' risk of receiving poor quality medicines from various distribution channels in the border counties of Yunnan Province



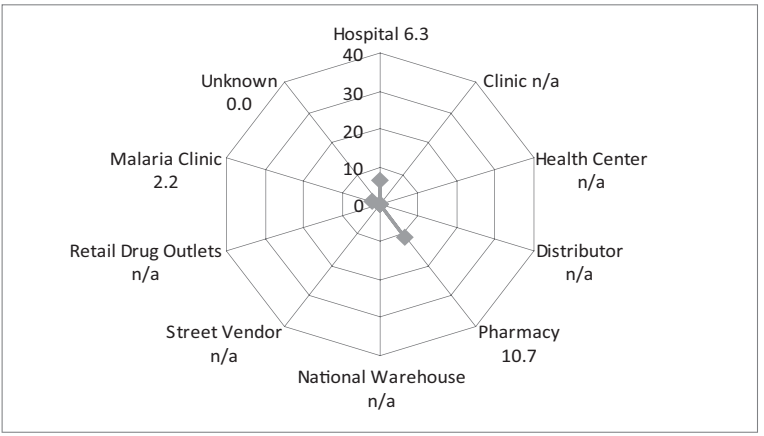
Note: the number indicates percentage

Figure 31: Consumers' risk of receiving poor quality medicines from various distribution channels in the border provinces of Lao PDR



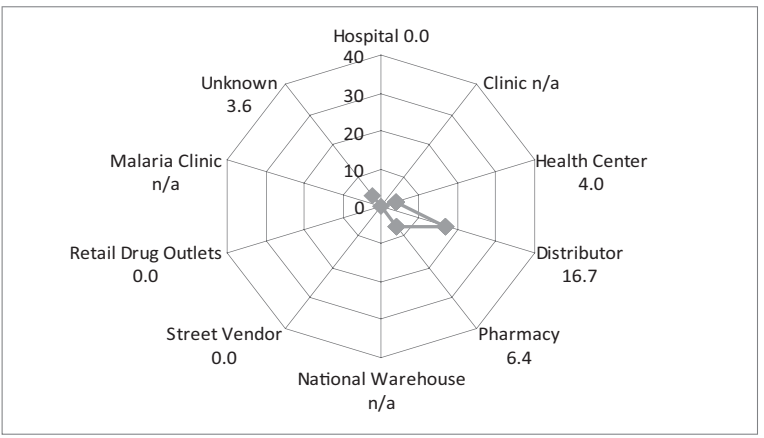
Note: the number indicates percentage

Figure 32: Consumers' risk of receiving poor quality medicines from various distribution channels in the border provinces of Thailand



Note: the number indicates percentage

Figure 33: Consumers' risk of receiving poor quality medicines from various distribution channels in the border provinces of Vietnam



Note: the number indicates percentage

4 - THE MULTIPLE REQUIREMENTS OF MEDICINE QUALITY

Many factors determine medicine quality[8]. To ensure that good quality medicine reaches the hands of consumers, all the necessary steps in the medicine manufacturing and handling process must be performed in accordance with quality standards. At the starting point, one must ensure that the formulation has the required properties for safety, efficacy and quality, as well as adequate stability for the valid period of use. Then, the quality of all the raw materials, especially active ingredients, must meet the standards. Packaging materials are also important in protecting the medicine from physical damage, and must not interact with any chemical. The packaging materials used must be appropriate for the specific product.

The structures housing the production and the infrastructures for the production process must be designed properly and be in suitable condition. The production procedures must follow Good Manufacturing Practice (GMP) requirements. Good Laboratory Practice (GLP) is also required for handling the analysis of intermediate and finished products.

Transportation is a much-overlooked critical stage in the medicine supply chain. The medicine must be kept in conditions preventing deterioration from heat, humidity and other environmental factors in the vehicle during the transportation phase from the suppliers to the various health care settings. A cold chain is needed for certain types of medicines, for example vaccines, which need special care in handling.

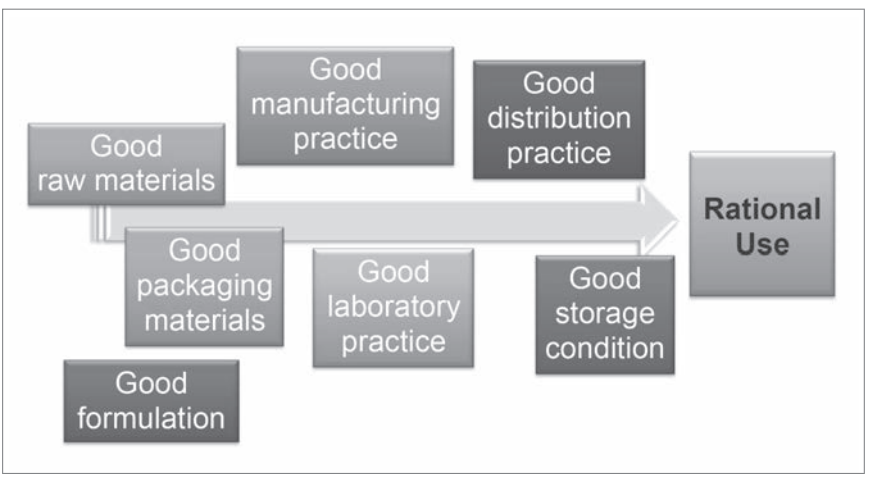
Storage conditions are crucial to the maintenance of quality. This is especially important for countries with tropical climates such as in the Mekong Subregion. If medicines are not stored in a well-controlled environment, the heat and humidity in those medicine distribution

[8] For a comprehensive guide on how to ensure a medicine's quality, readers may refer to 'United States Pharmacopeia Drug Quality and Information Program and collaborators. 2007. Ensuring the Quality of Medicines in Resource-Limited Countries: An Operational Guide. Rockville, Md.: The United States Pharmacopeial Convention. Available online: http://www.usp.org/pdf/EN/dqi/ensuringQualityOperationalGuide.pdf.

channels can cause deterioration before their expiry date. Many studies on medicine quality implicated storage condition as a major contributing factor leading to the degraded quality[9].

In the five-country study, as well as in the majority of the medicine quality monitoring surveys, samples were collected from the final channel in the manufacturing-distribution chain. Consequently, the quality of medicine can be influenced by the many conditions in the medicine process that came beforehand, as well as by the conditions in which the medicines were kept. Therefore, when a medicine product collected from a distribution channel fails the quality testing, which may be due to degradation during storage, the test result is not always able to pinpoint which factor actually caused the quality problem. This is particularly true for substandard medicines.

Figure 34: Diagrammatic depiction of the factors in the medicine process critical to quality



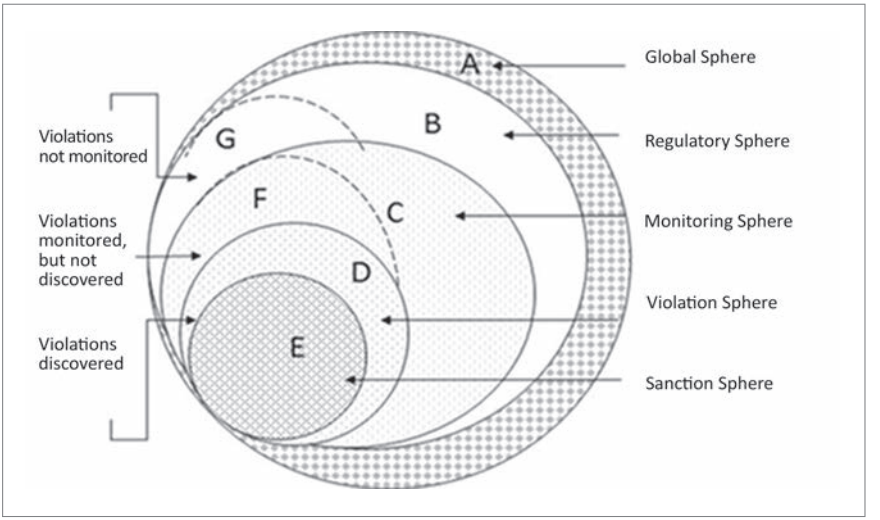
[9] For example, Yang et al. 2004, Mac et al. 2008

5 - REGULATING MEDICINE: REGULATORY SPHERES AND GAP

The reviews and analysis in the above sections demonstrate that there are differences in 1) the legal definitions regarding what medicine quality means and what is acceptable by law, as well as measures to regulate them; and 2) what is specified by the contents of the law and what is actually happening in the health care system. The conceptual framework of regulatory spheres can provide a theoretical foundation for examining these phenomena. The existence of a regulatory function in a country does not necessarily mean that the function covers the entire range of pharmaceutical products and/or activities. Nor does it mean that the control described in the country's legislation is always fully put into practice.

Moreover, a country may choose to enact laws to only regulate certain areas of its pharmaceutical supply system. For example, the universe of all the products claimed to have effects on human health (therapeutic, preventive, etc.) can be thought of as the area within the boundary of the outermost circle—the 'global sphere'. The medicine regulatory authority (MRA) may choose to register all products, or only certain categories. It may decide not to register herbal medicines, but to require that all other pharmaceutical products be registered. The exempted products thus fall into area A, while other drugs are within the boundary of the next circle, area B—the 'regulatory sphere'.

Figure 35: Conceptual spheres of regulatory control



Source: Ratanawijitrasin and Wondemagegnehu 2002

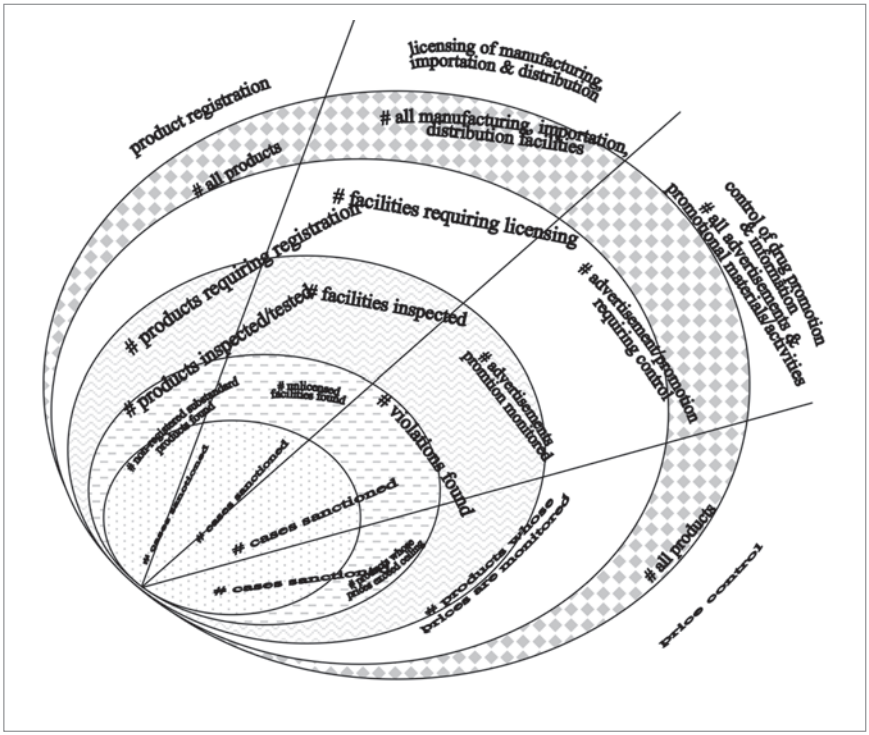
In any given year, the DRA may be able to inspect manufacturing, importation and distribution facilities, and to collect samples for quality testing in a limited number of product categories. These products can then be considered as being contained within the third largest circle—the 'monitoring sphere'. Some of these drugs pass the quality test, represented by area C, while a percentage of them may be found substandard or counterfeit, or else are not registered (defined as counterfeits in some country). These failed/illegal products can be visualized as falling within the next area, area D—the 'violation sphere'. Legal sanctions may be imposed in all or a proportion of the violation cases found, which are contained in the smallest circle, area E—the 'sanction sphere'. Discovered violations do not necessarily represent all the violations that exist. They are likely to be violations that are beyond the reach of regulatory authorities and other monitoring mechanisms (area G). It is also possible that monitoring fails to uncover a number of violations within the monitoring sphere (area F).

Additionally, although violations are not indicated for area A, this does not imply that all products that fall within this area are effective,

safe and of good quality. It is rather that the relevant legislation currently does not cover this area. The regulatory sphere can be expanded once it is deemed necessary for society to regulate additional products contained in area A, and when its capacity to do so is adequate.

The four main regulatory functions—product registration; licensing and inspection of manufacturing, importation and distribution, control of drug promotion and advertising; and price control—are conceptually presented below.

Figure 36: Conceptual spheres of the four main regulatory functions



Source: Ratanawijitrasin and Wondemagegnehu 2002

Each of the core drug regulatory functions is placed in a segment within the conceptual sphere. The outer layer of the second segment of the diagram covers all facilities engaged in the activities of pharmaceutical manufacturing, importation and distribution. The next layer of the segment represents those where a licence is required to operate. The third layer represents the manufacturing, importation and distribution facilities inspected. Cases of violation of GMP, GDP and other requirements are represented in the fourth layer, while sanctioned cases are found in the innermost layer. Similar diagrammatic representations can be made for product registration, control of drug promotion and information, and price control.

The lines that set the boundary between the spheres may not be at the same level from one segment to the next, since government regulations may be more extensive, monitoring more thorough, violations more rampant, and sanctions more strictly imposed in one functional area than in others. If quantitative data is available for each of the sub-segments in the spheres, the size of each sub-segment can be computed and a map of the drug regulatory system drawn for visualizing the legal domains and the extent to which drug regulation is undertaken.

6 - THE 'DEMAND' FOR POOR QUALITY MEDICINES

When supplies of a product continue to be available, it is a clear indication that there is a continued 'demand' for that product. Why, then, do people in the Mekong Subregion 'demand' poor quality medicines which might cause harm to their health? Most of the studies on medicines with poor quality focus on their supply. There have not been adequate concrete studies that help provide relevant insights into the demand side of this issue. Supply and demand meet at a given price. 'Demand' can be a result of a consumer's conscious selecting among a range of available choices; or it can be a result of a consumer's purchase that is not a matter of choice but rather a need to respond to the necessities of life.

Why do some people purchase poor quality medicines? Conceptually, a distinction should be made between the 'demand' for substandard and counterfeit medicines. Substandard medicines are those produced by legitimate producers. For a product from the same producer, the price of the same product that passed quality standards should be the same as one that failed quality standards. The cause or causes of poor quality might come from the manufacturers (for example, poor formulation, failure to follow good manufacturing practice, and/or poor transportation condition), and/or the sellers (for example, poor storage condition). On the other hand, the prices of products from a producer who does not invest to ensure good quality practices in the manufacturing processes might be lower than those from another producer who invests in these necessities. However, a consumer might not be aware of this difference. In a country where regulations are not sufficiently strong, it is probable that the purchase of a pharmaceutical product sold at substantially lower price might get the consumer a product with poor quality, though this might not always be the case.

In contrast to substandard products, one defining characteristic of a counterfeit product might be low pricing. Consumers generally purchase a counterfeit product because they are led to believe that these are genuine ones sold at a much lower price. In Cambodia, "suspiciously low prices" were cited as a reason for the initiation of a quality monitoring survey in 1999. The results showed that most of the bottles with mefloquine tablets and about half of the artesunate blister packs sampled appeared to be fakes (Rozendaal 2001). According to WHO, counterfeiting is greatest in regions where regulatory and enforcement systems for medicines are weakest. In most industrialized countries with effective regulatory systems and market control, the incidence of counterfeit medicines is extremely low. But in many African countries, and in parts of Asia, Latin America, and countries in transition, a much higher percentage of the medicines on sale may be counterfeit. Not only is there a huge variation between geographic regions in terms of incidence of counterfeit medicines, variation can also be significant within countries, for example between urban and rural areas, and between cities (WHO 2010). The case of Thailand reviewed in a section above illustrates this fact. While counterfeit antibiotics and anti-malarials were found in the border areas, police

raids in Bangkok uncovered expensive lifestyle and cancer counterfeit medicines.

Setting aside lifestyle medicines, demands for the types of medicines such as those for the treatment of cancer, antibiotics, and anti-malarials appear to come from real needs. Many cancer medicines are extremely expensive, and are unaffordable even for the middle class population in the city, not to mention the poor. And for poor populations, particularly those who live in the border areas, immigrants, and other disadvantaged groups, even the prices for anti-malarials and antibiotics might seem high. Affordability is likely to be a key issue. Furthermore, due to the fact that access to health services and medicines is difficult in the border areas, availability of medicines and services is likely to be another issue.

There is also another set of questions related to the consumers' knowledge of medicine quality and the potential harm these medicines might cause. How much do consumers understand about the importance of medicine quality on effectiveness and potential harm? And if consumers did have such knowledge, would they continue to purchase poor quality medicines? The current state of empirical knowledge in this area remains inadequate. To be able to meet the challenge of the issue of medicine quality in a comprehensive manner, there is a need to know more about the demand behaviour at a level that can enable the design of policy interventions.

Hence, in order to effectively solve the problem of medicine quality, it is necessary to address the demand-side of these issues, in addition to supply-side interventions. Key among the demand-side factors are, first, the availability and affordability of medicines; and second, the consumers' knowledge of medicine quality.

7 - IMPROVING THE STATE OF MEDICINE QUALITY IN THE MEKONG SUBREGION

Because of the wide availability of poor quality medicines and the broad and serious impacts generated by their use, many recommendations have been made on policy intervention in the aim to tackle this problem.

Key recommendations proposed by many concerned parties include:

(1) national medicines policy and medicines quality assurance system;
(2) strengthening of medicines regulatory authorities (MRA);
(3) regular inspections of pharmaceutical premises;
(4) establishment of medicines quality control laboratory with adequate equipment and trained personnel;
(5) effective law enforcement;
(6) measures to reduce corruption;
(7) judicial procedures and policies that reflect the seriousness of the problem and the offence;
(8) reducing the price and increasing the availability of genuine medicines;
(9) raising awareness among health professionals for heightened vigilance;
(10) developing reporting systems for health professionals;
(11) educating consumers to differentiate the curative from the dangerous medicines;
(12) good practices on the part of pharmaceutical manufacturers, wholesalers, and traders to ensure quality;
(13) using technologies to help in identification and monitoring, for example: electronic track-and-trace mechanisms, radiofrequency identification (RFID), authentication technologies;
(14) fostering international cooperation in the control of pharmaceuticals;
(15) development of an international convention to control the trade in counterfeit and substandard medicines (WHO 2011, Laven 2006, USP-DQI 2004 and 2007).

The majority of these recommendations involve supply-side measures. These are important strategies in the fight against poor quality

medicines. Nonetheless, there are gaps and areas for improvement in the efforts to reduce poor quality medicines. This study also highlights the importance of the demand-side of the medicine quality issue. It proposes increased emphasis on the following four key supply-and-demand strategies:

(1) ***Increase the power of intelligence:***
Develop a system that helps to enhance the use of intelligence and timely information sharing among key stakeholders to perform a rapid alert system. This can be achieved by creating an international database to make better use of data from various quality monitoring studies, continuously updating and analysing the data, applying geographical information techniques, and using them to track problem areas and issuing alerts to all relevant parities.

(2) ***Improve understanding of the demand behaviour:***
Generate knowledge about demand behaviour as related to the use of quality medicines through qualitative and quantitative research.

(3) ***Empower consumers:***
Develop and implement a multi-prong approach to help raise awareness and empower consumers to appropriately select and use medicines. This can be done through public education and campaigns, and through the advice of health professionals. In addition, creating a system to make relevant information readily available to consumers, such as web-based information, will help put know ledge at the consumers' fingertip. Outreach awareness and education programmes on medicines quality and the danger of using counterfeit and substandard medicines for the marginal and less advantaged population groups should also be carried out.

(4) ***Expand health services and insurance:***
Access to quality-assured medicines is a key factor in helping to reduce the use of medicines with questionable quality. Making health services and quality medicines available and affordable can be achieved by expanding health and medicine service settings in the more remote areas. Providing health insurance coverage to people in need will help solve the issue of affordability.

REFERENCES

Administrator, "The scourge of fake medicine", *Bangkok Post*, 14 February 2008, www.bangkokpost.com, Accessed Sep 2010.

Delacollette C., C. D'Souza, E. Christophel, K. Thimasarn, R. Abdur, D. Bell, TC. Dai, D. Gopinath, SH. Lu, R. Mendoza, L. Ortega, R. Rastogi, C. Tantinimitkul and J. Ehrenberg, "Malaria Trends and Challenges in the Greater Mekong Subregion", *Southeast Asian J Trop Med Public Health* 40/4 (2009).

Dondorp AM., F. Nosten, P. Yi, D. Das, AP. Phyo, J. Tarning, KM. Lwin, F. Ariey, W. Hanpithakpong, SJ. Lee, P. Ringwald, K. Silamut, M. Imwong, K. Chotivanich, P. Lim, T. Herdman, SS. An, S. Yeung, P. Singhasivanon, NP. Day, N. Lindegardh, D. Socheat, NJ. White. "Artemisinin resistance in Plasmodium falciparum malaria". *N Engl J Med* 361(2009) pp. 455-67.

Eggleston, K., R. Zhang, and RJ. Zeckhauser, "The Global Challenge of Antimicrobial Resistance: Insights from Economic Analysis", *Int. J. Environ. Res. Pub. Health* 7 (2010) pp. 3141-3149.

Noedl, H. et al., "Evidence of Artemisinin-Resistant Malaria in Western Cambodia". *N Engl J Med* 359;24 www.nejm.org December 11, 2008.

Laven, DL., "Introduction: Drug Diversion and Counterfeiting", *Journal of Pharmacy Practice* 19 (2006) p. 135.

Lewis, K., "China"s counterfeit medicine trade booming", *CMAJ* 10 November 2009, www.cmaj.ca, Accessed Oct 2010.

Lon, CT., R. Tsuyuoka, S. Phanouvong, N. Nivanna, D. Socheat, C. Sokhan, N. Blum, EM. Christophel, A. Smine, "Counterfeit and substandard antimalarial drugs in Cambodia", *Transactions of the Royal Society of Tropical Medicine and Hygiene* 100 (2006) pp. 1019-1024.

Mac, TL., J-M. Gaulierb, VT. Lec, AN Vuc, P-M Preux, V Ratsimbazafya, "Quality of antiepileptic drugs in Vietnam", *Epilepsy Research* 80 (2008) pp; 77-82.

McGinnis, M., "Matrix of Medicine Quality Reports Affecting USAID-assisted Countries" (Maryland: USP PQM, 2010).

Newton, P., S. Proux, M. Green, F. Smithuis, J. Rozendaal, S Prakongpan, K. Chotivanich, M. Mayxay, S. Loareesuwan, J. Farrar, F Nosten, NJ. White, "Fake artesunate in Southeast Asia", *The Lancet* 357 (2001) pp. 1948-9.

Newton PN., FM. Ferna´ndez, A. Plancon, DC. Mildenhall, MD. Green, et al. "A collaborative epidemiological investigation into the criminal fake artesunate trade in South East Asia", PLoS Med 5/2: e32. (2008).

Newton PN., SJ. Lee, C. Goodman, FM. Fernández, S. Yeung, S. Phanouvong, H. Kaur, AA. Amin, CJM. Whitty, go. Kokwaro, N. Lindegårdh, P. Lukulay, LJ. White, NPJ. Day, MD. Green, NJ. White (2009). Guidelines for field surveys of the quality of medicines: a proposal. *PLoS Medicine* 6(3), e1000052.

Phanouvong S., N. Blum, A. Smine. Guidelines for Sampling of Antimalarial Drug Samples in the USP DQI Antimalarial Drug Quality Monitoring Project in Mekong Subregion Countries (Rockville: USP DQI, 2004).

Phyo AP., S. Nkhoma, K. Stepniewska, EA. Ashley, S. Nair, R. McGready, C. ler Moo, S. Al-Saai, AM. Dondorp, KM. Lwin, P. Singhasivanon, NP. Day, NJ. White, TJ. Anderson, F. Nosten. "Emergence of artemisinin-resistant malaria on the western border of Thailand: a longitudinal study". *Lancet* 379 (2012) pp. 1960-6.

Ratanawijitrasin S. and E. Wondemagegnehu, "Effective Drug Regulation: A Multi-country Study" (Geneva: World Health Organization, 2002).

Ratanawijitrasin S., "System of Pharmacy Services", Proceedings, Conference on Health Insurance Systems in Thailand. (Bangkok, 2003).

Rozendaal J., "Ministry of Health and Asian Development Bank Intensified Communicable Diseases Control Project", *The Lancet* 357 (17 March 2001).

Sengaloundeth S, Green MD, Fernández FM, Manolin O, Phommavong K, Insixiengmay V, Hampton CY, Nyadong L, Mildenhall DC, Hostetler D, Khounsaknalath L, Vongsack L, Phompida S, Vanisaveth V, Syhakhang L, Newton PN (2009) "A stratified random survey of the proportion of poor quality oral artesunate sold at medicine outlets in the Lao PDR - implications for therapeutic failure and drug resistance". *Mal* J 8, 172.

Shakoor, O., RB. Taylor, RH. Behrens, "Assessment of the incidence of substandard drugs in developing countries", Trop Med Intl Health 2/9 (1997) pp. 839-45

Sovan, N. and C. Yin, "Bad medicine floods countryside", *The Phnom Penh Post*, 25 July 2008, www.phnompenhpost.com, Accessed Jul 2010.

The Kingdom of Cambodia, *Law on the Management of Pharmaceuticals* (1996).

The Kingdom of Thailand, *Drug Act BE* 2510 (1967).

The Lao People's Democratic Republic, *Law on Drugs and Medical Products* (2000)

The National Assembly of the Socialist Republic of Vietnam, *Pharmaceutical Law* (2005).

The People"s Republic of China, *Drug Administration Law* (2001).

U.S. Pharmacopeia Drug Quality and Information Program, "A Review of Drug Quality in Asia with Focus on Anti-Infectives" (2004).

U.S. Pharmacopeia Promoting the Quality of Medicines Program. "Guidance for Acting on Evidence-Based Data and Information on Counterfeits and Substandard Medicines to Take Appropriate Enforcement Action", Working document (2010).

U.S. Pharmacopeia Drug Quality and Information Program, "Medicine quality monitoring program in the Mekong region" (2009).

Wondemagegnehu, E., "Counterfeit and Substandard Drugs in Myanmar and Viet Nam: Report of a study carried out in cooperation with the Governments of Myanmar and Viet Nam" (Geneva: World Health Organization, 1999).

World Health Organization. "Guidelines for the Development of Measures to Combat Counterfeit Drugs." (Geneva: WHO, 1999).

World Health Organization. "General information on counterfeit medicines", http://www.who.int/medicines/services/counterfeit/overview/en/index2.html, Accessed Mar 2011.

World Health Organization. "Medicines: counterfeit medicines", Fact sheet N°275, http://www.who.int/mediacentre/factsheets/2003/fs275/en/, Accessed Jan 2011.

World Health Organization. "Report of the Workshop to review and plan therapeutic efficacy studies to monitor P. falciparum and P. vivax resistance to anti-malarial drugs in the Greater Mekong Sub-region." Mandalay, Union of Myanmar September 30th - October 2nd, 2009.

Yang D, Plianbangchang P, Visavaungroi N, Rujivipat S., "Quality of Pharmaceutical Items Available From Drugstores in Phnom Penh, Cambodia". *Southeast Asian, J Trop Med Public Health*. 35(3): 741-7 (2004).

____, "Arrests of illegal abortion clinics and counterfeit drugs manufacturer", *Matichon newspaper,*12 Jan 2011.

____, "Counterfeit expensive drugs seized from drugstore in Dindang area", *Matichon newspaper*, 1 Oct 2010.

____, "FDA seizes counterfeit Viagra and pain-killer with codeine in Patpong", *Matichon newspaper*, 14 Jan 2011.

____, "Vietnam to reinforce crackdown on fake medicine: official". *Thanh Nien News* 22 September 2008, www.thanhniennew.com, Accessed Sep 2010.

ANNEXES

ANNEX I

Legal Definitions of Medicines from the Quality Perspective - by country

Category /country	WHO	Cambodia	Lao PDR
Name of law in year of enactment		The 1996 Law on the Management of Pharmaceuticals	Law on Drugs and Medical Products promulgated in 2000
Substandard	Substandard medicines are products of which the composition and ingredients do not meet the correct scientific specifications and that are consequently ineffective and often dangerous to the patient. Substandard products may occur as a result of negligence, human error, insufficient human and financial resources or counterfeiting.	A substandard drug is defined as a registered product of which the specifications are out of defined pharmacopoeias or accepted standards.	A substandard drug is termed in this law as a "non-standard" drug, and is defined as any modern or traditional medicine, the composition of which is inconsistent with the drug's registered formula.

This Annex provides brief descriptions of legal definitions related to medicine quality, with special focus on substandard and counterfeit medicines, in the five countries—Cambodia, China, Lao PDR, Thailand and Vietnam.

Thailand	Vietnam	Yunnan of China
Drug Act of 1967 (BE 2510)	Pharmaceutical Law was adopted in 2005	The Drug Administration Law of the People's Republic of China, revised in 2001
A sub-standard drug as a drug: (1) which was not produced in accordance with standard such that the product contains the active ingredient in quantity or strength is lower than the minimum or higher than the maximum amount registered, but to a degree less than that stated in Article 73 (2) which is produced such that the purity and other characteristics which are deemed important to its quality deviate from the criteria specified in the registered formula or the formula modified according to the Minister's order.	A substandard drug as a drug that has failed to meet the quality standards registered with the competent authorities.	Any drug with content not up to the national drug standards is a substandard drug. In addition, the law specifies that any drug shall be treated as a substandard drug in any of the following cases: (1) the date of expiry is not indicated or is altered; (2) the batch number is not indicated or is altered; (3) it is beyond the date of expiry; (4) no approval is obtained for the immediate packaging material or container; (5) colourants, preservatives, spices, flavourings or other excipients are added without authorization; or (6) other cases where the drug standard are not conformed (Order of the President of the People's Republic of China 2001)

ANNEX I - Legal Definitions of Medicines from the Quality Perspective - by country

Category /country	WHO	Cambodia	Lao PDR
Counterfeit	A counterfeit medicine is one that is "deliberately and fraudulently mislabelled with respect to identity and/or sources." Counterfeiting can apply to both branded and generic products. These products may contain correct ingredients or wrong ingredients, without active ingredients, with insufficient active ingredients or with fake packaging. (WHO 2003)	as a drug: (1) which is deliberately produced with incorrect quantity of or wrong active ingredients, or (2) without active ingredients or an unregistered product in which the amounts of active ingredients are deliberately outside the defined pharmacopoeias or accepted standard, or (3) which is deliberately and fraudulently mislabelled with respect to the identity source or with fake packaging (4) which is repacked or produced by unauthorized person(s).	as any modern or traditional medicine that is a fake or is an imitation of a drug that is produced, distributed and legally registered

Thailand	Vietnam	Yunnan of China
The definition of counterfeit or fake drug is clearly specified in the law (Article 73) as any drug or substance: (1) which is wholly or partly an imitation of a genuine drug; or (2) which shows the name of another drug, or an expiry date which is false; or (3) which shows a name or mark of a producer, or the location of the producer which is false; (4) which falsely shows that they are in accordance with a pharmaceutical preparation that has been registered; or (5) which was not produced in accordance with standards such that the product contains the active ingredient in a quantity or strength is lower than the minimum or higher than the maximum amount registered by more than 20%.	A counterfeit drug is a product deliberately and fraudulently made in drug forms, including the followings: (1) containing no pharmaceutical substances; (2) containing pharmaceutical substances different from those stated on the label; (3) counterfeiting product names, industrial designs of drugs that have been already registered by other manufacturers for industrial property protection.	A counterfeit medicine is considered as a drug in any of the following cases: (1) the ingredients in the drug are different from those specified by the national drug standards; or (2) a non-drug substance is simulated as a drug or one drug is simulated as another. (3) its use is prohibited by the regulations of the drug regulatory department under the State Council; (4) it is produced or imported without approval, or marketed without being tested, as required by this Law; (5) it is deteriorated; (6) it is contaminated; (7) it is produced by using drug substances without an approval number as required by this Law; or (8) the indications or functions indicated are beyond the specified scope.

ANNEX II

Additional Data on Medicine Quality

This annex lists additional details of results from the medicine quality study.

Table A1 : Overview of the quality of four categories of anti-microbials medicines in the region

Medicine Group	Number of samples collected	Number of samples that passed	Number of samples that failed	Percentage of failure
ANTI-MALARIALS	1626	1431	195	12.0%
ANTIBIOTICS	1739	1639	100	5.8%
ANTI-TB	218	215	3	1.4%
ARV	67	67	0	0.0%

Table A2 : Quality of anti-malarials in each country

Country	Number of samples collected	Number of samples that passed	Number of samples that failed	Percentage of failure
Cambodia	519	413	106	20.4%
Yunnan, China	126	117	9	7.1%
Lao PDR	282	253	29	10.3%
Thailand	276	255	21	7.6%
Vietnam	423	393	30	7.1%
Total	**1626**	**1431**	**195**	**12.0%**

Table A3 : Quality of antibiotics in each country

ANTIBIOTICS				
Country	**Number of samples collected**	**Number of samples that passed**	**Number of samples that failed**	**Percentage of failure**
Cambodia	535	464	71	15.3%
Yunnan, China	0	n/a	n/a	n/a
Lao PDR	717	712	5	0.7%
Thailand	93	90	3	3.3%
Vietnam	394	373	21	5.6%
Total	**1739**	**1639**	**100**	**5.8%**

Table A4 : Quality of anti-TB medicines in each country

Country	**Number of samples collected**	**Number of samples that passed**	**Number of samples that failed**	**Percentage of failure**
Cambodia	51	48	3	5.9%
Yunnan, China				
Lao PDR	34	34	0	0.0%
Thailand				
Vietnam	133	133	0	0.0%
Total	**218**	**215**	**3**	**1.4%**

Table A5 : Quality of ARVs in each country

Country	**# samples collection**	**Number of samples that passed**	**Number of samples that failed**	**Percentage of failure**
Cambodia	45	45	0	0.0%
China				
Lao PDR				
Thailand				
Vietnam	22	22	0	0
Total	**67**	**67**	**0**	**0.0%**

ANNEX III

Research Project Team

Country Contributors and Other Organization Collaborators

Cambodia	Lao PDR	Thailand
Dr. Chroeng Sokhan Deputy-Director, FDD, Cambodia Ministry of Health	Dr. Somthavy Changvisommid Director General, Food and Drug Department, Ministry of Health, Lao PDR	Dr. Wichai Satimai Director Bureau of Vector-Borne Diseases Ministry of Public Health, Thailand
Ms. Mam Boravann Former Food and Drugs Department Cambodia Ministry of Health	Dr. Sivong Sengaloundeth Deputy Director FDD, Ministry of Health	Ms. Saowanit Vijaykadga Technical Officer 8 Bureau of Vector-Borne Diseases Department of Disease Control MOPH, Thailand
Dr. Lon Chanthap Former Deputy Director CNM, MOH (now at Armed Forces Research Institute of Medical Sciences)	Mr. Souksomkhouane Chanthamath, Technical Officer, Inspection Division FDD MOH Lao PDR	Mr. Dumrong Thitikornkovit Senior Pharmacist Drug Control Division FDA Ministry of Public Health, Thailand
Dr. Nivanna Nam Former Director Ministry of Health National Laboratory for Drug Quality Control	Dr. Latsamy Vongsack Director, Food and Drug Quality Control Center MOH Lao PDR	Ms. Rojana Kovithvattanaphong Former Director Bureau of Drug and Narcotics Department of Medical Sciences Ministry of Public Health

Planning and Coordination of Sample Collection and Testing

Patrick Lukulay, PhD	Director	USP-PQM
Souly Phanouvong, PharmD, PhD	Manager, Asia Programs	USP-PQM
Laura Krech, MPH	Program Manager, SE Asia	USP-PQM
Christopher B. Raymond, MPH	Regional Project Coordinator	USP-PQM
Nancy Blum, MPH	Former Director	USP DQI
Jennifer Murphy, PharmD	Former Program Manager, SE Asia	USP DQI
Abdelkrim Smine, PhD	Consultant (former Manager, QC Laboratory)	USP-PQM

Vietnam	Yunnan Province, China	Other Contributors
Ass. Prof. Trinh Van Lau Director MOH, NIDQC of Viet Nam	Dr. Zhang Zaixing Former Director Yunnan Institute of Parasitic Diseases	Dr. Krongthong Thimasarn Medical Officer, Malaria, WHO Country Office for Myanmar.
Mr. Trinh Ngoc Hai Chief, Pharmaceutical Division Institute of Malariology–Parasitology–Entomology, Ho Chi Minh City	Mr. Zhang Canglin Technical Officer Center Lab Yunnan Institute of Parasitic Diseases	Ms. Nancy Blum Former Director USP DQI
Dr. Nguyen Manh Hung Director of National Institute of Malariology, Parasitology and Entomology (NIMPE)	Mr. Chen Xu Director Division of Drug Inspection and Supervision. Department of Drug Market Compliance, SFDA, P.R. China	Dr. Richard Jahnke Project GPHF Germany
Prof. Le Khan Thuan Former Director National Institute of Malariology, Parasitology and Entomology (NIMPE)	Mr. Li Liangchang Vice Director Simao Institute of Drug Control, Yunan Province P.R. China	Dr. Reiko Tsuyuoka Communicable Diseases Surveillance and Response WHO Lao PDR

Country Contributors and Other Organization Collaborators

Cambodia	Lao PDR	Thailand
Mr. Tey Sovannarith Deputy Chief of Technical Laboratory National Lab for Drug Quality control Ministry of Health	Mr. Lamphet Khounsaknalath, Chief Technical Officer Food and Drug Quality Control Center, MOH, Lao PDR	Ms. Yaowalak Wattanapisit Senior Technical Officer Bureau of Drug and Narcotic, MOH, Thailand
Dr. Duong Socheat Former Director National Malaria Center Ministry of Health Cambodia	Mr. Khamphay Phoumanivong, QA Technical Officer Food and Drug Quality Control Center, MOH, Lao PDR	
	Dr. Bouasy Hongvanthong Director Center for Malariology Parasitology and Entomology Ministry of Health, Lao PDR	
	Dr. Samlane Pompida Former Director Center for Malariology Parasitology and Entomology Ministry of Health, Lao PDR	

Vietnam	Yunnan Province, China	Other Contributors
Dr. Nguyen Van Loi Director, Division of Drug and Costmetics Quality Control Drug Administration of Vietnam		Dr. Eva-Maria Christophel Regional Advisor Malaria Vectorborne and Other Parasitic Diseases, WHO Regional Office for the Western Pacific
Prof. Le Khan Thuan Former Director MOH, National Institute of Malariology, Parasitology and Entomology, Vietnam		Dr. Andrew Clements Former Infectious Diseases Advisor U.S. Agency for International Development Bureau for Asia and the Near East
		Dr. John R. MacArthur CAPT, US Public Health Service Chief, Program Implementation Unit Malaria Branch, CDC Former Team Leader Infectious Diseases Advisor RDMA
		Dr. Anthony Boni Senior Pharmaceutical Management Specialist Office of Health, Infectious Diseases and Nutrition USAID/GH/HIDN/HS

Financial Support of USP DQI and PQM in the Mekong Subregion

USAID/RDMA
With contribution from WHO/WPRO, SEARO and Mekong Malaria Programme

Database Conceptualization, Design, and Development

Sauwakon Ratanawijitrasin, PhD	Faculty of Social Sciences and Humanities, Mahidol University, and PhaReD Foundation
Puree Anantachoti, PhD	Faculty of Pharmaceutical Sciences, Chulalongkorn University, and PhaReD Foundation
Tweepong Areeyasopon, MS	PhaReD Foundation
Patchara Wongsuwan	PhaReD Foundation
Jittima Luckanakun	PhaReD Foundation
Souly Phanouvong, PharmD, PhD	USP-PQM
Laura Krech	USP-PQM

Comparative Analysis Methodology and Data Analysis

Sauwakon Ratanawijitrasin, PhD	Faculty of Social Sciences and Humanities, Mahidol University
Sanita Hirunrassamee, PhD	Phramongkutklao College of Medicine
Zhe Li, MA	Yunnan Health and Development Research Association (YHDRA)

Authors

Sauwakon Ratanawijitrasin, PhD	Faculty of Social Sciences and Humanities, Mahidol University
Souly Phanouvong, PharmD, PhD	USP-PQM

Publication Funding and Support

Anne-Lise Sauterey Alicia Hartmann	FSP Mekong Project / IRASEC, French Ministry of Foreign Affairs
Program in SE Asia	USAID-PMI/RDMA

IRASEC - Institut de Recherche sur l'Asie du Sud-Est Contemporaine
IRASEC - Research Institute on Contemporary Southeast Asia

179 Thanon Witthayu, Lumphini, Pathum Wan, Bangkok 10330, Thailand
Tel (+66) 026 70 42 91 - Fax (+66) 026 70 42 90
www.irasec.com

ISBN 978-616-7571-19-5