

**Analysis of the Regulatory Capacity to Assure the  
Quality of Antimalarial Medicines in Selected  
Countries of the Greater Mekong Subregion of Asia**

**March 2015**



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**SLAPS**   
Systems for Improved Access  
to Pharmaceuticals and Services



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The SIAPS logo consists of the word "SIAPS" in a bold, green, sans-serif font, followed by a stylized blue graphic of a person with arms raised in a V-shape.

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## **About SIAPS**

The goal of the Systems for Improved Access to Pharmaceuticals and Services (SIAPS) Program is to assure the availability of quality pharmaceutical products and effective pharmaceutical services to achieve desired health outcomes. Toward this end, the SIAPS result areas include improving governance, building capacity for pharmaceutical management and services, addressing information needed for decision-making in the pharmaceutical sector, strengthening financing strategies and mechanisms to improve access to medicines, and increasing quality pharmaceutical services.

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## **Key Words**

quality, antimalarial medicines, regulatory capacity, counterfeit/substandard medicines

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## ACRONYMS AND ABBREVIATIONS

ACT	artemisinin-based combination therapy
ADDO	accredited drug dispensing outlet
ADR	adverse drug reaction
AS/MQ	artesunate and mefloquine
APLMA	Asia Pacific Leaders Malaria Alliance
ASEAN	Association of South East Asian Nations
BDN	Bureau of Drugs and Narcotics (Thailand)
BREMERE	Building Regional Expertise in Medicines Regulation, Information Sharing, Joint Investigation and Enforcement
BVBD	Bureau of Vector-Borne Diseases (Thailand)
CDC	US Centers for Disease Control and Prevention
CNM	National Center for Parasitology, Entomology and Malaria Control (Cambodia)
DAV	Drug Administration of Vietnam
DDF	Department of Drugs and Food (Cambodia)
FDA	Food and Drug Administration
FDAD	Food and Drug Administrative Department (Myanmar)
FDC	fixed-dose combination
GGM	Good Governance for Medicines
Global Fund	Global Fund to Fight AIDS, Tuberculosis and Malaria
GMP	Good Manufacturing Practices
GMS	Greater Mekong Subregion
GPARC	Global Plan for Artemisinin Resistance Containment
IMPACT	International Medical Products Anti-Counterfeiting Taskforce
Lao PDR	Lao People's Democratic Republic
M&E	monitoring and evaluation
MOH	Ministry of Health
MQM	Medicines Quality Monitoring
MRA	medicine regulatory authority
NGO	nongovernmental organization
NHQC	National Health Product Quality Control (Cambodia)
NIDQC	National Institute of Drug Quality Control (Vietnam)
NIMPE	National Institute of Malariology, Parasitology and Entomology (Vietnam)
NMRA	national medicine regulatory authority
NRA	national regulatory authority
oAMT	oral artemisinin-based monotherapy
PIC/S	Pharmaceutical Inspection Convention and Pharmaceutical Inspection Co-operation Scheme
PMI	President's Malaria Initiative
PQM	Promoting the Quality of Medicines
PSI	Population Services International
QA	quality assurance
QC	quality control

RDT	rapid diagnostic test
RDMA	Regional Development Mission for Asia
SIAPS	Systems for Improved Access to Pharmaceuticals and Services
SSFFC	substandard, spurious, falsely labelled, falsified and counterfeit
UNOPS	United Nations Office for Project Services
USAID	US Agency for International Development
USP	US Pharmacopeial Convention
VBDC	Department of Vector Borne Disease Control (Myanmar)
VMW	village malaria worker
WHO	World Health Organization

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## BACKGROUND

Poor quality and counterfeit medicines are immediate threats to public health. They can contribute to otherwise preventable disease morbidity, mortality, incidence, and economic losses.<sup>1</sup> The widespread availability and use of fake and substandard antimicrobial medicines in particular impairs disease control efforts and is a cause of antimicrobial resistance, threatening the effectiveness of current therapies.<sup>2</sup> Counterfeit medicines are those that are “deliberately and fraudulently mislabeled with respect to identity and/or source.”<sup>3</sup> Counterfeit medicines may have the correct or incorrect ingredients, contain insufficient dosage of active ingredients, or contain no active ingredient. Substandard medicines are “genuine drug products which do not meet the quality standards set for them”<sup>4</sup> and do not have an adequate amount of the active ingredient.

Although the true extent of counterfeit and substandard antimalarial medicines in the Greater Mekong Subregion (GMS) is unknown, six studies investigating malaria medicine quality in the region have been published and indicate widespread availability of substandard medicines in the region with an increasing percentage in recent years.<sup>5</sup> The most effective treatment for malaria in Southeast Asia is artemisinin-derivative-based combination therapy, but poor quality artemisinin-based medicines may contribute to artemisinin resistance.<sup>6</sup> The emergence of artemisinin-resistant *Plasmodium falciparum* malaria along the Thailand border, coupled with evidence of widespread use of counterfeit and poor quality antimalarials, is cause for great alarm in the region.<sup>7</sup>

In addition to counterfeit and substandard medicines, the presence of illegal or banned malaria treatment medicines (oral artemisinin-based monotherapies) on the market also leads to artemisinin resistance. Current World Health Organization (WHO) treatment guidelines for uncomplicated *P. falciparum* malaria recommend artemisinin-based combination therapies (ACTs)<sup>8</sup> and warn that the continued use of oral artemisinin-based monotherapy (oAMT) “is considered to be a major contributing factor to the development of resistance to artemisinin derivatives.”<sup>9</sup>

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<sup>1</sup> Harris J, Stevens P, Morris J. *Keeping It Real: Combating the Spread of Fake Drugs in Poor Countries*. Washington, DC: International Policy Network; 2009.

<sup>2</sup> Kelesidis T, Kelesidis I, Rafailidis P, Falagas ME. Counterfeit and substandard antimicrobial drugs: a review of the scientific evidence. *Journal of Antimicrobial Chemotherapy* 2007;60:214–36.

<sup>3</sup> World Health Organization (WHO). Essential medicines and health products website. General information on counterfeit medicines, <http://www.who.int/medicines/services/counterfeit/overview/en/>. Accessed August 23, 2013.

<sup>4</sup> WHO. Medicines website. Frequently asked questions. “What are counterfeit medicines?” <http://www.who.int/medicines/services/counterfeit/faqs/en/>. Accessed November 23, 2012.

<sup>5</sup> Nayyar G, Breman J, Newton P, et al. Poor-quality antimalarial drugs in southeast Asia and sub-Saharan Africa. *Lancet Infectious Diseases* 2012;12:488–96.

<sup>6</sup> WHO. Battling malaria drug resistance along the Thai-Cambodian border. [http://www.who.int/malaria/diagnosis\\_treatment/arcp/background/en/index.html](http://www.who.int/malaria/diagnosis_treatment/arcp/background/en/index.html). Accessed November 23, 2012.

<sup>7</sup> Newton P, McGready R, Fernandez F, et al. Manslaughter by fake artusunate in Asia—will Africa be next? *PLoS Medicine* 2006;3(6):e197.

<sup>8</sup> WHO. Malaria webpage. Q&A on artemisinin resistance. [http://www.who.int/malaria/media/artemisinin\\_resistance\\_qa/en/index.html](http://www.who.int/malaria/media/artemisinin_resistance_qa/en/index.html).

<sup>9</sup> WHO. Malaria webpage. Withdrawal of artemisinin-based monotherapies. [http://www.who.int/malaria/areas/treatment/withdrawal\\_of\\_oral\\_artemisinin\\_based\\_monotherapies/en/index.html](http://www.who.int/malaria/areas/treatment/withdrawal_of_oral_artemisinin_based_monotherapies/en/index.html). Accessed July 10, 2013.

The President's Malaria Initiative (PMI) helps countries improve their ability to conduct infectious disease research and surveillance, increase their capacity to communicate the need for behavior change, train researchers and caregivers, effectively deliver health services, and provide community-based care and support. To combat counterfeit and substandard medicines and the emergence of artemisinin resistance in the GMS, PMI has been supporting the activities of the US Agency for International Development (USAID)'s Promoting the Quality of Medicines (PQM) program,<sup>10</sup> implemented by the US Pharmacopeial Convention (USP), in the Mekong Subregion, in an effort to strengthen medicine quality monitoring and technical capacity in national medicine quality control laboratories, information sharing, and other related activities.

PMI, with funding provided by the USAID Regional Development Mission for Asia (RDMA) and the USAID Missions in Burma (Myanmar) and Cambodia, requested the Systems for Improved Access to Pharmaceuticals and Services (SIAPS) program to conduct a study of donor, country, regional, and other efforts to combat the availability of substandard and counterfeit medicines in the GMS.<sup>11</sup> The study aims to inform stakeholders, including PMI, other donors, host-country governments, and regional institutions, of what has been accomplished to date to address medicine quality, gaps, and possible opportunities for further programming. The Global Fund to Fight AIDS, Tuberculosis and Malaria (Global Fund)'s Regional Artemisinin Resistance Initiative is in its design phase, and other donors, such as Australia's Department of Foreign Affairs and Trade, are thinking of investing resources to address medicine quality.

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<sup>10</sup> PQM works with medicine regulatory authorities to establish quality monitoring programs, national quality control laboratories to enhance testing capacity, and local manufacturers to meet good manufacturing practices and WHO prequalification.

<sup>11</sup> The GMS includes Burma (Myanmar), Cambodia, Yunnan Province of China, Lao PDR, Thailand, and Vietnam. However, the study did not include Yunnan Province (China) because of logistics and funding constraints.

## OBJECTIVES

SIAPS conducted a review of regulatory and quality assurance efforts in the GMS with the following objectives—

- To inform PMI of past and current initiatives to improve the capacity of the region to combat counterfeit, substandard, and banned antimalarial medicines
- To understand the current barriers to effective medicine quality control for malaria
- To recommend specific areas of focus or interventions to further improve regional and country capacity to combat counterfeit, substandard, and banned or illegal antimalarial medicines

## APPROACH

SIAPS conducted the analysis by a synthesis of data obtained through desktop review of published and unpublished official documents and reports and interviews with key informants (telephone and face to face) such as country officials and regional or subregional experts (see annex 1).

The SIAPS team compiled and reviewed more than 350 reports, mostly in English but also some in local languages accessed by the country-level consultants. These reports included peer-reviewed journal articles, unpublished official documents, and other reports posted on websites. The English-language information resources were identified through Google, Google Scholar, and PubMed. Review or screening of retrieved publications led to additional reports for review. However, most of these reports were not particularly relevant, and the information yield was modest, despite the systematic effort undertaken. SIAPS local consultants in Cambodia, Myanmar, Lao People's Democratic Republic (Lao PDR), and Thailand compiled and reviewed relevant reports in the respective local languages. The SIAPS team created a database in Google Drive to store all compiled documents and shared access to it with PMI and USAID staff. To facilitate access to these materials, which may be useful for further scrutiny and analysis, SIAPS will make available all the compiled materials in a CD-ROM.

Building on document review findings, the SIAPS team prepared a tool for conducting key informant interviews. The local consultants conducted personal and telephone interviews with 11 regional and 32 country experts. USAID staff conducted the interviews in Vietnam with coordination assistance from USP/PQM. These country interviews complemented the initial findings from the literature review. The SIAPS team held a teleconference with PMI/USAID to discuss preliminary findings in April 2014, while the interview process was still under way.

The study had several important limitations. These included—

- Lack of formal evaluations of the various technical assistance initiatives that were identified
- Funding constraints that limited international travel to gather and verify information and that placed greater reliance on information collected through in-country consultants
- Limited information obtained from the in-country interviews and delays in receiving the results

Findings are primarily based on data and observations from published and unpublished reports with some contribution from interview results.

## REGULATORY AND QUALITY ASSURANCE SYSTEM FINDINGS

Many factors contribute to antimalarial resistance. These include—

- Weak medicine regulatory systems (inadequate national medicines regulatory authority [NMRA] capacities, lack of postmarket surveillance, lack of medicine quality testing caused by weak national laboratory infrastructure, and weak coordination among NMRAs in the region)
- Product characteristics (coformulated products, quality of medicines with regard to amount of active ingredients, poor stability or degradation, manufacturer Good Manufacturing Practices [GMP] capacity)
- Market factors (e.g., insufficient availability of quality ACTs at affordable prices, migrating populations)
- Patient adherence to treatment (due to insufficient knowledge)
- Insufficient health provider knowledge or inadequate practice (prescribing and/or dispensing)

Based on these factors, this study reports findings related to policy and regulatory frameworks; regulatory action on oAMT; institutional regulatory and quality assurance capacity; enforcement of GMP and supply chain standards; product quality testing and postmarket surveillance; and counterfeit medicine control actions. The study also identified the major sources of external funding for malaria control and technical assistance and critical issues, such as sustaining and scaling up interventions, good governance and political commitment for combating counterfeit and substandard products, public awareness on the importance of medicines quality, and access to good-quality antimalarials.

### Frameworks for Combatting Artemisinin Resistance

WHO has published a global and a regional framework for addressing artemisinin resistance. The *Global Plan for Artemisinin Resistance Containment (GPARC)* is a call to action for members of the Roll Back Malaria Partnership,<sup>12</sup> as a complement to findings in *Global Report on Antimalarial Efficacy and Drug Resistance: 2000–2010*. It defines a high-level plan to preserve the effectiveness of artemisinin-based combination therapies for treatment of *P. falciparum* malaria.

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<sup>12</sup> WHO. *Global Plan for Artemisinin Resistance Containment (GPARC)*. Geneva: WHO; 2011. <http://www.who.int/malaria/publications/atoz/9789241500838/en/>.

The Emergency Response to Artemisinin Resistance in the GMS<sup>13</sup> is a regional framework for action, given the detection of suspected or confirmed artemisinin resistance in four GMS countries as of 2013. It proposes four priority areas for action—

- Reach all at-risk groups with full coverage of quality interventions in priority areas
- Achieve tighter coordination and management of field operations
- Provide better information for artemisinin containment
- Strengthen regional oversight and support

These two frameworks provided guidance for development of country strategies and action plans. The five GMS countries have developed national malaria elimination goals consistent with Emergency Response to Artemisinin Resistance recommendations. But the *Joint Assessment of the Response to Artemisinin Resistance in the GMS* concluded that, despite a good start and some impact, “not enough is being done, with enough intensity, coverage and quality.”<sup>14</sup>

## **Regulatory Action on Artemisinin Monotherapy**

Artemisinin monotherapy has been banned or product licenses have not been renewed in four countries (Cambodia, Lao PDR, Myanmar, and Vietnam). Enforcement of the ban is not fully effective because monotherapy products are still detected in the market. In Myanmar, oAMT is manufactured for use in the military, though there are indications that oAMT production may be discontinued. In Thailand, oral artesunate is still registered with restriction on use, which has reportedly significantly limited its use. Although Vietnam banned oAMT in 2013, products are still manufactured and exported to other countries.

## **Regulatory Framework for Addressing Fake and Substandard Medicines**

Relevant laws and regulations are in place to address fake medicines and substandard medicines. Although existing laws and regulations define what are counterfeit and substandard medicines, they lack clear and explicit definition of roles, responsibilities, and actions to be taken once any of these products are detected, particularly where the intervention of nonhealth agencies is needed (e.g., customs, police, the judicial system). Conversely, there may be a need to ensure that corresponding definitions and actions in other sectors (e.g., industrial, trade, criminal or judicial system) complement those of the health regulatory system. In some countries, interviewees stated that postmarket quality controls were not done routinely because of insufficient guidance in existing regulations; in Cambodia, specifically, more specific regulations and guidance on conducting postmarket surveillance may need to be formulated, including “the

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<sup>13</sup> WHO. *Emergency Response to Artemisinin Resistance in the Greater Mekong Subregion: Regional Framework for action 2013–2015*. Geneva: WHO; 2013.

[http://apps.who.int/iris/bitstream/10665/79940/1/9789241505321\\_eng.pdf](http://apps.who.int/iris/bitstream/10665/79940/1/9789241505321_eng.pdf).

<sup>14</sup> Christophel EM, Ear S, Meek S, et al. *Joint Assessment of the Response to Artemisinin Resistance in the Greater Mekong Sub-Region. Conducted November 2011 to February 2012*. Carried out in partnership with: WHO, Department for International Development (UK), USAID, PMI. Sponsored by: Australian Agency for International Development (AusAID), Bill & Melinda Gates Foundation (BMGF).

process to remove identified counterfeit medicines from the market.” In other countries, such as Thailand, the risks of prosecution and penalties for counterfeiting are inadequate.

## **Institutional Regulatory and Quality Assurance Capacity**

All GMS countries have medicine regulatory organizations, infrastructure, and relevant regulations to deal with substandard and counterfeit antimalarial medicines in the market. Regulatory and quality assurance capacity has improved over the past decade. Despite progress in recent years, most of these countries still encounter problems of enforcement caused by insufficient human resource capacity and financial resources. Although this issue relates to all countries, Cambodia, Lao PDR, and Myanmar regulatory systems will require greater efforts and resources than those of Thailand and Vietnam.

Improved technical processes and competencies are needed for preapproval evaluation for medicines and product registration. GMS NMRAs have little or no participation in regional technical harmonization efforts. All five countries are members of the Association of Southeast Asian Nations (ASEAN), but the Thai Food and Drug Administration (FDA) is the only one that has been actively participating in the ASEAN Pharmaceutical Product Working Group and has fully adopted the ASEAN Common Technical Dossier.<sup>15</sup>

All five countries have established quality control testing laboratories. Capacity is limited by insufficient funding and limited technical resources, more significantly in Cambodia, Lao PDR, Myanmar, and Vietnam. The Thai Bureau of Drug and Narcotic and the National Institute of Drug Quality Control of Vietnam have met WHO standards and are on the WHO List of Prequalified Quality Control Laboratories.<sup>16</sup> USP/PQM has been providing technical support to build the capacity of the national quality control laboratories in Cambodia, Lao PDR, Thailand, and Vietnam. As part of the Asian Network of Excellence in Quality Assurance of Medicines in Thailand, the Chulalongkorn University Faculty of Pharmaceutical Sciences Quality Control Laboratory and the Mahidol University Faculty of Pharmacy serve as regional resources for expertise in quality control of medicines and expertise in GMP, respectively.<sup>17</sup>

## **GMP and Supply Chain Standards Compliance Inspections**

GMP certification is based on national standards in Cambodia, Myanmar, and Vietnam. All of the manufacturers in Myanmar, but only some in Cambodia and Vietnam, are compliant with national GMP standards. Although it appears that GMP is not mandatory in Thailand, its FDA

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<sup>15</sup> The Common Technical Dossier is an internationally agreed set of specifications for the application dossier for registration of medicinal products. In countries participating in the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use, it is referred to as Common Technical Document. It specifies information requirements for documentation of pharmaceutical quality, nonclinical study reports, and clinical study reports.

<sup>16</sup> Available at [http://apps.who.int/prequal/lists/PQ\\_QCLabsList.pdf](http://apps.who.int/prequal/lists/PQ_QCLabsList.pdf).

<sup>17</sup> Promoting the Quality of Medicines Program. *Strengthening National Capacity in Medicines Quality: Five-Year Summary (2005–2009) Promoting the Quality of Medicines Program in Southeast Asia and the Philippines*. Rockville, MD: United States Pharmacopeial Convention; 2010.

plans to apply for Pharmaceutical Inspection Convention and Pharmaceutical Inspection Co-Operation Scheme (PIC/S)<sup>18</sup> membership in 2014.

USAID-USP/PQM is providing technical support on GMP standards, good distribution practices, and good storage practices in Cambodia, Lao PDR, Thailand, and Vietnam.

## **Postmarketing Surveillance**

All GMS countries carry out facility inspections and collect samples for testing. Because of significant budget and human resources limitations, extensive geographic coverage and regularity of such activities are unlikely, with gaps particularly in the remote and border areas.

USAID-USP/PQM has been providing technical support to establish or expand medicine quality monitoring programs as part of postmarketing surveillance in Cambodia, Lao PDR, Thailand, and Vietnam. Data from program activities contribute to the USAID-USP/PQM Medicines Quality Monitoring programs Medicines Quality Database.<sup>19</sup> Substandard and fake medicines detected through sampling and testing at sentinel sites set up in Cambodia, Lao PDR, and Vietnam include antimalarials (artesunate, chloroquine, quinine, sulfadoxine-pyrimethamine) and antibiotics (amoxicilline, ampicillin, chloramphenicol, co-trimoxazole, erythromycin, metronidazole, penicillin V potassium, rifampicin, sulfadoxine-pyrimethamine). Although sentinel sampling and testing results seem to suggest substandard and fake product prevalence may have decreased to low levels between 2005 and 2009,<sup>20,21,22</sup> this evidence should be critically reviewed and verified.

## **Fake Medicine Control Actions**

It is unclear whether countries regularly undertake self-initiated interventions to actively control circulation of fake medicines, but they have participated in international operations. All five GMS countries participated in Operation Storm, a multicountry operation combating counterfeit pharmaceuticals in Southeast Asia.<sup>23</sup> Under the framework of WHO's International Medical Products and Anti-Counterfeiting Taskforce (IMPACT) initiative, Operation Storm was led by INTERPOL in collaboration with the World Customs Organization, and included representatives

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<sup>18</sup> PIC/S comprises two international cooperation international instruments for member countries and pharmaceutical inspection authorities to collaborate on GMP standards and their compliance. About 40 countries participate in PIC/S. <http://www.picscheme.org>.

<sup>19</sup> USP website. Medicines Quality Database (MQDB). <http://www.usp.org/global-health-impact-programs/promoting-quality-medicines-pqmusaid/medicines-quality-database-mqdb>.

<sup>20</sup> Ministry of Health. *Medicines Quality Monitoring Programme 5 Years Report (2005–2009)*. Supported by USAID through USP DQI/PQM. Cambodia, March 2010.

<sup>21</sup> Food and Drug Department. *Medicines Quality Monitoring Program 5 Year Report, Reporting Period (2005–2009)*. Supported by USAID through USP DQI/PQM. Lao PDR; March 2010.

<sup>22</sup> Ministry of Health of Vietnam. *Medicines Quality Monitoring Program 5 Year Report Viet Nam 2005–2010*. Supported by USAID through USP DQI/PQM. National Institute of Malariology, Parasitology & Entomology/ National Institute of Malariology, Parasitology & Entomology Ho Chi Minh City, USP DQI. Hanoi, 2010.

<sup>23</sup> Interpol, IMPACT, and WHO. *Operation Storm: final report*. Undated. <http://www.interpol.int/Crime-areas/Pharmaceutical-crime/Operations/Operation-Storm>.

from customs, medicines regulatory authorities, and the police in Cambodia, China, Indonesia, Laos PDR, Myanmar, Thailand, and Vietnam. The initiative conducted Storm I in 2008 and Storm II in 2010. Storm I resulted in 186 raids, 27 arrests, and more than 16 million tablets seized, valued at USD 6.65 million. Storm II resulted in more than 100 pharmacies and illicit medicine outlets closed, 33 arrests, and 20 million pills seized, including antibiotics, antimalarial and birth-control medicines, anti-tetanus serums, aspirin, and erectile dysfunction medicines. More than 12 million pills were counterfeit, and 8 million pills were expired, not registered, or diverted medicines.

Operation Storm and a similar operation in Africa (Operation Mamba) reported implementation challenges related to support from top-level hierarchy, support from the owner of the shops, intelligence sharing among stakeholders, timing of preparation for operations, testing capacity and timeliness of responses, corruption, follow-up on interventions, reports on cases, identifying the responsible organized criminals, and follow-up after the operation.<sup>24</sup> It was not possible to determine from the report which of these challenges referred to GMS and which to the African countries.

Cambodia and Vietnam reportedly participate in the WHO Project for the Surveillance and Monitoring of Substandard, Spurious, Falsely Labelled, Falsified and Counterfeit (SSFFC) Medical Products.<sup>25</sup> This rapid-alert system is a Web-based communications network involving focal persons and representatives of participating countries, WHO, and partner agencies. The rapid-alert system was originally developed in the WHO Western Pacific Region but was not being used regularly and has been enhanced for global application.

## **Intercountry Collaboration between Regulatory Authorities**

Effective collaboration between medicine regulatory authorities and law enforcement agencies in each country and between countries is critical for combating counterfeit medical products. Operation Storm (I and II) was a very successful multicountry collaboration in the Southeast Asia Region. But it has been four years since the last operation, and country-initiated surveillance and enforcement operations have not been documented. Existing mechanisms for information sharing and collaboration, such as the WHO Project for the Surveillance and Monitoring of SSFFC Medical Products that expanded the previous rapid-alert system, continue to be underused. PQM recently launched Building Regional Expertise in Medicines Regulation, Information Sharing, Joint Investigation, and Enforcement (BREMERE) as an intersector initiative to strengthen interagency and intercountry collaboration and timely exchange of information between GMS countries.<sup>26</sup> It shows promise as a regional collaboration mechanism but still needs to demonstrate impact.

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<sup>24</sup> Operation Storm and Operation Mamba. Slide Presentation. 3rd IMPACT Annual Meeting, Hammamet, Tunisia, December 3–5, 2008.

<sup>25</sup> WHO project for the surveillance and monitoring of SSFFC medical products. *WHO Drug Information* 2013;27(2):97–100.

<sup>26</sup> USAID/USP/Promoting the Quality of Medicines. Collaborative focus on fight against counterfeit, substandard medicines in Greater Mekong Sub-Region. Press release, 2012. <http://us.vocuspr.com/Newsroom/ViewAttachment.aspx?SiteName=uspharm&Entity=PRAsset&AttachmentType=F&EntityID=109560&AttachmentID=031e3acf-79b3-471d-909d-bb9191e41d98>.

## **Technical Assistance**

WHO and USP/PQM are the major providers of technical assistance to the regulatory and quality assurance system. WHO has been providing support through global and regional frameworks, policy guidance, advocacy, and coordination. As part of its strategy for improving access to good-quality essential medicines, over the years WHO has been supporting Mekong countries, especially Cambodia, Lao PDR, and Vietnam, in strengthening their regulation and quality assurance system through country and intercountry training and workshops, setting up an electronic registration system (Lao PDR), a pharmacovigilance system (Vietnam), and a quality survey (Cambodia). However, specific reports of country-specific technical support were not available for review.

USP/PQM (and previously USP/DQI) appears to be the main provider of technical assistance for strengthening quality assurance and quality control capacity in the GMS. Annex 3 lists PQM activities in each of the countries. PQM also helped establish the Asian Network for Excellence in Quality Assurance of Medicines as an approach to increase national capacity in GMP and quality assurance and quality control of medicines.<sup>27</sup>

Other organizations that have provided technical assistance include the Japan Pharmaceutical Manufacturers Association, funded by the Japan International Cooperation Agency, which supported the Pharmaceutical Development Center in Lao PDR.

## **Sustaining and Scaling Up Effective Interventions**

GMS countries have limited financial as well as technical capacities in scaling up medicine quality monitoring and in preventing the movement of substandard products to high-risk areas. Most of the initiatives with positive outcomes, such as USAID's USP/PQM,<sup>28</sup> have been externally funded. A need exists to assist countries to mobilize funding from both internal and external sources for scaling up activities and to sustain gains. The majority of funding from 2007 to 2011 for elimination of malaria was provided by multilateral donors (94%) and mostly by the Global Fund.<sup>29</sup> However, external funding for malaria elimination may decline in the future. Other funding sources are required, and GMS countries need further support for mobilizing funding.

The major source of financing for malaria program activities in the GMS countries is the Global Fund.<sup>30</sup> Most of the funding supports health product procurement. Government funding in Cambodia, Lao PDR, and Myanmar is very limited compared to Global Fund contributions. The Global Fund has also provided significant funding in Thailand and Vietnam over the past five

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<sup>27</sup> USAID/USP. Promoting the Quality of Medicines (PQM) program in Southeast Asia. Bangkok: USAID Regional Development Mission for Asia; May 2012. [http://www.usp.org/sites/default/files/usp\\_pdf/EN/fact\\_sheet-southeast\\_asia-apr\\_11\\_2013.pdf](http://www.usp.org/sites/default/files/usp_pdf/EN/fact_sheet-southeast_asia-apr_11_2013.pdf).

<sup>28</sup> Ibid.

<sup>29</sup> Cambridge Economic Policy Associates with Global Health Group at UCSF. Policy Brief: Financing malaria elimination: current trends and recommendations. October 2013. <http://globalhealthsciences.ucsf.edu/sites/default/files/content/ghg/mei-financing-malaria-elimination-brief.pdf>.

<sup>30</sup> WHO. *World Malaria Report 2013*. Geneva: WHO; 2013.

years. Vietnam has maintained steady levels of financing since 2004, which has also been significantly supplemented by the Global Fund. As of November 2012, the Global Fund had disbursed USD 243 million, or 5% of USD 5 billion of its global contributions, since 2005. Although other donors have contributed to malaria control efforts, the funding levels have been much less in comparison with those of Global Fund; these donors include the World Bank, the US Government, WHO/UNICEF, and others. The Governments of Japan, Australia, and the United Kingdom and the Bill & Melinda Gates Foundation have also supported malaria projects and activities.

Since 2011, the PMI has provided USD 29.5 million to support malaria control in the GMS.<sup>31</sup> No details were found on funding amounts for regulatory capacity strengthening, but in recent years PMI has invested in support to prevent the introduction of counterfeit medicines into supply chains, to help national regulatory authorities improve medicine quality, to provide technical assistance on quality assurance testing, and to strengthen capacity for monitoring and regulation in the public and private sectors.

Technical capacity for scaling up effective interventions is limited in GMS countries, especially in Cambodia, Lao PDR, and Myanmar, and continued and additional support for strengthening the regulatory system, medicine quality surveillance, and bringing regulatory enforcement up to an acceptable regulatory standard is needed.

## **Good Governance and Political Commitment for Combating Fake and Substandard Products**

Lack of support from the policy makers and possible conflicts of interest have been regarded as impediments in combating fake and substandard products. While alluded to in reports and some interviews, adequately documenting “lack of commitment,” “weak political will,” existence of “conflict of interest” (particularly when government officers are known to own pharmaceutical companies), or “nontransparency” is difficult based on interview data alone.<sup>32</sup> Occasional media reports may be a source of documentation of these situations in the absence of formal studies.<sup>33</sup> Nevertheless, participation in initiatives such as the WHO Good Governance for Medicines program may be a promising starting point (Annex 4). Lao PDR and Thailand are two countries engaged in this process.<sup>34</sup> Following assessments of levels of transparency and vulnerability to corruption in medicine registration, selection, and procurement (Phase I), Lao PDR is developing

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<sup>31</sup> USAID, CDC, DHHS. *The President’s Malaria Initiative: Eighth Annual Report to Congress, April 2014*. Washington, DC: USAID; 2014. [http://www.pmi.gov/docs/default-source/default-document-library/pmi-reports/pmi-report\\_final.pdf?sfvrsn=6](http://www.pmi.gov/docs/default-source/default-document-library/pmi-reports/pmi-report_final.pdf?sfvrsn=6).

<sup>32</sup> Experience in Cambodia illustrates the power of political commitment. Authorities shut down 65% of Cambodia’s unlicensed pharmacies to comply with previously unenforced pharmaceutical legislation. See <http://www.essentialdrugs.org/edrug/archive/201005/msg00005.php>.

<sup>33</sup> PQM. *Media Reports on Medicine Quality: Focusing on USAID-Assisted Countries*. Rockville, MD: USP; 2014. [http://www.usp.org/sites/default/files/video/pqm/media\\_reports-2014-march\\_jan-feb.pdf](http://www.usp.org/sites/default/files/video/pqm/media_reports-2014-march_jan-feb.pdf).

<sup>34</sup> AusAID and World Health Organization. *Measuring Transparency in Medicines Registration, Selection and Procurement: Four Country Assessment Studies*. Geneva: WHO; 2006. <http://www.who.int/medicines/areas/policy/goodgovernance/Transparency4CountryStudy.pdf>.

a Good Governance Strategy (Phase II), while Thailand is implementing its national Good Governance Strategy (Phase III).<sup>35</sup>

## **Public Awareness on the Importance of Medicine Quality**

Community awareness about the importance of medicine quality is still poor, as shown from a study undertaken in Lao PDR.<sup>36</sup> Although some examples of public education campaigns exist, for example in Cambodia, country-level informants emphasized the need for public education and advocacy on the importance of medicine quality and the danger of substandard and counterfeit medicines in other GMS countries. Such advocacy should also be directed to health care providers and managers at different levels of care.

## **Access to Good-Quality Antimalarials**

Access to good quality antimalarials remains problematic in most of the GMS countries, especially in remote places, as demonstrated by various surveys.<sup>37,38,39,40</sup> Strengthening of supply management (procurement and distribution) in both public and private sectors for antimalarials and other essential medicines is still needed. Poor quality or cheaper, inappropriate products fill the void created by stock-outs of quality medicines.

Population Services International (PSI) initiatives in Cambodia and Myanmar provide important lessons learned on market interventions as a strategy to reduce availability and use of artemisinin-based monotherapies. Cambodia was the first country to implement a social marketing program with subsidized ACTs and rapid diagnostic tests (RDTs). It started as a successful pilot conducted by the European Commission Cambodia Malaria Control Project, in partnership with the National Centre for Parasitology, Entomology, and Malaria Control and the WHO. Since 2003 PSI/Cambodia has implemented the Nationwide Social Marketing Programme, which provides branded co-blistered artesunate and mefloquine (AS/MQ) to the private sector (Malarine) and the public sector (AS/MQ). By 2009 the program was providing half of all malaria treatment in the country and 75% of all AS/MQ distributed.<sup>41</sup> The social marketing intervention included (a) supply of co-blistered AS/MQ (Malarine) to private clinics,

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<sup>35</sup> WHO. *Good Governance for Medicines: Progress Report 2010*. Geneva: WHO; 2010.

<http://cdrwww.who.int/medicines/areas/policy/goodgovernance/GGM2010ProgressReport.pdf>.

<sup>36</sup> Syhakhang L, Freudenthal S, Tomson G, et al. Knowledge and perception of drug quality among drug sellers and consumers in Lao PDR. *Health Policy and Planning* 2004;19(6):391–401.

<sup>37</sup> Syhakhang L, Sengaloundeth S, Paphassarang C, Freudenthal S, Wahlström R. Availability of essential drugs and sustainability of village revolving drug funds in remote areas of Lao PDR. *Studies in HSO&P* 2008;23: 519–43.

<sup>38</sup> Yeung S, Van Damme W, Socheat D, White NJ, Mills A. Access to artemisinin combination therapy for malaria in remote areas of Cambodia. *Malaria Journal* 2008;7:96 doi:10.1186/1475-2875-7-96.

<http://www.malariajournal.com/content/7/1/96>.

<sup>39</sup> PSI/Myanmar. *Outlet Survey: Baseline Study: The Republic of the Union of Myanmar 2012 Survey Report*. Yangon, Myanmar: PSI/Myanmar; 2012.

<sup>40</sup> ACTwatch Group and PSI/Cambodia. *Kingdom of Cambodia Household Survey Report, 2011*. Phnom Penh, Cambodia: PSI/Cambodia; 2012.

<sup>41</sup> Montagu D. *Large-Scale Malaria Treatment in the Private Sector: A Case Study of the Cambodian Experience*. San Francisco: The Global Health Group, Global Health Sciences, University of California, San Francisco; 2010.

pharmacies, and shops across most of rural Cambodia; (b) sales to wholesalers and retailers at subsidized prices; (c) training of health care providers; and (d) behavior change communications (medical detailing to promote the product, mass media campaigns targeting the community). No formal evaluation of the program has been done, but review of the experience suggests that public and private sector AS/MQ stock-outs caused by procurement delays of quality-assured products may have contributed to slow uptake and the importance of ensuring reliable availability of supplies in the least accessible areas to avoid shift from ACT therapy to non-artemisinin therapy (e.g., chloroquine),<sup>42</sup> which may be therapeutically inappropriate. Data from 2011 also show that oAMT availability had also decreased but was not completely eliminated.<sup>43</sup>

PSI's Containment of Artemisinin Resistance in Eastern Myanmar (PSI Myanmar project)<sup>44</sup> aims to implement a key objective of the Myanmar Artemisinin Resistance Containment strategy. To achieve rapid replacement of oAMT with quality-assured and highly subsidized ACT, PSI manages the donor subsidy, product procurement and importation, subsequent sales at agreed prices to contracted national distributors, monitoring of supply chains, providing supportive communications and medical detailing interventions, and baseline and impact measurement.<sup>45</sup> Initial results show that between 2012 and 2013 the availability of ACT in the private sector increased significantly in pharmacies, retail stores, and drug vendors, and demand for oAMT dropped dramatically. Relative to oAMT, the market share for ACT increased from 3% to 73% among the priority outlet types in nine months.

These ongoing initiatives show that a market approach, through provision of heavily subsidized ACTs, may displace the demand and use of oAMT. However, this approach depends on uninterrupted supply by reliable supply chains. Regulatory approaches need to go hand in hand with market approaches to ensure that the appropriate products are available, affordable, and accessible.

## **Asia Pacific Leaders Malaria Alliance**

Following the call by leaders at the 7th East Asia Summit in 2012 for coordinated action to fight malaria and address artemisinin-resistant malaria, the Asia Pacific Leaders Malaria Alliance (APLMA) was established in October 2013. APLMA is a high-level political advocacy platform for accelerating political commitment, mobilizing country and regional action, and tracking

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<sup>42</sup> Yeung S, Patouillard E, Allen H, Socheat D. Socially-marketed rapid diagnostic tests and ACT in the private sector: ten years of experience in Cambodia. *Malaria Journal* 2011;10:243. <http://www.malariajournal.com/content/10/1/243>.

<sup>43</sup> White C, Allen H, Littrell M, Spiers A. Market interventions to improve access to quality medicines and diagnostics: generating evidence for malaria policy in the Asia-Pacific region. Paper submitted to the Access to Quality Medicines and Other Technologies Task Force. Asia Pacific Leaders Malaria Alliance; March 2014.

<sup>44</sup> It is cofunded by the UK Department for International Development, the Bill & Melinda Gates Foundation, and Good Ventures. See a description of the project at <http://www.givewell.org/PSI-Myanmar-Artemisinin-Resistance-Containment>.

<sup>45</sup> White C, Allen H, Littrell M, Spiers A. Market interventions to improve access to quality medicines and diagnostics: generating evidence for malaria policy in the Asia-Pacific region. Paper submitted to the Access to Quality Medicines and Other Technologies Task Force. Asia Pacific Leaders Malaria Alliance; March 2014.

progress to reduce malaria in line with global targets, including efforts to eliminate resistance to artemisinin.

APLMA is cochaired by Australia and Vietnam, and the Asian Development Bank hosts its secretariat. Its two task forces—the Access to Quality Medicines and Other Technologies Task Force and the Regional Financing Malaria Task Force—held meetings between March and June 2014 to develop recommendations that were presented at the Ninth East Asia Summit in Nay Pyi Taw, Myanmar, in November 2014. Commissioned papers, presentations, and recommendations are available at [http://aplma.org/rsdd057p.nsf/content/ROOT/about\\_aplma?openDocument](http://aplma.org/rsdd057p.nsf/content/ROOT/about_aplma?openDocument). This recent development may contribute to generate the political commitment and mobilization of resources to effectively contain and slow down the spread of artemisinin resistance.

## OPTIONS FOR THE WAY FORWARD

Although the regulatory and quality assurance systems have improved, further efforts are needed. But progress is likely to be slow compared to the potential spread of malaria to other areas, now that artemisinin resistance has been documented. Regulatory action and quality assurance measures alone will not be sufficient.

The key contributors to resistance must be addressed with a sense of urgency. Interventions need to be integrated, which will require comprehensive approaches, ensuring that regulatory and access interventions are mutually supportive to achieve short- to medium-term results while the system is strengthened to establish resilience.

Currently, GMS countries are strongly dependent on external funding support for malaria control, particularly in Cambodia, Lao PDR, and Myanmar. Efforts to ensure sustainability of strengthened regulatory and quality assurance systems must take into account governance, financing, information, human resources, and health and pharmaceutical services delivery.

Options to support continued improvement of regulatory and quality assurance systems for containment of antimalarial resistance include the following—

1. Continue to strengthen medicine regulatory and quality assurance systems and enforcement capacities

Through USP/PQM (and its predecessor USP/DQI), PMI and USAID have contributed to improvements in the technical capacities of medicine regulatory authorities and quality control laboratories for testing, monitoring quality of medicines, and use of the data to support quality standards enforcement. Regulators have expressed the need for continued efforts. Strengthening regulatory authorities, quality assurance and quality control, and regulatory enforcement is a continuous and long-term process. It will entail not only enhancing technical capacity but also strengthening governance<sup>46</sup> and leadership and management capacities, given adequate financing and human resources. Specific actions that build on achievements to date could include—

- Continuing to support technical capacity building for product evaluation, GMP inspections (by regulatory agency) and compliance (by industry), WHO prequalification (for manufacturers and for quality control laboratories), medicine quality surveillance, regulatory and quality control information exchange, and national intersectoral collaboration and enforcement of laws and standards

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<sup>46</sup> Good governance relates to the relationships between individuals or institutions and the way in which decisions are made and implemented. Characteristics of good governance include strategic vision, participation, transparency, consensus-orientation, rule of law, equity, effectiveness and efficiency, responsiveness, and accountability. These apply to the regulatory system. Strengthening Pharmaceutical Systems (SPS). *Pharmaceuticals and the Public Interest: The Importance of Good Governance*. Submitted to the US Agency for International Development by the SPS Program. Arlington, VA: Management Sciences for Health.

- Encouraging and supporting country participation in the WHO Good Governance for Medicines program, following the examples of Lao PDR and Thailand, which would inform what specific country actions are needed (in Cambodia, Myanmar, and Vietnam)
- Assisting in updating or revising appropriate policies, laws, and regulations; strengthening organizational structures to exercise appropriate decision making, authority, and oversight; enhancing systems and processes to be transparent, ethical, accountable, and grounded in well-formed policies and laws; and improving human resources management systems that promote effective performance and ethical practices; these interventions support Good Governance for Medicines
- Assisting in identifying, planning, advocating for, and establishing sustainable sources of revenue (e.g., increased government budget, updated user fees, innovative taxation and collection, others) that will contribute to growing country and institutional ownership of financing the regulatory and quality assurance system
- Supporting intercountry collaboration and information exchange, including regional medicines registration harmonization efforts, GMP standards and compliance, and medicine safety surveillance
- Supporting country capacity to engage in regional police enforcement initiatives to combat fake or counterfeit medicines, such as Operation STORM

2. Support to develop individual country strategy and implementation plans for APLMA recommendations

The APLMA Access to Quality Medicines and Other Technologies Task Force Regulators Group provided 12 recommendations in four key areas, which included 42 actions (24 prioritized for immediate action) to address self-acknowledged weaknesses. GMS countries will need to assess their relevance and develop specific strategic action plans for implementation. Assuming that this new advocacy platform effectively mobilizes strong political support, these recommended actions will still need adequate funding and technical assistance, first to develop the action plan, and later, for implementation, particularly in Cambodia, Lao PDR, and Myanmar. Support may include—

- Undertaking comprehensive stakeholder mapping and developing an engagement plan
- Determining priority actions and realistic target outputs and outcomes
- Assessing short- and medium-term feasibility (legal framework, expected political commitment/support, operational requirements, budgetary needs)
- Mobilizing financial and potential technical assistance resources
- Ensuring that key APLMA-endorsed recommendations are aligned with other options for the way forward

3. Continue to coordinate PMI (and other USAID) GMS regulatory and quality assurance technical support with other development partners and initiatives, particularly WHO and APLMA

The recent development of APLMA, supported by the Australian Department of Foreign Affairs and Trade and the Asian Development Bank, is an initiative that promises to mobilize funding and action to contain the spread of artemisinin resistance. What specific assistance will be provided to implement the ambitious set of recommendations is still unclear, pending their endorsement by the Asia Pacific heads of state. PMI and USAID, which have been supporting key supporters of country antimalarial resistance containment capacity building activities in the GMS, will continue to play this important role. Coordination and collaboration at subregional and country levels will be critical to ensure effectiveness and efficiency of PMI and USAID support.

4. Complement regulatory strengthening with improved access to quality antimalarial medicines

Regulatory action alone is only part of the solution. Ensuring access to quality medicines, particularly coformulated ACTs, is needed to prevent further development and spread of artemisinin resistance. An integrated approach linking regulation with a market or distribution channel should be explored. Such an approach should target (a) areas where resistance has been documented (geographically remote and border areas) and (b) vulnerable population subgroups (the poor and the migrant populations). This will entail engagement in cross-border activities.

A complementary regulatory-market access approach would have the following components—

- Regulations that support (minimum) standard quality infrastructure and services in target geographic areas and their appropriate enforcement by local authorities
- Uninterrupted supply of quality ACT products to outlets or services acceptable and accessible to the community (high-risk group)
- Subsidized prices to facilitate product affordability
- Training of appropriate (diagnostic and) treatment management to public and private providers
- Incentives to private providers and retailers
- Behavior change communications to providers and consumers

Some promising experiences may provide some lessons for development and testing of such a complex and comprehensive package of interventions. The PSI market access interventions in Cambodia and Myanmar are two ongoing examples, as mentioned previously. An example from Africa is the accreditation and regulation model to improve access to quality pharmaceutical

products and services in Tanzania—the Accredited Drug Dispensing Outlet (ADDO) program (or Accredited Drug Seller Initiative).<sup>47</sup> The ADDO program strategy included—

- Developing accreditation based on ministry of health–instituted standards and regulations
- Creating a strong public sector–based regulatory and inspection system and strengthening local regulatory processes and capacity
- Developing drug shop owners’ business skills and providing them mentoring
- Changing the behavior of drug shop owners by providing commercial incentives (e.g., access to loans)
- Providing legal access to a limited list of basic, quality prescription essential medicines for sale in accredited shops, which usually involves changes in existing regulations
- Changing behavior of dispensing staff through training, education, and supervision
- Improving awareness of customers regarding quality and the importance of treatment compliance through marketing and public education

The pilot in one region showed that accessibility, availability, and acceptability of quality assured medicines (antimalarials) could be improved through a regulation and accreditation approach, combined with appropriate incentives to shop owners. The initiative was then adopted by the government as national policy and, with a mix of donor (USAID, Danida, Global Fund), central government, and local government financing, the accredited drug seller model was fully implemented throughout mainland Tanzania by 2012.

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<sup>47</sup> Launched in 2003, the ADDO program was funded by the Bill & Melinda Gates Foundation and implemented by Management Sciences for Health. Subsequent grants supported technical assistance to refine the model, allowing it to be scaled up to cover the whole country.

## ANNEX 1. LIST OF PERSONS INTERVIEWED

### Regional Interviews

Person Interviewed	Affiliation
Dr. Souly Phanouvong	United States Pharmacopeia
Dr. Walter Mulombo Kazadi	World Health Organization Western Regional Office, Cambodia
Dr. Klara Tisocki	World Health Organization, Western Pacific Regional Office, Manila
Dr. Eva Maria Christophel	World Health Organization, Western Pacific Regional Office, Manila
Dr. Michael Deats	World Health Organization, Geneva
Dr. Phillippe Passmore	Freelance consultant
Dr. Chroeng Sokhan	Former, Deputy Director Department of Drugs and Food, Cambodia
Ms. Mam Boravan	National Malaria Control Program, Cambodia
Dr. Lamphone Syhakang	Food and Drug Department, Lao PDR
Dr. Myat Phone Kyaw	Director (Research) Department of Medical Research (Lower Myanmar)
Dr. Soccoro Escalante	WHO Vietnam

### Cambodia

Person Interviewed	Affiliation
Em Khim Vorac	Customs and excise agency
Dr. Heng Bun Kiet	Department of Drugs and Food
Dr. Tep Keyla	National Health Product Quality Control
Dr. Khlaing Sameth	National Drugs Inspector
Dr. Yim Yann	Pharmacist Association
Mrs. Mam Boravann	AMFm Coordinator/National Malaria Control Program (CNM)
Dr. Hang Meun	CAMCONTROL
Pharm. Siv Lang	USP/DQI

### Myanmar

Person Interviewed	Affiliation
Interviewee wished to remain anonymous	National Malaria Control Program (Ministry of Health)
Dr. Ei Ei Khin	Township Health Department
Dr Theingi Zin	Food and Drug Administration
Dr Soe Myat Tun, Dr Lu Lu Kyaw Tin Oo	USP/PQM
Dr Saw Lwin	University Research Co., LLC (URC)
Anonymous	WHO Country Office National Professional officer
Dr. Hnin Su Su Khin	PSI

## Thailand

<b>Person Interviewed</b>	<b>Affiliation</b>
Dr. Apinya Niramitsantipong, Country Program Manager	National Malaria Control program, Malaria cluster of BVBD, Department of Disease Control, Ministry of Public Health
Ms. Surawadee Kitchakarn, Focal point for antimalarial medicines quality monitoring	
Mrs. Saowanit Vijaykadga (former Officer in Charge of Malaria Cluster of BVBD)	
Dr. Deyer Gopinath, Medical Officer Dr. Martin Eisenhawe, Technical Officer	WHO country office
Dr. Wiyada Akarawut, Acting Director	Bureau of Drugs and Narcotics (national quality control lab), Department of Medical Sciences, MOPH
Dr. Vorasit Vongsutilers, Director of Pharmaceutical Technology Service Center	Chulalongkorn University – ANEQAM QC Lab

## Vietnam

<b>Person Interviewed</b>	<b>Affiliation</b>
Nguyen Hoang Anh (Vice Head)	National Drug Information & ADR Center Hanoi University School of Pharmacy <a href="http://canhgiacduoc.org.vn/">http://canhgiacduoc.org.vn/</a>
Nguyen Thi Minh Thu (Pharmacist, MSc, PhD) Dr. Duong Tran Thanh (NIMPE Director)	National Institute of Malariology, Parasitology and Entomology (NIMPE)
Nguyen M Phar. Van Vien (Director, Drug Quality Control Unit)	Drug Administration of Vietnam (DAV)
Dr. Doan Cao Son (Director) Dr. Tran Viet Hung (Vice Director)	National Institute for Drug Quality Control (NIDQC)
Vice Head of the Provincial Center for Malaria Control	Provincial Center for Malaria Control, Binh Phuoc Province
Trinh Ngoc Hai (Head of a HCM – IMPE Laboratory)	Institute of Malariology, Parasitology and Entomology, Ho Chi Minh City (HCM – IMPE)
VanTuan Le (Acting Officer in Charge of HMCM Office / National Professional Officer)	World Health Organization – HCMC Office
Nguyen Thanh Ha (Head of Research and Training Department)	Institute of Drug Quality Control Ho Chi Minh City

## ANNEX 2. GREATER MEKONG SUBREGION COUNTRY SUMMARY REPORTS

### Medicine Regulatory Capacity for Antimalarial Product Quality Assurance in Five GMS Countries

Area	Cambodia	Lao PDR	Myanmar	Thailand	Viet Nam
Legal framework	Laws mandate drug registration and GMP compliance.	The Law on Drugs and Medical Products (amended in 2011) defines the regulations related to registration of drugs and medical products.	National Drug Law 1992 mandates quality assurance in manufacturing medicines and laboratory analyses of all pharmaceutical products.	Drug Act of B.E. 2510 (1967), Drug Act of B.E. 2530 (1987), and Drug Act of B.E.2546 (2003) mandates drug registration and its requirements.	Pharmaceutical Law (2005), Law on People's Health Protection (Chapter VI), and Criminal Law (Article 156 and 157) define mandates related to drugs.
Laws address counterfeit medicines	Laws are in place to ban production, circulation, importing, and exporting of the products.	Drug policy prohibits production of fake drugs and defines measures against violations.	The National Drug Law prohibits production, import, export, storage, distribution, or sale of fake drugs.	Including Drug Act 1967, several laws define defective medicinal products, including counterfeit medicines.	Pharmaceutical Law strictly prohibits acts related to trading counterfeit drugs.
Medicine regulatory agency	Ministry of Health (MOH) Department of Drugs and Food (DDF)	MOH Food and Drug Department (FDD)	MOH Department of Health Food and Drug Administration (FDA)	Bureau of Drug Control under Thai FDA	MOH Drug Administration of Vietnam (DAV)
Medicine regulatory capacity	Inadequate staffing (38) vs. number of registered products (10,355)	Information not available	Human resources limitation (among 650 permanent positions, only 60 scientific staff working on regulatory work)	Limited staff vs. number of registered drugs (among 304 permanent staff, only 96 staff working on regulatory affairs)	Limited human resources and technical capacity

<b>Area</b>	<b>Cambodia</b>	<b>Lao PDR</b>	<b>Myanmar</b>	<b>Thailand</b>	<b>Viet Nam</b>
Medicine quality control	National Health Product Quality Control Center (NHQLC) is responsible for sampling tests and post marketing surveillance.	Both preapproval and postmarketing surveillance sampling by the Food and Drug Quality Control Centre (FDQCC) are unsustainable because of lack of operating funds.	National Drug Testing Laboratory functions to test the samples (1,799 in 2012) of premarket and postmarket samples.	The Bureau of Drug and Narcotics (BDN) under the Department of Medical Sciences conducts laboratory tests and certifies quality of drugs before Thai FDA approves and licenses new drug applications.	National Institute of Drug Quality Control (NIDQC) in Hanoi, the Sub-Institute of NIDQC in Ho Chi Minh City at central level and laboratories at provincial level are responsible for quality control.
Medicine quality control capacity	Lack of relevant regulations and guidance on quality assurance of medicines limits the performance of drug quality tests and compliance.	FDQCC conducts pre- and postmarketing testing, but the operations of FDQCC are limited by budget and capacity of trained technicians.	National Drug Testing Laboratory does not conduct all the necessary sampling tests because of overflow of samples for testing compared to the limited number of technical staff.	Total number of staff is 137, including 68 pharmacists, 14 scientists, and 12 laboratory assistants. BDN annually conducts about 2,500 samples (of which 19% are illegal drugs).	Premarket sampling tests on imported and exported pharmaceutical products are currently done only on limited numbers of products because of lack of budget and capacity.
Fake medicines in the market	In 2013, seven types of fake injectable medicines were found and confiscated. Counterfeit antimalarials through unlicensed drug outlets are still found in border areas.	Information not available	Counterfeit medicines are still reported especially in Thai-Myanmar border area. In 2013, 63 drugs were reported, including fake medicines.	Counterfeits and substandard medicines are still found in border areas.	In 2010 and 2011, various types of fake medicines were found, especially in border areas, and the violators were charged.

*Annex 2. Greater Mekong Subregion Country Summary Reports*

<b>Area</b>	<b>Cambodia</b>	<b>Lao PDR</b>	<b>Myanmar</b>	<b>Thailand</b>	<b>Viet Nam</b>
Ban on oAMT	Oral artemisinin monotherapies have been banned since 2008, and market authorization for all oAMT was withdrawn in 2009. The availability of artemisinin-based monotherapies has decreased dramatically, but they are still available in the market.	Lao PDR has taken administrative measures to prohibit the use of artemisinin monotherapy. Oral AMT was used for at least six years before 2005 when the government changed the national policy for uncomplicated <i>P. falciparum</i> malaria treatment to ACT.	The licenses of monotherapy formulations were to have expired by December 2012; however artemisinin monotherapy products are still found in the market.	Although monotherapy is not entirely banned, Thai government allowed the registered oral artemisinin with restriction in use, which resulted in very limited use.	In 2013, the government issued official letter to ban the oAMT products.
Fake medicine control	Operation Storm I & II WHO SSFC programs  Police enforcement is limited in identifying and seizing counterfeit/substandard medicines. There is no policy or regulation in place regarding the process to remove identified counterfeit medicines from the market.	Operation Storm I & II WHO SSFC programs  Drug policy related to counterfeit medicines prohibits production of counterfeit medicines and defines measures against violations. However, implementation is weak.	Operation Storm I & I WHO SSFC programs  Police enforcement on counterfeit medicines has not been well established or exercised because of underdefined roles and responsibilities of relevant government agencies.	Operation Storm I & II  Consumer Protection Division, Royal Thai Police and Food and Drug Administration are responsible government agencies for law enforcement on defective medicines in Thailand.	Operation Storm I & II  Pharmaceutical Law strictly prohibits acts related to conducting drug trade of counterfeits. However, it has been reported that unregistered and counterfeit drugs are still found in the market.
ASEAN pharmaceutical harmonization participation	-Member of ASEAN since 1999.  -Not actively participating in ASEAN Pharmaceutical Product Working Group (PPWG).	-Member of ASEAN since 1997.  -Not actively participating in ASEAN PPWG.		Thai FDA is one of five original members of ASEAN PPWG. Thai FDA fully adopted ASEAN Common Technical Dossier since 2008.	-Member of ASEAN since 1995.  -Not actively participating in ASEAN PPWG.

*Analysis of Regulatory Capacity to Assure the Quality of Antimalarials in Selected Countries of the GMS of Asia*

<b>Area</b>	<b>Cambodia</b>	<b>Lao PDR</b>	<b>Myanmar</b>	<b>Thailand</b>	<b>Viet Nam</b>
PIC/S membership	Not the member of PIC/S			Thai FDA plans submit the PIC/S membership application in 2014.	Not member of PIC/S
GMP compliance	Only three of nine local manufacturers are local GMP compliant.	In 2003, GMP was adopted.	All seven local manufactures (government owned or semi-public entity) are GMP compliant.	GMP is not mandatory yet. Thai FDA moves to mandate GMP in order to join PIC/S.	121 of 178 manufacturers are GMP certified.
Market access initiative	PSI Cambodia: In the private sector, RDTs and prepackaged ACT (Malarine) have been supplied by PSI at subsidized prices to wholesalers and retail outlets.	Not available	PSI Myanmar: Through Artemisinin Monotherapy Replacement project, PSI has been replacing artemisinin monotherapy with quality assured ACTs.	Not available	
External technical assistance	USP/DQI (since 2003) USP/PQM WHO		USP/PQM (since 2010)	USP/DQI (since 2003) USP/PQM WHO	
Action frameworks	-National Malaria Control Program (CNM) -National Elimination Strategy 2011–2025	National Strategy for Malaria Control and Elimination 2011–2015	Myanmar Artemisinin Resistance Containment	National Strategic Plan for Malaria Control and Elimination in Thailand 2011–2016	National Monitoring and Evaluation Plan for Malarial Control and Elimination 2011–2020
APLMA	Yes				Cochair, APLMA
Artemisinin resistance detected	Yes				
WHO rapid-alert system on SSFFC medicines	Actively participating	Not applicable			Actively participating

### ANNEX 3. PROMOTING THE QUALITY OF MEDICINES ACTIVITIES IN THE GMS

Promoting the Quality of Medicines (PQM) is a global program funded by the US President’s Malaria Initiative (PMI) and USAID and implemented by the US Pharmacopeial Convention (USP). PQM program objectives are to—

- Strengthen quality assurance (QA) and quality control (QC) systems
- Increase the supply of quality assured medicines
- Combat the availability of substandard and counterfeit medicines
- Provide technical leadership and global advocacy

It continues work started in 2003 under its predecessor Drug Quality and Information program, funded by USAID.

PQM works in nine countries in Asia, including five GMS countries.

Country	PQM Activities
Cambodia	Assessing QA/QC systems and capacity Maintaining and expanding a Medicines Quality Monitoring (MQM) program as part of postmarketing surveillance Building capacity of the Official Medicine Control Laboratory Conducting onsite training on test methods, Minilab® use, GMP standards, good distribution practices, and good storage practices Raising awareness through communication campaigns Conducting research Establishing a pharmacovigilance program Assisting INTERPOL on enforcement activities Presenting workshops on medicine quality Testing stored avian influenza medicines and mapping distribution channels Providing technical assistance toward ISO 17025:2005 accreditation
Lao PDR	Assessing QA/QC systems and capacity Establishing an MQM program as part of postmarketing surveillance Building capacity of the Official Medicine Control Laboratory Conducting onsite training on test methods, Minilab® use, GMP standards, good distribution practices, and good storage practices Assisting INTERPOL on enforcement activities Presenting workshops on medicine quality Testing stored avian influenza medicines and mapping distribution channels Raising awareness through communications campaigns Providing technical assistance toward ISO 17025:2005 accreditation
Myanmar	Assessing QA/QC systems and capacity
Thailand	Assessing QA/QC systems and capacity Establishing a MQM program as part of postmarketing surveillance Building capacity of the Official Medicine Control Laboratory Conducting onsite training on test methods, Minilab® use, GMP standards, good distribution practices, and good storage practices Conducting research Providing services with a Center of Excellence Assisting INTERPOL on enforcement activities

<b>Country</b>	<b>PQM Activities</b>
	Presenting workshops on medicine quality Testing stored avian influenza medicines and mapping distribution channels
Vietnam	Assessing QA/QC systems and capacity Establishing an MQM program as part of postmarketing surveillance Conducting onsite training on test methods, Minila ® use, GMP standards, good distribution practices, and good storage practices Preparing for WHO laboratory prequalification application Presenting workshops on medicine quality Testing stored avian influenza medicines and mapping distribution channels

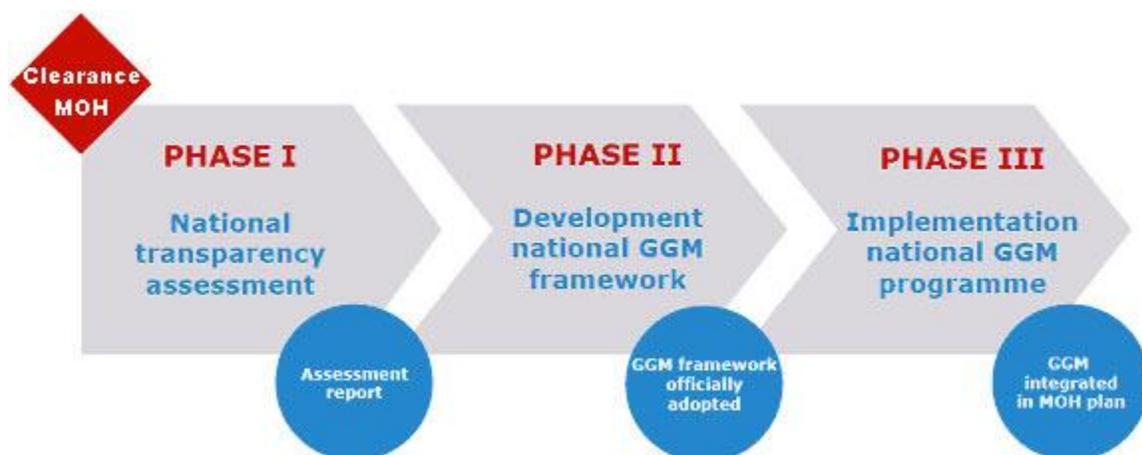
Source: USP. PQM: Promoting the Quality of Medicines in Developing Countries website.  
<http://www.usp.org/global-health-impact-programs/promoting-quality-medicines-pqmusaid>

## ANNEX 4. WHO GOOD GOVERNANCE FOR MEDICINES

The Good Governance for Medicines (GGM) program was launched in 2004 with the goal of contributing to health systems strengthening and preventing corruption by promoting good governance in the pharmaceutical sector. The concept underlying the GGM approach is that by supporting policy makers and national officials to understand where the strengths and weaknesses lie in national pharmaceutical systems, appropriate interventions can be developed and applied.

A three-step approach gives a framework to the project, but these steps may be adapted to suit the specific country situation.

- **Phase I: National assessment of transparency and potential vulnerability to corruption**  
An assessment is carried out using the WHO standardized assessment instrument, which focuses on central functions of the pharmaceutical regulation and supply systems.
- **Phase II: Development of a national program on Good Governance for Medicines**  
Based on the national assessment results, the basic components of the GGM program are defined through a nationwide consultation process with key stakeholders and lessons from other country experiences. These components may include an ethical framework and code of conduct, regulations and administrative procedures, collaboration mechanisms with other good governance and anti-corruption initiatives, whistle-blowing mechanisms, sanctions for reprehensible acts and a GGM implementing task force.
- **Phase III: Implementing the national Good Governance for Medicines program**  
The national GGM program is a fully integrated institutional learning process, facilitating the application of new administrative procedures for increased transparency/accountability and the development of leadership capabilities.



**Figure 4.1 The three phases of the Good Governance for Medicines process**

Source: WHO. Good Governance for Medicines Approach.

<http://www.who.int/medicines/areas/policy/goodgovernance/implementation/en/>.

## ANNEX 5. SELECTED GPARC RECOMMENDATIONS

The Global Plan for Artemisinin Resistance Containment (GPARC) recommendation is to aggressively eliminate monotherapies and poor-quality drugs in tier I areas and actively eliminate them in tier II areas.

Tier I: Areas for which there is credible evidence of artemisinin resistance

Tier II: Areas with significant inflows of people from tier I areas, including those immediately bordering tier I

Tier III: Areas with no evidence of artemisinin resistance and limited contact with tier I areas

Selected recommendations related to regulation and access to affordable, quality-assured artemisinin-based combination therapy include—

- Encourage the manufacture and use of fixed-dose combinations and provide preferential funding for such formulations in areas where the recommended treatment is available as a fixed-dose combination.
- Withdraw marketing authorization for oral artemisinin-based monotherapies and remove these medicines from the essential medicines list.
- Interrupt importation and distribution of oral artemisinin-based monotherapies.
- Commit public providers and retailers to ensure effective withdrawal and increase other activities to encourage removal.
- At global level, work with countries and pharmaceutical companies to stop manufacture and export.
- At global level, put pressure on countries in which there are illegal drug manufacturers to stop production and distribution of substandard and counterfeit drugs.
- Provide incentives and tools to retailers to identify and remove poor-quality drugs from their facilities.
- Conduct quality control screening and field operators to remove poor-quality products.

*Source:* WHO. *Global Plan for Artemisinin Resistance Containment*. Geneva: WHO; 2011.

## ANNEX 6. EMERGENCY RESPONSE TO ARTEMISININ RESISTANCE: PRIORITY ACTIONS

- I. Full coverage with high-quality interventions in priority areas
  - Action 1. Increase quality of and coverage with key interventions in the private and public sector
  - Action 2. Engage health and nonhealth sectors to reach high-risk populations
  - Action 3. Implement measures to ensure continuous and uninterrupted supply of essential commodities
  
- II. Tighter coordination and management of field operations
  - Action 4. Strengthen coordination of field activities
  - Action 5. Monitor staff performance and increase supportive supervision
  - Action 6. Promote the integration of resistance containment, in malaria elimination and control efforts while maintain a focus on resistance
  
- III. Better information for artemisinin resistance containment
  - Action 7. Improve collection and use of data to target operations
  - Action 8. Fast-track priority research and refine tools for containment and elimination
  - Action 9. Increase monitoring of antimalarial therapeutic efficacy and strengthen the therapeutic efficacy networks worldwide
  - Action 10. Increase monitoring of insecticide resistance
  
- IV. Regional oversight and support
  - Action 11. Enhance accountability and exchange of information
  - Action 12. Build political support at all levels
  - Action 13. Facilitate progress and regional cooperation on pharmaceutical regulation, production, export and marketing
  - Action 14. Create a regional community of practice on approaches to high-risk and hard-to-reach populations
  - Action 15. Support cross-border coordination

*Source: WHO. Emergency Response to Artemisinin Resistance in the Greater Mekong Subregion: Regional Framework for Action 2013–2015. Geneva: WHO; 2013.*

## ANNEX 7. APLMA MALARIA MEDICINES REGULATORS' GROUP RECOMMENDATIONS

- I. Ensuring that the quality of malaria commodities is consistent with international standards
  1. Implement specific regulatory market authorization actions to improve access to the most appropriate antimalarial medicines and diagnostic tools.
  2. Establish fast-track regulatory approval mechanisms to encourage the market availability of fixed dose combination (FDC) formulations and combinations of new active ingredients.
  3. Implement regulatory actions to improve access to appropriate RDTs for the diagnosis of malaria.
  4. Undertake action to withdraw inappropriate malaria treatments.
  5. Implement communication initiatives to improve quality use of antimalarials.
- II. Removing oAMT and SSFFC medical products
  6. Use the range of regulatory options permitted by law in each country to a greater extent, and where required strengthen the legal basis of regulatory powers, to support the halt of oAMTs along the supply chain.
  7. Implement systematic programs for monitoring the quality of ACTs, particularly in districts where artemisinin resistance has been detected or is suspected.
  8. Use robust commodity market assessment and monitoring methods to inform regulatory policy and practice across the region.
- III. Strengthening regulatory capacity and regional collaboration of NMRAs with responsibility for malarial drugs and diagnostics
  9. Strengthen regional collaboration between NMRAs to build capacity and increased convergence of good regulatory practices.
  10. Where possible, work through existing national and regional initiatives to deliver capacity building support to assist countries with monitoring and testing the quality of malaria diagnostics and medicines.
  11. Encourage national governments to provide adequate support, powers, and investment to NMRAs.
- IV. Improving access to and supply of quality preventative measures and therapies, particularly for high-risk groups
  12. NMRAs work more proactively with other government agencies, malaria control programs, and stakeholders, recognizing the particular vulnerability of mobile and remote populations and the prevalence of artemisinin resistance in border regions.

*Source:* Skerrit J, Wiseman M, Papthanasiou P, Hart A, de Gooyer H. *Malaria Medicines Regulators' Group Report*. Asia Pacific Leaders Malaria Alliance (APLMA), Access to Quality Medicines and Other Technologies Task Force; June 3, 2014.

<http://aplma.org/upload/resource/Papers/malaria%20medicines%20regulators%20group%20report.pdf>.

## **ANNEX 8. ACTIONS TO IMPLEMENT APLMA MALARIA MEDICINES REGULATORS' GROUP RECOMMENDATIONS**

1. Implement specific regulatory market authorization actions to improve access to the most appropriate antimalarial medicines and diagnostic tools.

### Immediate

- 1.1. Ensure all relevant WHO prequalified essential medicines and diagnostic tools have market authorization for malaria-affected countries.
- 1.2. Fast-track regulatory evaluation for market authorization of equally effective but less expensive “partner” antimalarial components of ACTs.
- 1.3. NMRAAs to work with National Malarial Control Programs and National Procurement Agencies (as relevant) to develop quality standards consistent with nationally/internationally recognized quality requirements for antimalarial medicines and diagnostic tools to support quality assurance during procurement and that only products of appropriate quality are procured, irrespective of funding source.

### Later

- 1.4. Work with industry and public health systems to ensure appropriate ACTs, particularly those required to address current or potential resistance to artemisinin, have market authorization in each affected country.
  - 1.5. Ensure that only malaria drugs at the correct doses recognized in clinical treatment guidelines are approved by NMRAAs.
  - 1.6. For countries where regulatory market authorization and postmarket powers currently extend only to medicine use within the public health system, extend the powers to medicines used in the private and informal sectors.
2. Establish fast-track regulatory approval mechanisms to encourage the market availability of FDC formulations and combinations of new active ingredients.

### Immediate

- 2.1. Establish fast-track regulatory approval mechanisms to encourage the market availability of FDC formulations (rather than co-blistering of two tablets/capsules) and combinations of new active ingredients, to improve patient compliance and provide flexibility for addressing changes in antimalarial resistance.

3. Implement regulatory actions to improve access to appropriate RDTs for the diagnosis of malaria.

### Later

- 3.1. Develop more consistent national regulatory frameworks to ensure that RDTs are assessed to nationally/internationally agreed standard for performance and stability, and that instructions for use are appropriate.

3.2. Develop a capacity building program to establish local mechanisms for assessing diagnostics and their quality management by building on WHO prequalification of in vitro diagnostics and their assessments.

4. Undertake action to withdraw inappropriate malaria treatments.

Immediate

4.1. Where possible, NMRAs to withdraw the registration of medicines that are still registered for malaria but no longer recommended because of safety, known resistance, or lack of efficacy.

4.2. In collaboration with public health authorities, NMRAs to review the drugs currently authorized for supply to ensure the registered/recommended doses are appropriate and consistent with the WHO treatment guidelines/National Drug Policy on Malaria of the respective country. Licenses to be revoked for products containing subtherapeutic levels of antimalarials or with therapeutically irrational combinations of active ingredients.

Later

4.3. Ensure that ineffective malaria medicines are no longer included in national formularies and/or national essential medicines lists

4.4. Discourage (and deregister where possible) “cocktails” of inappropriate medicines (such as mixtures of analgesics, vitamins, or antibiotics) used for malaria prevention or treatment.

5. Implement communication initiatives to improve quality use of antimalarials.

Later

5.1. Strengthen communication about the appropriate use of registered products to doctors, pharmacy and clinic workers, and patients (including mobile and migrant populations) both through formal approval of product information/consumer medicines information as well as broader public communication activities.

Removing oAMT and SSFFC medical products

6. Use the range of regulatory options permitted by law in each country to a greater extent, and where required strengthen the legal basis of regulatory powers, to support the halt of oAMTs along the supply chain.

Immediate

6.1. NMRAs to ensure sufficient regulatory power exists and enforcement actions are implemented to allow for—

- Forbidding or withdrawing the market authorization for oAMT
- Suspension of manufacture and import licenses
- Forbidding or withdrawing export licenses for manufacturers of oAMT products
- Active monitoring of premises of oAMT and SSFFC malaria medicines and diagnostics (including wholesale and retail pharmacy outlets as well as any facility selling malaria medicines and diagnostics)
- Recall and destruction of oAMT and SSFFC finished products

Later

6.2. Develop communication materials and programs aimed at consumers, health care providers, and industry about the hazards of oAMTs and substandard and counterfeit medicines, including how to report SSFFC products to authorities.

7. Implement systematic programs for monitoring the quality of ACTs, particularly in districts where artemisinin resistance has been detected or is suspected.

Immediate

7.1. Increase postmarket surveillance of ACTs across the full distribution chain (for example, manufacturers, importer, wholesalers, health posts), including periodic retesting of already licensed products.

7.2. Increase the focus on product shelf life and storage of medicines and RDTs as a contributor to substandard performance.

7.3. Regularly and systematically report all incidents of suspected cases of SSFFC medicinal products and actions taken through the WHO Rapid Alert System.

7.4. Ensure adequate access by NMRAs to accredited analytical testing facilities. Where appropriate facilities do not exist (and for more complex analyses), develop mechanisms for sending samples to accredited testing facilities in partner countries for confirmatory testing.

7.5. Work with regional governments to streamline timeframes through customs agencies for the importation of suspect samples for full laboratory testing in accredited regional laboratories so that timely regulatory action is possible.

8. Use robust commodity market assessment and monitoring methods to inform regulatory policy and practice across the region.

8.1. Use rapid supply chain assessments and targeted outlet surveys to generate a consistent baseline picture of the total antimalarial market across the region.

8.2. Analyze baseline data to ascertain if time-limited price subsidy interventions are warranted (in conjunction with regulatory enforcement) to accelerate displacement of oAMTs and improve access (availability, market share, and price) to quality assured ACT and RDTs.

Later

8.3. Assess the impact of interventions, regulatory and market-based, on access to quality antimalarials and diagnostic relative to SSFC products through outlet surveys and real-time monitoring.

8.4. Strengthen regulatory capacity and regional collaboration of NMRAs with responsibility for malarial drugs and diagnostics.

9. Strengthen regional collaboration between NMRAs to build capacity and increased convergence of good regulatory practices.

Immediate

- 9.1. Fast-track national registration of an agreed list of WHO prequalified medicines through sharing of assessment reports generated by the WHO prequalification process if permissible under the regulatory framework of the respective country and work sharing on drug applications between countries.
  - 9.2. Develop mechanisms for collaboration between regulators on GMP inspections of local manufacturers of antimalarials.
  - 9.3. Strengthen collaboration with major “stringent” regional regulators and WHO prequalification programs, and increase investment in training programs.
  - 9.4. Harmonize regulatory requirements and processes for market authorization of RDTs.
  - 9.5. Support cross-border coordination of regulatory and enforcement actions, especially as they relate to high-risk and hard-to-reach populations.
  - 9.6. Strengthen local and regional exchange of intelligence on counterfeit and substandard products. Recognize and endorse the WHO Member State Mechanism on SSFFC work plan, identifying priority actions and resources for NMRA participation. Translate SSFFC norms and standards into use.
  - 9.7. Encourage multicountry rather than single country involvement in major regional and donor antimalarial initiatives. Existing processes and governance mechanisms should be utilized wherever possible.
10. Where possible, work through existing national and regional initiatives to deliver capacity building support to assist countries with monitoring and testing the quality of malaria diagnostics and medicines.

Immediate

- 10.1. Strengthen capacity for postmarket surveillance of malaria diagnostics and medicines across the distribution chain, including manufacturers, importers, wholesales and health posts. Specific actions include—
  - Strengthening pharmacovigilance capacity, including the reporting of treatment failure and adverse events
  - Oversight of manufacturers and the supply chain through greater GMP capacity and other mechanisms to strengthen inspection capacity
  - Improved laboratory testing capacity, and use of consistent laboratory accreditation standards (including ISO or WHO prequalification) for testing of suspect products
  - Training in regulatory compliance and enforcement.

Later

- 10.2. Strengthen market authorization roles for both medicines and RDTs by increasing the capacity of NMRAs to work in collaboration with the WHO prequalification program.
- 10.3. Explore the potential for formal work sharing between regional NMRAs.
- 10.4. Develop regulatory frameworks for market authorization of in vitro diagnostics (which include RDTs).
- 10.5. Develop capacity of NMRAs to produce communication materials and education programs on appropriate use of antimalarials and diagnostics and the dangers of poor-quality medicines.

10.6. Evaluate portable technologies such as the US FDA rapid CD-3 device for the detection of counterfeit medicines.

11. National governments to provide adequate support, powers, and investment to NMRAs

Immediate

11.1. Strengthen and formalize the links between NMRAs, public health authorities, and national malaria control programs. NMRAs and national malaria control programs to ensure these links include involvement of both functions at appropriate national and regional malaria meetings.

11.2. As a matter of urgency, review the adequacy of powers available to NMRAs, with a view to putting in place powers with similar intent in difference countries across the region, to enable coordinated response, for example, to SSFFC and oAMT medicines.

11.3. Ensure NMRAs functions receive a sufficient share of funding within national budgets and international programs to enable the recommendations to be adequately implemented.

Later

11.4. Investment in technical capacity building within NMRAs.

12. NMRAs to more proactively work with other government agencies, malaria control programs, and stakeholders, recognizing the particular vulnerability of mobile and remote populations and the prevalence of artemisinin resistance in border regions.

Later

12.1. NMRAs to work with—

- Public health authorities when they receive information on adverse events, treatment failure, and/or resistance to particular medicines
- Police where smuggling of oAMTs across borders is suspected
- National medical research centers, to develop strategies for the use of diagnostic tests to detect artemisinin resistance markers and integrate guidelines for alternative therapy into medicines product and prescribing information as required

12.2. Strengthen the involvement of NMRAs in communicating and managing shortages (stock-outs) of malaria medicines and rapid diagnostic kits, for example, by implementing streamlined regulatory approaches to facilitate short-term access to antimalarials that have been approved by a recognized regulator in another country for substitution.

*Source:* Skerrit J, Wiseman M, Papthanasiou P, Hart A, de Gooyer H. *Malaria Medicines Regulators' Group Report*. Asia Pacific Leaders Malaria Alliance (APLMA), Access to Quality Medicines and Other Technologies Task Force; June 3, 2014.

<http://aplma.org/upload/resource/Papers/malaria%20medicines%20regulators%20group%20report.pdf>.

## ANNEX 9. USP/PQM ACTIVITIES THAT SUPPORT IMPLEMENTATION OF GPARC AND APLMA REGULATORS' GROUP RECOMMENDATIONS

Recommendations	USP/PQM Support to Country System Capacity
<b>GPARC</b>	
1. Manufacture and use of fixed-dose combinations	USP/PQM GMP and prequalification support
2. Interrupt importation and distribution of AMT	
3. Incentives and tools to retailers to identify and remove poor-quality drugs from their facilities	
4. Conduct quality control screening and field operators to remove poor-quality products	USP/PQM MQM programs
<b>APLMA</b>	
1. Implement specific regulatory market authorization actions to improve access to the most appropriate antimalarial medicines and diagnostic tools	
2. Establish fast-track regulatory approval mechanisms to encourage the market availability of FDC formulations and combinations of new active ingredients	USP/PQM prequalification support
3. Implement regulatory actions to improve access to appropriate RDTs for the diagnosis of malaria	
4. Undertake action to withdraw inappropriate malaria treatments	
5. Implement communication initiatives to improve quality use of antimalarials	USP/PQM communications campaigns
6. Use the range of regulatory options permitted by law in each country to a greater extent, and where required strengthen the legal basis of regulatory powers, to support the halt of artemisinin-based monotherapies along the supply chain	
7. Implement systematic programs for monitoring the quality of ACTs, particularly in districts where artemisinin resistance has been detected or is suspected	USP/PQM MQM programs
8. Use robust commodity market assessment and monitoring methods to inform regulatory policy and practice across the region	
9. Strengthen regional collaboration between NMRAs to build capacity and increased convergence of good regulatory practices	USP/PQM BREMERE
10. Where possible, work through existing national and regional initiatives to deliver capacity building support to assist countries with monitoring and testing the quality of malaria diagnostics and medicines	USP/PQM quality control laboratory capacity building USP/PQM MQM programs
11. National governments to provide adequate support, powers, and investment to NMRAs	
12. NMRAs to more proactively work with other government agencies, malaria control programs, and stakeholders, recognizing the particular vulnerability of mobile and remote populations and the prevalence of artemisinin resistance in border regions.	

## ANNEX 10. FINDINGS FROM REGIONAL AND GLOBAL PERSPECTIVES

All countries in the Greater Mekong subregion have medicine regulatory organizations, infrastructure, and relevant regulations to deal with the problems of substandard and fake antimalarials in the market. Despite progress in recent years, most of them still encounter problems of enforcement caused by insufficient human resources capacity and financial resources. Especially in Cambodia, Lao PDR, and Myanmar, where the regulatory systems are less functional compared with the other GMS countries such as Thailand, a need exists to adequately address regulatory minimum standards.

A number of relevant regional and global initiatives have been implemented in Greater Mekong countries to improve access to good quality antimalarials. Basically, they are focused either on strengthening the regulation and quality assurance of antimalarials (regulatory approach) or on improving access, availability, and affordability of antimalarials in the community through public and private sectors (access approach).

Among different initiatives in the region, the PQM/USAID project can be considered as a successful initiative, reducing the incidence of product failure in quality surveillance at sentinel sites, although the national governments of Greater Mekong countries have only limited funding and capacities in scaling up to other uncovered high-risk areas.

PSI has successfully distributed good-quality subsidized ACTs in Cambodia and Myanmar and has improved access and availability of these medicines in the market. Expanding the experience in Cambodia and Lao PDR to other GMS countries would help improve access to good-quality ACT antimalarials and limit the availability of artemisinin monotherapy

Good governance and avoiding conflict of interest in registration, selection, and procurement, and making these processes transparent, are critical in improving access to good-quality antimalarials. However, only Thailand and Lao PDR among the GMS countries have implemented the WHO Good Governance for Medicines Programme.<sup>48</sup>

We recommend the continuation, improvement, and expansion of medicine quality monitoring, training of medicine regulatory authorities (MRAs) on enforcement and national quality control laboratory, and improvement of public awareness on the importance of quality medicines. We also recommend the improvement and expansion of subsidy of good-quality ACT antimalarials through private sectors in improving access to good-quality antimalarials in Greater Mekong countries.

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<sup>48</sup> WHO. *Good Governance for Medicines: Progress Report 2010*. Geneva: WHO; 2010.  
<http://cdrwww.who.int/medicines/areas/policy/goodgovernance/GGM2010ProgressReport.pdf>.

## **Key Findings**

### ***Past and Ongoing Regional and Global Initiatives***

In recent years, a number of relevant initiatives have been undertaken to address the issues of access to good-quality antimalarials at subregional, regional, and global levels, with varying degrees of effect.

#### *Subregional Initiatives*

### **1. Emergency Response to Artemisinin Resistance in the GMS, WHO Regional Framework for Action, 2013–2015<sup>49</sup>**

This is a collective strategy agreed by national governments in GMS countries and partners, with a framework for actions in priority areas, to contain malaria resistance to current medicines in the GMS, where 15 actions were recommended to be undertaken by national governments and partners. These include (1) increase coverage of and with key interventions in the public and private sector; (2) engage health sector and non-health-sector to reach high-risk populations; (3) implement measures to ensure continuous and uninterrupted supply of essential commodities; (4) strengthen coordination of field activities; (5) monitor staff performance and supportive supervision; (6) promote the integration of resistance containment in malaria elimination and control measures, while maintaining focus on resistance; (7) improve collection and use of data for target operation; (8) fast-track priority research and refine tools for containment and elimination; (9) increase monitoring of antimalarial therapeutic efficacy and strengthen therapeutic efficacy network; (10) increase monitoring of insecticide resistance; (11) enhance accountability and exchange of information; (12) build political supports at all levels; (13) facilitate progress and regional cooperation on pharmaceutical regulation, production, and export; (14) create a regional community of practice on approaches to high-risk and hard-to-reach populations; and (15) support cross-border coordination.

A regional hub has been set up by the WHO in Cambodia to coordinate the implementation and to provide technical support for the implementation. Relevant indicators have been devised to monitor the progress. A progress report based on these indicators is to be made annually. Elimination of monotherapies and substandard-quality medicines is one of the important components of the strategy. The framework is also in line with the World Health Assembly Resolution, WHA 60.18, calling for removal of artemisinin-based monotherapies from the market.<sup>50</sup>

#### **Potential impacts**

It is a comprehensive framework of actions agreed by national governments. If implemented consistently, the framework will have a positive impact because the strategy consists of relevant

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<sup>49</sup> WHO, *Emergency Response to Artemisinin Resistance in the Greater Mekong Subregion: Regional Framework for Action 2013–2015*. Geneva: WHO; 2013. <http://www.who.int/malaria/publications/atoz/9789241505321/en/2013>.

<sup>50</sup> WHO. Sixtieth World Health Assembly, WHA 60.18. Malaria, including proposal for establishment of World Malaria Day. 2007. [http://apps.who.int/gb/ebwha/pdf\\_files/WHA60/A60\\_R18-en.pdf?ua=1](http://apps.who.int/gb/ebwha/pdf_files/WHA60/A60_R18-en.pdf?ua=1).

actions addressing risk factors for artemisinin resistance especially in the Greater Mekong countries. The framework can also serve as a tool for coordination between partners/donors and guidance for the Mekong countries in their intensified effort to contain artemisinin resistance.

### Gaps

During the interviews, the respondents who are directly involved in coordinating the implementation of the strategy mentioned that the issue of funding is a serious impediment in its implementation. Although the strategy is endorsed by national governments of GMS countries, they do not automatically allocate funding for its implementation. In a fact sheet issued after launching the strategy, the WHO mentioned that “support is needed at the very highest levels of government—an element that is largely missing at the moment.”<sup>51</sup> Efforts are being undertaken by the WHO to apply funding from the Global Fund and other sources.

## 2. Promoting the Quality of Medicines Program in South East Asia (PQM/USP/USAID)<sup>52,53</sup> Including GMS Countries

One of the successful initiatives implemented in Southeast Asia with a positive impact on medicine product quality, this program started in 2003 and is implemented in GMS countries (Cambodia, Myanmar, Lao PDR, Thailand, Vietnam), Indonesia, and the Philippines. This initiative covers a wide range of activities, which include the following—

1. **Build capacity of MRAs.**
  - Establish dynamic postmarketing surveillance.
  - Provide technical assistance in medicine registration and dossier evaluation.
  - Develop technical guidelines to strengthen pharmaceutical systems.
  - Help manufacturers meet GMP standards and achieve WHO prequalification.
  - Train inspectorate in GMP inspection.
  - Establish regional centers of excellence network in medicine quality assurance.
2. **Strengthen QC labs to meet international standards of practices.**
  - Train staff in analytical techniques and QC procedures.
  - Provide lab equipment and training in its proper use and maintenance.
  - Provide reference materials, reagents, and other needed chemicals.
  - Provide technical assistance toward ISO 17025 accreditation and WHO prequalification of laboratories
3. **Conduct operational research on medicines quality.**
  - Conduct studies on medicine quality in public and private health facilities.

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<sup>51</sup> WHO. Artemisinin resistance in the Greater Mekong subregion.

[http://www.wpro.who.int/mvp/documents/docs/Artemisinin\\_resistance\\_fact\\_sheet.pdf](http://www.wpro.who.int/mvp/documents/docs/Artemisinin_resistance_fact_sheet.pdf).

<sup>52</sup> USAID/USP. Promoting the Quality of Medicines (PQM) Program in South East Asia. May 2012.

[http://www.usp.org/sites/default/files/usp\\_pdf/EN/fact\\_sheet-southesast\\_asia-apr\\_11\\_2013.pdf](http://www.usp.org/sites/default/files/usp_pdf/EN/fact_sheet-southesast_asia-apr_11_2013.pdf).

<sup>53</sup> USP/PQM. *Strengthening National Capacity in Medicines Quality: Five-Year Summary (2005–2009) Promoting the Quality of Medicines Program in Southeast Asia and the Philippines*. Rockville, MD: USP; 2010.

[http://www.usp.org/sites/default/files/usp\\_pdf/EN/PQM/RDMARReport.pdf](http://www.usp.org/sites/default/files/usp_pdf/EN/PQM/RDMARReport.pdf).

- Investigate quality of high-priority essential medicines in border areas.
4. **Monitor medicine quality and use data to support enforcement.**
    - Help establish regional surveillance sites and equip with Minilabs to screen medicines for quality.
    - Train site staff in sampling techniques, test methods, and data reporting.
    - Collect evidence-based data and make results available in a publicly accessible database.
    - Facilitate regional network to act on substandard and counterfeit medicines detected.
  5. **Raise awareness about how medicines quality affects public health.**
    - Create public service announcements and videos on the dangers of substandard and counterfeit medicines.
    - Conduct communication campaigns advocating medicine quality.
    - Publish articles, reports, and promotional materials on medicine quality issues and importance of buying from approved outlets.

### **Impacts**

Based on the evaluation report, the project has contributed to consistent reduction of product failure for antimalarials and other essential medicines from 3.5% (2005) to 1.4% (2010), better quality surveillance, and enforcement. The program also clearly helps improve capacities of quality surveillance and laboratory testing.

### **Gaps**

Limited government funding in scaling up to other high-risk areas, the medicine quality monitoring, and sustaining the program in the future because the funding comes from external sources.

### **3. Building Regional Expertise in Medicines Regulation, Information Sharing, Joint Investigation and Enforcement (BREMERE), an intersectoral initiative for GMS (PQM/USP/USAID, 2012)<sup>54</sup>**

This is a new initiative to strengthen interagency and intercountry collaboration and timely exchange of information between GMS countries and is supported by PQM/USP/USAID.

The objectives of this collaboration include the following—

- Build capacity through sharing of regional expertise among members, provision of training (e.g., in QA/QC, GMP, BA/BE) by partners and members, and technical/financial support (e.g., testing of special cases of poor-quality medicines) from partners to create a regional “pool of experts” who share information and expertise in medicines regulation, registration, postmarketing surveillance, and enforcement.

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<sup>54</sup> USAID/USP/Promoting Quality of Medicines. Collaborative focus on fight against counterfeit, substandard medicines in Greater Mekong sub-region. Rockville, MD; 2012.  
<http://us.vocuspr.com/Newsroom/ViewAttachment.aspx?SiteName=uspharm&Entity=PRAsset&AttachmentType=F&EntityID=109560&AttachmentID=031e3acf-79b3-471d-909d-bb9191e41d98>.

- Strengthen support and collaboration in the field of medicines quality and regulation between political bodies (ministries) and technical bodies (MRAs; WHO at the country, regional, and central levels) within each country and the region.
- Improve the processes among regulatory/technical agencies and other involved sectors (e.g., customs, police/Interpol, prosecutors) at the national and regional levels for—
  - Enforcement (e.g., improving existing protocols and measures according to best practices)
  - Information sharing (e.g., optimizing use of and access to existing medicines quality databases and/or building a new database, if necessary)
  - Collective investigation (e.g., reporting alleged counterfeiters to representatives of the claimed countries of origin and agreeing upon procedures)

The collaboration does not act as a policing body or as an enforcement body. It does not replace the existing administrative or regulatory processes, procedures, or practices of the countries in the region. It simply provides an avenue for cooperation and collaboration between and among country agencies in the area of medicines quality. In the long run, it could become a good model for GMS intercountry and interagency collaboration.

### **Potential impacts and gaps**

The program would help improve strengthening medicines regulation and quality surveillance through intercountry and interagency collaboration and intercountry exchange of information.

This is a new initiative of less than two years. According to one interviewee who is involved in the formation of the initiative, only a few cases have been shared. However, the exchange of information seems promising.

### **4. Operation STORM, a joint operation to combat counterfeit medicines (INTERPOL, WHO, World Customs Organization, and national authorities, 2006, 2008)<sup>55</sup>**

This is a joint collaborative activity led by INTERPOL, involving WHO and the World Customs Organization, national MRAs, national police, and customs organizations, to undertake simultaneous enforcement operation against counterfeit medicines. The operations were conducted in all Mekong countries and Indonesia.

### **Impacts**

It is an effective joint operation involving intercountry collaboration, as well as interagency collaboration within country, which is very important in combating counterfeit medicine. In most GMS countries, MRAs are not endowed with police power or sufficient expertise and facilities to undertake forensic investigation. The initiative also provides training for MRAs, police, and custom officials.

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<sup>55</sup> Interpol, IMPACT, and WHO. Operation Storm: final report. Undated. <http://www.interpol.int/Crime-areas/Pharmaceutical-crime/Operations/Operation-Storm>.

## Gaps

It is a kind of ad hoc enforcement operation with simultaneous inspections at various points such as customs, pharmacy distribution points, and outlets. MRAs in Mekong countries do not have police power in combating substandard and fake products, so they always need to collaborate closely with police. There is plenty of room for improvement of collaboration between regulatory authorities and law enforcement agencies. Respondents, especially from Cambodia, mentioned that lack of support from policy makers reflecting lack of commitment, lack of punishment to perpetrators, and existence of conflict of interests is implicated with issues concerning counterfeit drugs.

## 5. The President's Malaria Initiative in the Greater Mekong Subregion<sup>56,57,58,59,60</sup>

PMI is part of the Global Health Initiative in combating malaria. As established when PMI was started in 2005, the US government measures progress toward achieving national and international goals and targets that result from the combined efforts of host-country governments and other partners involved in malaria control in that country, without attempting to attribute reduction of mortality or morbidity to the efforts of only the US government. Although it started with a focus on 15 African countries, in 2009 PMI was expanded to other regions.

In Southeast Asia and the Americas, where antimalarial multidrug resistance is one of the greatest threats to global malaria control, the US government works with national malaria control programs and partners to strengthen efforts to contain the spread of multidrug-resistant *Plasmodium falciparum* malaria. This is expected to be accomplished by—

- Supporting well-functioning antimalarial drug resistance surveillance networks in each country in the region
- Establishing national systems to monitor the quality of antimalarial drugs as a means of preventing the introduction and dissemination of substandard or counterfeit drugs, which contribute to increased drug resistance

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<sup>56</sup> USAID. The President's Malaria Initiative in the Greater Mekong Sub-Region. July 2012. [http://lowermekong.org/sites/default/files/pdf/USAIDAsia\\_LMI\\_The\\_President%27s\\_Malaria\\_Initiative\\_July2012\\_0.pdf](http://lowermekong.org/sites/default/files/pdf/USAIDAsia_LMI_The_President%27s_Malaria_Initiative_July2012_0.pdf).

<sup>57</sup> President's Malaria Initiative—Greater Mekong SubRegion Planned Obligations FY 2011. Revised July 14, 2014. [http://www.pmi.gov/docs/default-source/default-document-library/malaria-operational-plans/fy11/mekong\\_tables-fy11.pdf?sfvrsn=4](http://www.pmi.gov/docs/default-source/default-document-library/malaria-operational-plans/fy11/mekong_tables-fy11.pdf?sfvrsn=4).

<sup>58</sup> USAID PMI. *President's Malaria Initiative: Malaria Operational Plan—FY 2012, Greater Mekong Sub-Region*. [http://www.pmi.gov/docs/default-source/default-document-library/malaria-operational-plans/fy12/mekong\\_mop\\_fy12.pdf?sfvrsn=6](http://www.pmi.gov/docs/default-source/default-document-library/malaria-operational-plans/fy12/mekong_mop_fy12.pdf?sfvrsn=6).

<sup>59</sup> USAID PMI. *President's Malaria Initiative: Greater Mekong Sub-Region, Malaria Operational Plan FY 2013*. [http://www.pmi.gov/docs/default-source/default-document-library/malaria-operational-plans/fy13/mekong\\_mop\\_fy13.pdf?sfvrsn=6](http://www.pmi.gov/docs/default-source/default-document-library/malaria-operational-plans/fy13/mekong_mop_fy13.pdf?sfvrsn=6).

<sup>60</sup> USAID PMI. *President's Malaria Initiative: Greater Mekong Subregion, Malaria Operational Plan FY 2014*. [http://www.pmi.gov/docs/default-source/default-document-library/malaria-operational-plans/fy14/mekong\\_mop\\_fy14.pdf?sfvrsn=12](http://www.pmi.gov/docs/default-source/default-document-library/malaria-operational-plans/fy14/mekong_mop_fy14.pdf?sfvrsn=12).

- Contributing to a further reduction in the level of transmission of *P. falciparum* malaria and the number of reported cases in the Greater Mekong Region and the Amazon Basin, with a goal of elimination of malaria in these areas by 2020<sup>61</sup>

In the Greater Mekong region, PMI funds a partnership project between USAID, the US Centers for Disease Control and Prevention (CDC), USAID/Deliver Project, and USP.

Since 2011, the PMI program in the GMS has supported national malaria control programs and strengthened management at the national and community levels for containment of drug-resistant malaria. This includes support for commodity supply chain management at national level, improved drug quality, community mobilization, and behavior change communication.

Through this project, the national malaria programs in Cambodia, Myanmar, and Thailand have been supported to establish an effective system to control malaria in the affected border regions with standardized treatment, enhanced interventions, information sharing, and surveillance of disease incidents. Thus the support has been focused on the surveillance network, quality monitoring, and access to quality antimalarials. The project procures RDTs, antimalarials, and other commodities.

### **Impact**

The project helps improve access to the needed antimalarial and other commodities and their quality monitoring, especially in border areas. It has also helped minimize the distribution and use of substandard products and artemisinin monotherapy.

### **6. Population Services International<sup>62,63</sup>**

Population Services International has embarked on an initiative to contain artemisinin resistance in Mekong countries, especially Myanmar and Cambodia, through various activities in the private sector: (1) subsidizing ACTs sold through the private market, (2) advocating to providers to improve prescribing practice, (3) advocating to the national government for legal restrictions on selling single artemisinin, (4) promoting PSI-branded ACTs and other behavior change communication, and (5) training informal drug providers in the use of RDTs and supplying RDTs to these providers.

Whereas most other initiatives focus on a regulatory approach to strengthen national capacities in quality surveillance and enforcement of regulation, this initiative focuses on an access approach to improve access to and availability of good-quality antimalarials and other commodities and their rational use in the private sector. In Cambodia, the initiative started in 2003, and in 2009 it distributed up to 50% of all antimalarials and 75% subsidized, branded, quality-assured AS/MQ in the country. PSI/Cambodia imports the ACTs and distributes them through PSI-employed

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<sup>61</sup> PMI. *Lantos-Hyde United States Government Malaria Strategy 2009–2014*. Washington, DC: USAID; 2010.

<sup>62</sup> GiveWell. Containment of Artemisinin Resistance in Eastern Myanmar (PSI Myanmar Project). <http://www.givewell.org/PSI-Myanmar-Artemisinin-Resistance-Containment#Abouttheproject>.

<sup>63</sup> Montagu D. *Large-Scale Malaria Treatment in the Private Sector: A Case Study of the Cambodian Experience*. San Francisco: The Global Health Group, Global Health Sciences, University of California, San Francisco; 2010. <http://globalhealthsciences.ucsf.edu/sites/default/files/content/ghg/hsi-cambodia-case-study.pdf>.

sales representatives, private outlets, and private pharmacies and clinics. PSI-employed medical detailers provide training, counseling, and support on the appropriate use of ACTs, malaria test kits, and other medicines.

The lesson learned from the experience is that large-scale provision of good-quality ACTs is possible through the private sector. The subsidy should lead to more affordable prices as long as availability and supply can be ensured. In Cambodia, the average price to private outlets (USD 0.29) and recommended average selling price (USD 0.45) allow reasonable commercial incentives for the private outlets. The real selling price may fluctuate because of stock-outs. Therefore, availability and price monitoring are important elements for this initiative.

### **Impact**

Improved access, availability, and affordability of quality-assured antimalarials in the private market.

### **Gaps**

Stock-outs have been identified as a major problem in the project that need to be dealt with through efficient coordination in the supply chain distribution channel, including monitoring of availability and price and an efficient backup support for resupply.

## **7. US Centers for Disease Control and Prevention**

The US CDC has been actively providing technical support to Mekong Malaria Partnership, a partnership between Mekong countries (Cambodia, Lao PDR, Myanmar, China's Yunnan Province, Thailand, and Vietnam), WHO, USAID, and other partners for malaria control. The technical support focuses on providing strategic information to the national malaria control program and a coordinated subregional response for containment of antimalarial resistance.<sup>64</sup> CDC's recent collaborations include providing technical assistance for a qualitative study on the sociocultural context of malaria transmission among mobile and migrant populations in Cambodia, a consultancy to develop and implement cross-border surveillance for malaria between Cambodia and Thailand, and a consultancy to draft a regional strategic framework for malaria control and elimination in the subregion.

CDC has been actively involved in the development of malaria control and elimination strategy in GMS countries. The strategy is an effective tool in coordinating malaria control and responses to malaria drug resistance in Mekong countries, in which the objectives and expected funding from each partner, WHO (WPRO and SEARO), USAID, and other partners, are shown clearly. The *Strategic Plan for Malaria Control and Elimination in the Greater Mekong Subregion: 2010–2014*<sup>65</sup> addresses key issues in malaria control and elimination in the subregion with the monitoring and evaluation (M&E) framework.

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<sup>64</sup> CDC Activities in the Mekong Region. CDC website.

[http://www.cdc.gov/malaria/malaria\\_worldwide/cdc\\_activities/mekong.html](http://www.cdc.gov/malaria/malaria_worldwide/cdc_activities/mekong.html).

<sup>65</sup> WHO and CDC. *Strategic Plan to Strengthen Malaria Control and Elimination in the Greater Mekong Subregion: 2010–2014*. WHO-Mekong Malaria Programme; 2009.

<http://whothailand.healthrepository.org/bitstream/123456789/696/1/Strategic%20Plan%20to%20Strengthen%20Mal>

## Regional Initiatives

### 1. WHO Regional Framework for Action on Access to Essential Medicines<sup>66</sup>

This is a regional framework for actions endorsed by the WHO, member states, and partners, outlining policy principles and actions to ensure access to good-quality medicines and their proper use by providers and consumers. It consists of 11 technical areas in medicines, including medicines regulation and quality assurance, counterfeit and substandard medicines. Some countries use the framework as a guide for developing their strategic plan in the medicines sector.

#### Potential impacts

It is a comprehensive guide for action on improving access to essential medicines, including antimalarials. Countries often use it as a guide in developing their strategic plan.

#### Gaps

Although it is useful as a guide for actions, the implementation may vary from country to country.

### 2. Regional Strategic Response to Malaria and Other Communicable Diseases in Asia and the Pacific<sup>67</sup>

During the East Asia Summit in 2012, East Asian leaders agreed to establish an Asia Pacific Leaders Malaria Alliance (APLMA) to help facilitate control of malaria and other communicable diseases in the Asia Pacific region. The Asian Development Bank then created a special project to provide technical assistance, focusing on regional cooperation for funding for the elimination of malaria and other communicable diseases.

#### Potential impact

The agreement was made by country leaders, thus ensuring higher commitment from countries for better implementation. The focus of the initiative is on financing, where most GMS countries have difficulty. This is a relatively a new initiative; implementation at country levels remains to be followed.

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[aria%20Control%20and%20Elimination%20in%20the%20Greater%20Mekong%20Subregion%20%2020102014.pdf](http://apps.who.int/medicinedocs/documents/s20123en/s20123en.pdf).

<sup>66</sup> WHO Western Pacific Region. *Regional Framework on Access to Essential Medicines in the Western Pacific (2011–2016)*. Geneva: WHO; 2012. <http://apps.who.int/medicinedocs/documents/s20123en/s20123en.pdf>.

<sup>67</sup> 47272-001: Regional Strategic Response to Malaria and Other Communicable Diseases in Asia and the Pacific. Project Data Sheet: Overview. 2013. Asian Development Bank website. <http://www.adb.org/projects/47272-001/main>.

## Global Initiatives

### 1. WHO resolution WHA 60.18 calls for progressive removal of oral artemisinin-based monotherapies from markets<sup>68</sup>

#### Potential impact

The WHO resolution is not mandatory for member states to implement; however, GMS countries, except Myanmar, have taken regulatory action to withdraw artemisinin single products from the market.

#### Gap

Monitoring of available artemisinin monotherapies in the market is necessary.

### 2. WHO Rapid Alert System on SSFFC medical products

This is a global monitoring system to replace the earlier WHO/WPRO Regional Rapid Alert System, which had not been frequently used. This global monitoring and reporting system has already undergone a pilot study in 2012, where GMS countries (Vietnam, Cambodia, etc.) are also active in participating in the system.<sup>69</sup> It serves as a useful global surveillance mechanism. The system needs a strong government commitment to undertake regulatory action at the national levels for any SSFFC medical products identified in the market.

#### Potential impacts

It enables rapid reporting and alerting as well as global monitoring on the distribution of substandard and counterfeit medical products. Relevant follow-up measures can then be undertaken to minimize the risks.

#### Gaps

Follow-up regulatory action after the detection of substandard products would depend on the commitment and capacities of the national medicines regulatory authorities.

### 3. ACTwatch Evidence for Malaria Policy<sup>70,71,72</sup>

ACTwatch is a multicountry project, supported by the Bill and Melinda Gates Foundation, to investigate the availability, price, and volumes of ACT antimalarial medicines and diagnostic tests in Cambodia and Myanmar. Based on the survey in Myanmar, for instance, the availability

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<sup>68</sup> WHO, [http://apps.who.int/gb/ebwha/pdf\\_files/WHA60/A60\\_R18-en.pdf?ua=1](http://apps.who.int/gb/ebwha/pdf_files/WHA60/A60_R18-en.pdf?ua=1).

<sup>69</sup> WHO project for the surveillance and monitoring of SSFFC medical products. *WHO Drug Information* 2013;27(2):97–100. [http://www.who.int/medicines/publications/druginformation/issues/DI\\_27-2\\_SSFFC.pdf](http://www.who.int/medicines/publications/druginformation/issues/DI_27-2_SSFFC.pdf).

<sup>70</sup> ACTwatch website, <http://www.actwatch.info/>.

<sup>71</sup> PSI/Myanmar. *Outlet Survey: Baseline Study: The Republic of the Union of Myanmar 2012 Survey Report*. Yangon, Myanmar: PSI/Myanmar; 2012. <http://www.actwatch.info/sites/default/files/content/outlet-reports/Myanmar%20Baseline%20AMTR%20Outlet%20Survey%20Report.pdf>.

<sup>72</sup> ACTwatch Group and PSI/Cambodia. *Kingdom of Cambodia Household Survey Report, 2011*. Phnom Penh, Cambodia: PSI/Cambodia; 2012. [http://www.actwatch.info/sites/default/files/content/publications/attachments/Cambodia\\_HH%20Baseline\\_ACTwatch\\_06\\_2011.pdf](http://www.actwatch.info/sites/default/files/content/publications/attachments/Cambodia_HH%20Baseline_ACTwatch_06_2011.pdf).

of antimalarials on the day of interview was as follows: 32% of outlets screened reported having at least one antimalarial in stock, including 82% of private health facilities, 79% of pharmacies, 55% of itinerant drug vendors, 15% of general retailers, and 73% of health workers. Availability was relatively low among general retailers (village stores, grocery stores) though they are the most numerous outlet types in the census. A similar survey in Cambodia indicates that the proportion of public health facilities with quality-assured ACTs in stock (as a percentage of facilities with any antimalarial in stock at time of survey visit) is 93.7% (2011), and the proportion of drug stores with quality-assured ACTs in stock (as a percentage of facilities with any antimalarial in stock at time of survey visit) is 56.2% (2011).

### **Potential impact**

The program is very useful in monitoring the availability and prices of antimalarials, especially ACTs, from time to time, where relevant remedial action can be undertaken.

### **Gaps**

The monitoring should be linked with policy and programs that can respond to the findings, to improve supply and to address the price, especially in the private sector.

## **4. Good Governance for Medicines program<sup>73</sup>**

This is a WHO global program aimed at improving transparency and good governance in medicines registration, selection, and procurement, implemented in 27 countries. In strengthening medicines regulatory systems and the supply change management systems, it is important to improve transparency and good governance and to minimize corruption in the pharmaceutical sector. Among Greater Mekong countries, only Lao PDR and Thailand join the program on improving transparency and good governance in medicines. The model of operational process of the program is based on a stepwise approach. Phase 1 is national transparency assessment, measuring the levels of transparency and vulnerability to corruption in medicines registration, selection, and procurement. Phase 2 is development and adoption of national good governance strategy to address weaknesses and issues found in Phase 1. Phase 3 is implementation of the national good governance strategy in medicines. Following national assessment in Lao PDR and in Thailand,<sup>74</sup> based on the 2010 progress report, Lao PDR has been categorized in Phase 2 and Thailand in Phase 3.

### **Potential impacts**

Improving transparency in medicines registration, selection, and procurement will help reduce conflict of interest and corruption in medicine sectors and help improve access to good-quality medicines.

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<sup>73</sup> WHO. *Good Governance for Medicines: Progress Report 2010*. Geneva: WHO; 2010.

<http://cdrwww.who.int/medicines/areas/policy/goodgovernance/GGM2010ProgressReport.pdf>.

<sup>74</sup> AusAID and WHO. *Measuring Transparency in Medicines Registration, Selection and Procurement: Four Country Assessment Studies*. Geneva: WHO; 2006.

<http://www.who.int/medicines/areas/policy/goodgovernance/Transparency4CountryStudy.pdf>.

## **Gaps**

The program needs to be expanded to improve transparency and good governance in medicines registration, selection, and procurement in other GMS countries: Cambodia, Myanmar, and Vietnam. Respondents, especially from Cambodia, mentioned that improving transparency and avoiding conflict of interest are important for Cambodia to deal with issues of counterfeit and substandard products. But dealing with transparency and conflict of interest can become a sensitive issue for a country like Cambodia. Improving transparency and good governance is one of the agreed 10 priorities of the WHO-Vietnam collaboration in medicines for strengthening the medicine regulatory system and medicine supply system (but we have not had the official document on this).

## **Common Gaps in Addressing Access to Good-Quality Antimalarial Medicines**

All countries in the Greater Mekong region have MRA infrastructure that includes quality control laboratories and relevant regulations to deal with the problems of substandard and fake antimalarials in the market. Despite progress in recent years, most of them still encounter problems of enforcement caused by insufficient human resources and technical capacity and lack of financial resources. It is important to keep support for strengthening of regulatory functions up to acceptable standards, especially for Cambodia, Lao PDR, and Myanmar.

## **Scaling Up Effective Intervention**

States in GMS countries have limited financial as well as technical capacities in scaling up medicine quality monitoring and dealing with export of substandard products to other high-risk areas. Most of the initiatives with a positive outcome, for example, the PQM/USAID initiatives,<sup>75</sup> have been externally funded. Thus a need exists to assist the governments of GMS countries to mobilize funding from other sources for scaling up project activities. According to a review by Global Health Sciences, the majority of funds from 2007 to 2011 for elimination of malaria come from multilateral donors (94%), and most of these are from the Global Fund.<sup>76</sup> However, the funds for malaria elimination may decline in the future. Other funding sources are required, and GMS countries need further support for mobilizing funding.

The technical capacities for scaling up effective interventions are often limited in GMS countries—especially in Cambodia, Lao PDR, and Myanmar—and continued and additional support for strengthening the regulatory system (e.g., strengthening quality surveillance and bringing regulatory enforcement up to acceptable regulatory standard) is needed.

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<sup>75</sup> United States Pharmacopeia/USAID. Promoting the Quality of Medicines (PQM) Program in Southeast Asia. 2012. [http://www.usp.org/sites/default/files/usp\\_pdf/EN/fact\\_sheet-southeast\\_asia-\\_apr\\_11\\_2013.pdf](http://www.usp.org/sites/default/files/usp_pdf/EN/fact_sheet-southeast_asia-_apr_11_2013.pdf).

<sup>76</sup> Cambridge Economic Policy Associates. Financing malaria elimination: current trends and recommendations. *Policy Brief*, October 2013. <http://globalhealthsciences.ucsf.edu/sites/default/files/content/ghg/mei-financing-malaria-elimination-brief.pdf>.

### *Collaboration between Regulatory Authorities and Law Enforcement Agencies; Intercountry Exchange of Information and Collaboration*

Effective collaboration between MRAs and law enforcement agencies in each country is critical in combating counterfeit medical products, and plenty of room for improvement exists in GMS countries. Similarly, the mechanism for exchange of information and collaboration between countries needs to be strengthened. The BREMERE project initiated by the PQM/USP program will address this issue and needs to be continued and strengthened.

### *Political Commitment for Combating Fake and Substandard Products*

Lack of support from policy makers and possible conflicts of interest have been regarded as impediments in combating fake and substandard products. Interviews do not allow easy documentation and substantiation of “lack of commitment” and “existence of conflict of interest” unless specific studies are undertaken to do so. For this reason, we also propose introduction of the Good Governance for Medicines program in Cambodia, Myanmar, and Vietnam, where systematic assessment on the levels of transparency and system vulnerability to conflict of interest and identification of weaknesses can be undertaken and relevant measures subsequently developed to deal with those weaknesses.

### *Public Awareness of the Importance of Medicine Quality*

The awareness of communities about the importance of quality of medical products is still poor, as shown from a study undertaken in Lao PDR.<sup>77</sup> Respondents also emphasized the need for public education and advocacy on the importance of medicine quality and the danger of substandard and counterfeit medicines in other GMS countries. Such advocacy should also be directed to health care providers and managers at different levels of care.

### *Access to Good-Quality Antimalarials*

Access to and availability of good-quality antimalarials remain problematic in most GMS countries, especially in remote places in GMS countries, as demonstrated by various surveys.<sup>78,79,80,81</sup> Strengthening supply chain management of antimalarials and other essential commodities is still needed, including monitoring and backup support for resupply.

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<sup>77</sup> Syhakhang L, Freudenthal S, Tomson G, et al. Knowledge and perception of drug quality among drug sellers and consumers in Lao PDR. *Health Policy and Planning* 2004;19(6):391–401.

<sup>78</sup> Syhakhang L, Sengaloundeth S, Paphassarang C, Freudenthal S, Wahlström R. Availability of essential drugs and sustainability of village revolving drug funds in remote areas of Lao PDR. *Studies in HSO&P* 2008;23: 519–43.

<sup>79</sup> Yeung S, Van Damme W, Socheat D, White NJ, Mills A. Access to artemisinin combination therapy for malaria in remote areas of Cambodia. *Malaria Journal* 2008;7:96 <http://www.malariajournal.com/content/7/1/96>.

<sup>80</sup> PSI/Myanmar. *Outlet Survey: Baseline Study: The Republic of the Union of Myanmar 2012 Survey Report*. Yangon, Myanmar: PSI/Myanmar; 2012.

<sup>81</sup> ACTwatch Group and PSI/Cambodia. *Kingdom of Cambodia Household Survey Report, 2011*. Phnom Penh, Cambodia: PSI/Cambodia; 2012.

## *Transparency and Good Governance in the Medicines Sector*

There is plenty of room for improving transparency and good governance in medicine registration, selection, and procurement in GMS countries, especially in Cambodia, Myanmar, and Vietnam. Only Thailand and Lao PDR, which join the global program on Good Governance for Medicines, have undertaken necessary measures to improve transparency and good governance in medicine registration and procurement.

### ***Options for the Way Forward***

The desktop review and interviews with relevant respondents from each GMS country indicate a number of past and ongoing initiatives have been undertaken at national or regional/global levels to address the issue of access to good-quality antimalarials in the Greater Mekong countries. Those initiatives and projects can be classified as follows—

- **Regulatory approaches to strengthen the medicine regulatory system and its enforcement in ensuring the safety, efficacy, and quality of products and in combating substandard and fake products in the market**  
These approaches are undertaken through various project activities, including capacity building of MRAs, strengthening quality control laboratories, operational research on quality, and quality surveillance including monitoring medicine quality and enforcement.
- **Access approaches to improve the availability, affordability, and rational use of antimalarials in health facilities and in the market**
  - Providing subsidies for good-quality antimalarials and other commodities
  - Strengthening supply chain distribution
  - Capacity building in supply chain management and rational use
  - Monitoring of availability, price of antimalarials and commodities
- **Other complementary approaches**
  - Advocacy and public education on the importance of quality
  - Advocacy and public education on rational use of antimalarials and other commodities
  - Improving transparency and good governance in medicine regulation, selection, and procurement

In general, the following program activities are recommended for the future—

#### ***1. Strengthening medicines regulatory system and enforcement capacities***

All countries in the Greater Mekong region have medicine regulatory organizations, infrastructure, and relevant regulations to deal with the problems of substandard and fake antimalarials in the market. Despite progress in recent years, most of them still encounter problems of enforcement caused by insufficient human resources capacity and financial resources. Especially in Cambodia, Lao PDR, and Myanmar, disparity between these and the other GMS countries to adequately address regulatory minimum standards needs attention.

PQM/USAID projects have over the years successfully focused on regulatory approach and public advocacy.

### **Medicine quality surveillance**

The program activities and other related activities have indeed significantly affected the reduction of product failure in all Mekong countries. Although the governments of GMS countries may have limited capacities in scaling up to other high-risk areas, this program may deter the production and distribution of counterfeit products. In recent years, medicine quality monitoring showed no more reports of counterfeit medicines. A clear need exists to continue the program. The government has to start partially shouldering the cost of the quality surveillance.

Considering the limited funding availability, our recommendation is to continue the surveillance program in high-risk areas, such as remote and border areas.

**Countries:** Cambodia, Lao PDR, and Myanmar

### **Strengthening national quality control laboratory**

Improving capacities of national and regional laboratories is needed to enable them to undertake confirmatory laboratory testing for substandard and counterfeit products. The laboratories also need support to reorganize so they can collect revenue from their services.

**Countries:** Cambodia, Lao PDR, Burma, and Vietnam

### **Human resources training on medicine regulation and quality assurance**

Improving human resources capacities of MRAs in enforcing regulations for substandard and counterfeit antimalarial products is important as part of quality assurance.

**Countries:** Cambodia, Lao PDR, Myanmar

### **Improving interagency and intercountry collaboration and sharing of information on antimalarial quality**

Strengthening interagency and intercountry collaboration and exchange of information is important in combating fake and substandard products, including antimalarials, because the products can move across borders from one country to another. The newly established BREMERE needs to be supported and continued.<sup>82</sup>

**Countries:** Cambodia, Myanmar, Lao PDR, Vietnam, and Thailand

### **Public education and advocacy on the importance of quality**

The general public and health care providers need to be informed from time to time about the importance of quality, the impact of low-quality antimalarials on health, and any regulatory decision on substandard and counterfeit products in the market. The consumers need to be

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<sup>82</sup> USAID/USP/Promoting the Quality of Medicines. Collaborative focus on fight against counterfeit, substandard medicines in Greater Mekong Sub-Region. Press release, 2012.  
<http://us.vocuspr.com/Newsroom/ViewAttachment.aspx?SiteName=uspharm&Entity=PRAsset&AttachmentType=F&EntityID=109560&AttachmentID=031e3acf-79b3-471d-909d-bb9191e41d98>.

reminded to buy medicines from licensed outlets and facilities and to avoid buying and taking medicines from unreliable sources. PQM projects have done this and need to be continued.

**Countries:** Cambodia, Lao PDR, Myanmar, Thailand, and Vietnam

## *2. Improving access to, availability of, and affordability of good-quality antimalarials*

The PSI project has successfully distributed subsidized and good-quality antimalarials through the private sector in Myanmar<sup>83</sup> and Cambodia.<sup>84</sup> The project has improved access to good-quality antimalarials in these countries. But the problem of stock-outs remains to be resolved. Tanzania has had a similar successful experience. One of the respondents in Cambodia, who is familiar with the issues of drug quality, regulation, and supply in the country and who had the opportunity to visit and to share the experience in Tanzania, mentioned that the project in Cambodia needs to be expanded and to adopt the approaches of Tanzania. Our recommendation is to expand the program to Lao PDR and Vietnam. The lessons learned from Cambodia, Myanmar, and Tanzania<sup>85,86,87</sup> can be accommodated.

For example, in Tanzania, to improve access to treatment in the private retail sector, a new class of outlet known as an accredited drug dispensing outlet (ADDO) was created, and first-line treatment for malaria was shifted from sulfadoxine-pyrimethamine to artemether-lumefantrine in 2007. Subsidized artemether-lumefantrine was made available in both health facilities and ADDOs. The effect of these interventions on access to malaria treatment was studied in rural areas in Tanzania, and between 2004 and 2008 access to malaria treatment greatly improved and the number of antimalarial treatment doses dispensed increased by 78%. The intervention has also resulted in an increase of the market share from 49% of antimalarial sales 2005 to 59% in 2008. Lessons learned from Myanmar, Cambodia, and Tanzania have indicated that provision of antimalarials through the private sector is possible. Some of the following activities need to be considered when designing and expanding the program—

- Advocacy on rational use of malaria treatment with ACT-based regimens and the importance of quality to private providers, distributors, and outlets
- Training on supply chain management of antimalarials and commodities to private suppliers/distributors and outlets

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<sup>83</sup> GiveWell. Containment of Artemisinin Resistance in Eastern Myanmar (PSI Myanmar Project).

<http://www.givewell.org/PSI-Myanmar-Artemisinin-Resistance-Containment#Abouttheproject>.

<sup>84</sup> Montagu D. *Large-Scale Malaria Treatment in the Private Sector: A Case Study of the Cambodian Experience*. San Francisco: The Global Health Group, Global Health Sciences, University of California, San Francisco; 2010. <http://globalhealthsciences.ucsf.edu/sites/default/files/content/ghg/hsi-cambodia-case-study.pdf>.

<sup>85</sup> Battersby A, Goodman C, Abondo C, Mandike R. *Improving the Supply, Distribution and Use of Antimalarial Drugs by the Private Sector in Tanzania*. Malaria Consortium; 2003.

[http://www.malariaconsortium.org/userfiles/file/Malaria%20resources/antimalarials\\_final\\_draft\\_08\\_jul\\_03.pdf](http://www.malariaconsortium.org/userfiles/file/Malaria%20resources/antimalarials_final_draft_08_jul_03.pdf).

<sup>86</sup> Hetzel MW, Iteba N, Makemba A, et al. Understanding and improving Access to prompt and effective malaria treatment and care in rural Tanzania: the ACCESS programme. *Malaria Journal* 2007;6:83.

<http://www.malariajournal.com/content/pdf/1475-2875-6-83.pdf>.

<sup>87</sup> Alba S, Hetzel MW, Goodman C, et al. Improvements in Access to malaria treatment in Tanzania afloat to artemisinin combination therapy and the introduction of accredited drug dispensing outlets: a provider perspective. *Malaria Journal* 2010;9:164. <http://www.malariajournal.com/content/9/1/164>.

- Training informal drug providers in the use of RDTs, and supplying RDTs to these providers
- Accreditation of private suppliers/distributors
- Provision of subsidized good-quality ACT antimalarials to (accredited) private suppliers/distributors and outlets
- Monitoring of prices, availability of ACTs in private and public facilities, and a reliable system for resupply for stock-outs
- Use of IT (cellular phone) for communication between providers, suppliers, and outlets for monitoring product availability and resupply

### *3. Improving transparency and good governance in medicine registration, selection, and procurement, especially of antimalarials*

Transparency and good governance in medicine registration, selection, and procurement are critical in improving access to good-quality medicines, including antimalarials. Anecdotal examples in this area indicate that a wrong decision caused by lack of transparency in selection could jeopardize the whole objective of the malaria control program. Only Lao PDR and Thailand of the Greater Mekong countries have a program on Good Governance for Medicines. The respondent from Cambodia emphasized the need for transparency and good governance in medicine registration, selection, and procurement in that country. Therefore, we recommend the expansion of transparency and good governance in medicine registration, selection, and procurement in other GMS countries, namely Cambodia and Vietnam. In Vietnam, improving transparency and good governance has been identified and included as one of 10 priorities of the WHO and Vietnam collaboration in medicines, but it has not yet started. Guidelines from the WHO are available and can be adopted for these countries.<sup>88</sup>

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<sup>88</sup> WHO. *Good Governance for Medicines: Progress Report 2010*. Geneva: WHO; 2010.  
<http://cdrwww.who.int/medicines/areas/policy/goodgovernance/GGM2010ProgressReport.pdf>.

## **Persons Interviewed, Regional**

<b>Organization</b>	<b>Type of organization</b>	<b>Interviewees</b>
United States Pharmacopeia	Nonprofit organization	Dr. Souly Phanouvong
World Health Organization Western Regional Office, Cambodia	International organization	Dr. Walter Mulombo Kazadi
World Health Organization, Vietnam		Dr. Soccoro Escalante
World Health Organization, Western Pacific Regional Office, Manila	International organization	Dr. Klara Tisocki Dr. Eva Maria Christophel
World Health Organization, Geneva	International organization	Dr. Michael Deats
National Malaria Control Program, Cambodia	Government agency	Ms. Mam Boravan
Director (Research) Department of Medical Research (Lower Myanmar)	Academic institution	Dr. Myat Phone Kyaw
Food and Drug Department, Lao PDR	Government agency	Dr. Lamphone Syhakang
Former deputy director, Department of Drugs and Food, Cambodia	Government agency	Dr. Choeng Sokhan
Unaffiliated	Freelance consultant	Dr. Phillipe Passmore

## ANNEX 11. COUNTRY REPORT: CAMBODIA

### Summary

In Cambodia, the number of deaths and the annual number of malaria cases have steadily decreased after the peak in 1999. However, the threat of *Plasmodium falciparum* resistance to artemisinin drugs in Cambodia has endangered the country's efforts to contain malaria. Failure in artemisinin-based combination therapy has been reported from multiple sites on the Thai-Cambodia border area, and an early warning sign of artemisinin resistance has been reported from the Thailand-Burma and Burma-China borders and in southern Vietnam.<sup>89</sup> If artemisinin resistance continues to rise, the cost to treat malaria can be 50 times higher compared to the cost of ACTs.<sup>90</sup>

The National Center for Parasitology, Entomology and Malaria Control (CNM), in collaboration with multiple donor organizations, leads the malaria control efforts in Cambodia, which encompass stopping the spread of antimalarial drug resistance, including monitoring of efficacy of antimalarial drugs, improving the quality of antimalarials and combating counterfeit medicines, improving the rational use of antimalarial medicines, and intensifying malaria control activities in the western border provinces. However, counterfeit and substandard antimalarial medicines are still found in high-risk areas, such as border and forest areas where good-quality medicines are not easily available and people are not well aware of the risks of poor-quality medicines. Border areas also have weak public health care infrastructure, and border control officers are not well trained or informed on detecting counterfeit medicines.

CNM has supported provision of prepackaged antimalarial medicines (blister-packaged artesunate and mefloquine ACT) in the public sector with RDTs since 2000 to address the drug resistance issues. In the private sector, a social marketing scheme has been adopted to supply heavily subsidized good-quality ACT treatment, Malarine, through PSI/Cambodia since the pilot's success in 2002. However, sustainability of the antimalarial subsidy program can be challenging because of heavy financial dependence on donor funding for purchasing quality medicines.

The USAID-funded Promoting Quality of Medicines Program implemented by USP/PQM also has been contributing to strengthen the capacity of QA/QC functions of National Health Product Quality Control at central and provincial levels by providing technical assistance as well as test reagents.

However, the drug regulatory capacities of responsible government authorities have not been improved significantly because of lack of budget, low priority, and insufficient political will.

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<sup>89</sup> USAID PMI. *President's Malaria Initiative: Greater Mekong Subregion, Malaria Operational Plan FY 2014*. [http://www.pmi.gov/docs/default-source/default-document-library/malaria-operational-plans/fy14/mekong\\_mop\\_fy14.pdf?sfvrsn=12](http://www.pmi.gov/docs/default-source/default-document-library/malaria-operational-plans/fy14/mekong_mop_fy14.pdf?sfvrsn=12).

<sup>90</sup> McBain S. Drug-resistant malaria on the Cambodian border: a new health challenge. *The Guardian*, November 22, 2013. <http://www.theguardian.com/global-development-professionals-network/2013/nov/22/drug-resistant-malaria-on-cambodian-border>.

Clear guidance and relevant regulations are still not available on how to regulate drug quality issues. Law enforcement is still very weak in responding to counterfeit and substandard medicines. Transparency of the drug regulatory authority also has to be improved because some government officers hold stock in or own pharmaceutical companies. Improving the GMP compliance will also need technical assistance because only three of nine local pharmaceutical companies are GMP compliant.

## **Key Findings**

### **Regulatory Framework**

#### *Legislation*

In Cambodia, legislation has evolved from Book I (Drug Regulations) in 1994 to Book III in 2012. Book I mandates that all locally produced and imported pharmaceutical products, medical devices, consumables, reagents, cosmetics, health supplements, and traditional medicines be registered to be sold in the market. A number of official declarations (*Prakas*) relating to medicine quality have been issued by the Ministry of Health (MOH) to adopt new guidelines on drug registration and to implement GMP compliance (2006).<sup>91</sup>

**Drug policy related to counterfeit medicines:** Laws are in place to ban production, circulation, and importing and exporting of the products. Article 12 of “KRAM (LAW) on the Management of Pharmaceuticals dated June 17, 1996” defines the legal penalty for persons who are deliberately engaged in producing, importing, exporting, or trading of pharmaceuticals containing addictive substances without authorization, counterfeit pharmaceuticals, or pharmaceuticals of damaged quality that affect to the health or lives of the consumers. The penalty may be a fine from 20 million to 50 million riels, imprisonment from 5 to 10 years, or both. Article 13 from the same law defines the legal penalties for public servants who commit an abuse of their duties during the law’s implementation.

#### *Regulatory Functions*

**Drug licensing:** Cambodia has procedures including official submission of applications and a drug review committee responsible for registration.<sup>92</sup> The Registration Bureau of the Department of Drugs and Food (DDF) under the MOH is responsible for registering all drugs coming into the country. All medicines available and used in the private sector must be registered. However, for medicines procured through the public sector, there was no specific regulatory requirement in the past. In December 2005, the MOH issued an official note to companies to register their pharmaceutical products destined to be purchased through the public procurement process.

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<sup>91</sup> Book I, Year 2006 *Prakas*.

<sup>92</sup> WHO. *Measuring Transparency to Improve Good Governance in the Public Pharmaceutical Sector: A Comparative Analysis of Five Country Assessment Studies; Bolivia, Cambodia, Indonesia, Mongolia, Papua New Guinea*. Geneva: WHO; 2008.

**Quality testing of medicines:** DDF activities to verify the quality medicines include active participation in implementing the project of combating counterfeit antimalarial and other types of medicine, banning artemisinin monotherapy by cancelling registration of previously authorized antimalarial medicines, providing Minilabs, and postmarketing surveillance activities such as routine visits by inspectors including focused inspection on the existence of artesunate monotherapy and seizing the products when found.

**Regulatory capacity:** Regulatory capacity of the national regulatory authority (NRA) in Cambodia on the issue of quality medicines has been improved in the past years as the MOH has imposed stricter policies by issuing official proclamations, including implementing GMPs. However, the overall regulatory capacity of the NRA is still very limited because of various contributing factors, as illustrated in figure 1.

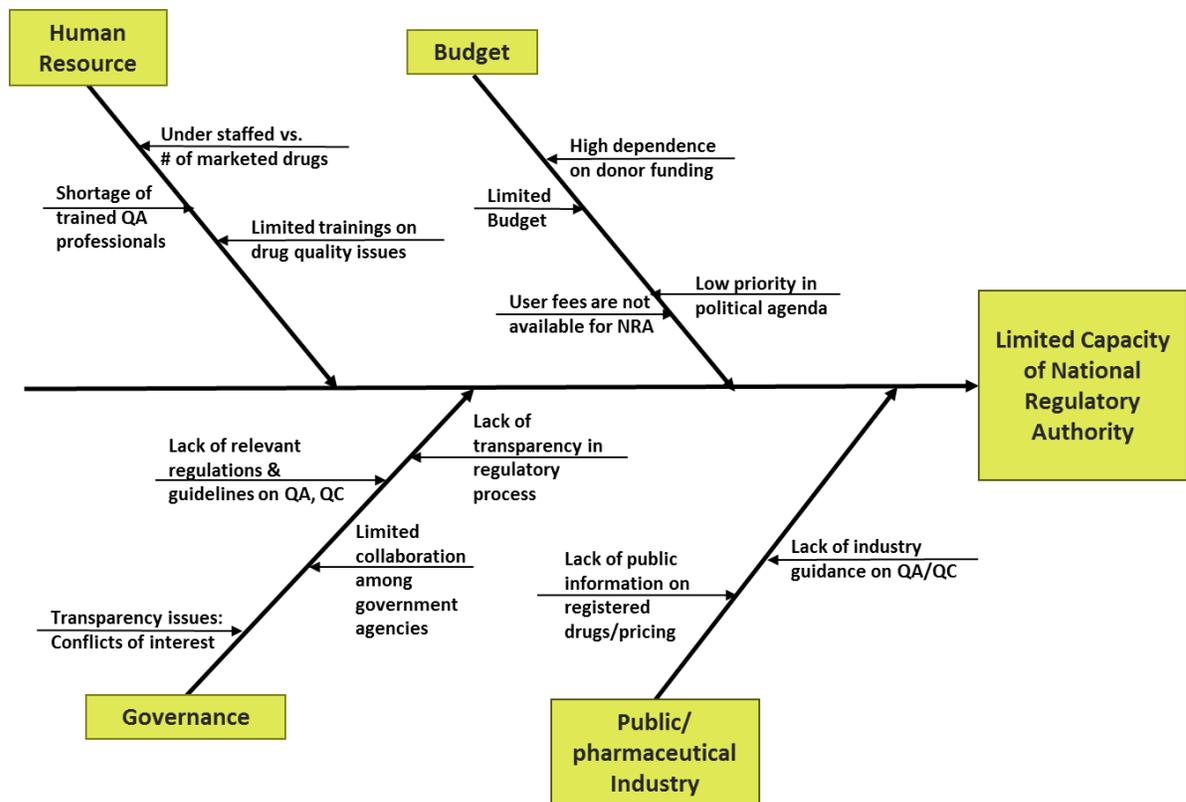


Figure 1. Factors contributing to limited NRA capacity in Cambodia

**Drug licensing:** Currently 10,355 pharmaceutical products are registered at the DDF, among them 24 antimalarial medicines. Despite the large number of registered medicines, only 38 (37 pharmacists + 1 expert in law) technical staff are involved in regulatory functions. A list of all registered pharmaceuticals is available only when it is purchased at DDF.<sup>93</sup>

<sup>93</sup> Ibid.

**Quality testing of medicines:** Since the revision of the drug law in 2007, the DDF was established and a QA inspection team at central and provincial levels was created; the inspectors were assigned as Judiciary Police. National Health Product Quality Control (NHQC) was also created to check the quality of medicines for marketing authorization and to monitor the quality of marketed medicines through postmarketing surveillance by sample testing.

For the antimalarial medicines procured with national budget, the cost for local laboratory QA testing is covered by suppliers. For the antimalarial medicines purchased under the Global Fund, the selection is made by the United Nations Office for Project Services (UNOPS) in collaboration with the MOH, and the product samples are sent to NHQC for testing.

**Ban on artemisinin monotherapy:** Oral artemisinin monotherapies have been banned in Cambodia since 2008, and market authorization for all oAMTs was withdrawn in March 2009. Historically, widespread use of counterfeit medicines and artemisinin monotherapy has led to the occurrence of drug resistance to artemisinin-derived antimalarial drugs because oAMTs have been cheaper than ACTs in Cambodia. According to the 2011 ACTwatch household survey,<sup>94</sup> the availability of oAMTs has been decreased to 0.2% of the public not-for-profit sector and 1.6% of the private sector. Although 20% of private sector outlets stocking antimalarials stocked oAMT in 2009, it was decreased to 4.2% in 2011.

**Pharmacovigilance on substandard and counterfeit medicines:** Pharmacovigilance activities have recently started and are not yet fully functioning. Together with USP/PQM, the MOH adopted Minilabs to conduct first screening tests at sentinel level. The prevalence of counterfeit and substandard medicines in Cambodia has been decreasing gradually year to year according to the results of test results done by the USP/PQM program.<sup>95</sup> However, a study funded by the Japan Pharmaceutical Manufacturers Association on quality of anthelmintic medicines conducted in 2008 in Cambodia showed that one-third of the imported samples were nonregistered and 71% of the nonregistered drugs were collected from Depot B or nonlicensed drug outlets. Studies have found that drug outlets with no license are more prevalent in rural areas.<sup>96</sup>

**Administrative measures and police enforcement on counterfeit and substandard medicines:** No official recalls or suspension of product marketing authorization have been exercised in the past because no relevant regulation or guidelines existed on substandard or poor-quality medicines. The DDF officer testified to an urgent need for technical assistance to establish QA regulations and guidelines to enhance postmarketing surveillance activities not only on antimalarials but also the entire pharmaceutical products market. During the past 10 years, only one counterfeit medicine case was officially reported by the MOH, in early 2013. At the time, seven types of fake injectable medicines were seized, and the violators were sent to court for a jurisdictional decision.

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<sup>94</sup> ACTwatch Group and PSI/Cambodia. *Kingdom of Cambodia Household Survey Report, 2011*. Phnom Penh, Cambodia: PSI/Cambodia; 2012. [http://www.actwatch.info/countries/evidence.php?id\\_country=29](http://www.actwatch.info/countries/evidence.php?id_country=29).

<sup>95</sup> Ministry of Health. *Medicines Quality Monitoring Programme 5 Years Report (2005–2009)*. Supported by USAID through USP DQI/PQM. Cambodia, March 2010.

<sup>96</sup> Mohiuddin HK, Okumura J, Sovannarith T, et al. A survey on the quality of anthelmintic medicines in Cambodia. Poster presentation. 2008.

## **Current Efforts That Support Country Capacity Building in Cambodia**

- 1. The Cambodian government adopted as policy ACT for its first-line antimalarial treatment in 2000.** The government decided to provide prepackaged drugs (a combination of mefloquine + artesunate) to improve the quality of first-line antimalarial medicines for *P. falciparum* malaria by ensuring stability tests and GMP compliance of suppliers of raw materials. As a result, only WHO-prequalified products were procured for the public sector through donor funding. The public health sector has been providing prepackaged ACTs (AS/MQ) and RDTs free of charge at public health facilities and through village malaria workers (VMWs).

**Achievements:** Only WHO-prequalified products were procured for the public and private sectors through donor funding. Public health centers have provided quality antimalarials through health centers and VMWs to improve the access to quality antimalarials. In the private sector, subsidized quality antimalarials gained a large market share in a rather short time and increased the access to quality antimalarials where public health facilities are not available.

**Concerns:** Because the budget for procuring antimalarials is highly dependent on funding from outside and the products are supplied from outside the country, obtaining a steady supply of medicines has been a recurring issue. The local repackaging issue has been problematic because of GMP compliance with regard to Global Fund procurement requirements; it resulted in stock-outs at central level and affected the distribution of medicines at operational district levels. Because of the recurring procurement delays, the repackaging was finally contracted out to Cipla Ltd in 2009.<sup>97</sup>

- 2. National malaria control program (CNM):** The National Center for Parasitology, Entomology and Malaria Control is a specialized institution set up by the Cambodian MOH to function as the department responsible for the control of vector-borne diseases, including malaria. CNM activities include investigation, training, and supervision of health staff and other interventions. CNM has been actively participating in the committee for combatting counterfeit medicines, which is composed of DDF, CNM, the Central Medical Store, and NHQC, for the study of and research on counterfeit medicines in collaboration with the WHO. Together with the DDF, CNM conducted postmarket surveillance on quality of antimalarial medicines supported by USP/DQI.

**Achievements:** The interministerial committee was officially established in 2005 and started taking actions to combat counterfeit medicines.

**Concerns:** However, information sharing among relevant agencies and health care professionals is still very limited. Collaboration among relevant stakeholders is still limited regarding procurement and delivery of medicines and often results in delay of delivery of medicines and stock-outs.

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<sup>97</sup> Yeung S, Patouillard E, Allen H, Socheat D. Socially-marketed rapid diagnostic tests and ACT in the private sector: ten years of experience in Cambodia. *Malaria Journal* 2011;10:243. <http://www.malariajournal.com/content/10/1/243>.

- 3. VMW Project (funded by Global Fund):** Since 2004 a community-based malaria control initiative was initiated in remote and hyperendemic villages in Cambodia to provide diagnostic tests and quality antimalarials. VMWs are volunteers who are trained to detect and treat simple malaria cases in their village of residence. The VMW Project improved the access to quality antimalarials in remote areas by providing standard treatments and diagnosis tools free of charge. However, funding to sustain the project has been challenging because of high transportation costs and poor infrastructure of health care services.

In addition, the USAID-funded Malaria Control in Cambodia (MCC) project was implemented by University Research Co. in collaboration with the CNM in September 2007, to strengthen the network of VMWs by providing trainings on how to engage in community networks to promote the use of proper diagnostic tests and treatment according to the national malaria treatment guideline.<sup>98</sup> The University Research Co. Malaria Control in Cambodia program also conducted a surveillance and mapping of malaria drug resistance at the facility and community levels through its network of VMWs and village health volunteers.<sup>99,100</sup>

**Achievements:** The VMW program has significantly improved access to rapid diagnosis and quality antimalarial medicines in remote malaria-endemic villages that are located far from health facilities.<sup>101</sup>

**Concerns:** Funding is a key issue to sustain the program. Low motivation of VMWs has been identified. The VMW program has not addressed the issues of counterfeit or substandard medicines, but it can be a good mobilizing resource for information dissemination.

- 4. PSI/Cambodia subsidizes ACTs and RDTs for private sector to deliver public health:** In the private sector, through the social marketing program implemented by PSI, RDTs and prepackaged ACTs (Malarine) have been supplied at subsidized prices to wholesalers and retail outlets. PSI-provided subsidized services in the private sector include fever diagnosis and malaria case management and ACTs at a lower price in the market.
- 5. Ban on artemisinin monotherapies:** The market share of artemisinin monotherapies in the private sector dropped from 6.3% to 0.7% between 2009 and 2011. Funders of the project include the Global Fund and the Bill and Melinda Gates Foundation. However, financial sustainability can be an issue if donor funding is not secured. Because of the ACT malaria treatment change from AS/MQ to DHA-PIP (Eurartesim), PSI/Cambodia has distributed

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<sup>98</sup> Malaria Control in Cambodia (MCC) Project, University Research Co. website, <http://www.urchs.com/project?ProjectID=7>.

<sup>99</sup> University Research Co. Malaria control in Cambodia: Surveillance and mapping of malaria drug resistance at the facility and community levels. Technical Brief. USAID; 2011. [http://www.urchs.com/uploads/resourceFiles/Live/MCC\\_drug\\_resistance\\_brief\\_final.pdf](http://www.urchs.com/uploads/resourceFiles/Live/MCC_drug_resistance_brief_final.pdf).

<sup>100</sup> ICF International. *Global Fund-Supported Community Systems Strengthening Programs in Cambodia: Evaluation Report, March 2012*. Submitted to the Global Fund to Fight AIDS, Tuberculosis and Malaria; 2012. [http://cedarscenter.com/resources/CSS\\_Cambodia\\_report\\_March\\_27\\_final.pdf](http://cedarscenter.com/resources/CSS_Cambodia_report_March_27_final.pdf).

<sup>101</sup> Soy TK. Increasing access to early malaria diagnosis and prompted treatment in remote Cambodian villages. *American Journal of Public Health* 2011;101(12):e6–e8.

Euratesim to the private sector. This Euratesim was sold to drug outlets at highly subsidized prices.

**Achievements:** Since the price of RDTs is set at USD 0.25 per test with 400% profit, it provides motivation to sell the test kit. Demand-creating activities using mass media, point-of-sales materials, mobile video units, and medical detailing have helped increase the awareness and motivation to sell quality antimalarials at low prices but with high profits. Malarine now has nearly over 50% of market share for antimalarial medicines and is available in all districts throughout the country.<sup>102</sup>

**Concerns:** High dependence on health treatment in the private for-profit sector in Cambodia should be improved. Financial sustainability of the program can negatively affect the supply of antimalarial medicines.

6. **Since the Prime Minister launched the National Elimination Strategy 2011–2025, malaria-related news and stories have been often shared by TV, radio, and journals.** To improve public awareness, information on risks of artesunate monotherapy was shared through mass media through radio TV spots and banners on streets; VMWs provided information on risks of artesunate monotherapy through face-to-face meetings. However, monitoring the availability of poor-quality medicines through postmarketing surveillance system is still very limited.

7. **Multisector collaboration for malaria control and elimination efforts:** The government has established Technical Working Group for each sector as a monthly forum for coordination with relevant development partners. Through the collaboration between the Anti-Economic-Crime Police and the Drug Inspector, efforts were made to control counterfeits and to ban artemisinin monotherapies. Through the Global Fund–sponsored AMFm program for the Anti-Economic-Crime Police, 418 police officers have been trained to identify and investigate counterfeit antimalarials and enforce the ban on oAMT.

**Achievements:** Improving public awareness on the risks of artesunate monotherapy was initiated by sharing the information through mass media outlets including radio; TV spots; information, education, and communication; Banner and VMW volunteers.

**Concerns:** Although the General Department of Customs and Excise is responsible for taking action when counterfeit medicines are identified by MOH, the information-sharing process is often delayed and make taking prompt action difficult.

8. **USP/PQM Program:** The USP, funded by USAID, has been working with the government of Cambodia to address drug quality issues by providing technical assistance to strengthen the capacity of its national programs for sustained quality assurance and quality control of medicines.<sup>103</sup>

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<sup>102</sup> Montagu D. *Large-Scale Malaria Treatment in the Private Sector: A Case Study of the Cambodian Experience*. San Francisco: The Global Health Group, Global Health Sciences, University of California, San Francisco; 2010.

<sup>103</sup> Ministry of Health. *Medicines Quality Monitoring Programme 5 Years Report (2005–2009)*. Supported by USAID through USP DQI/PQM. Cambodia, March 2010.

**Achievements:** USP/PQM has improved the detection of poor-quality medicines and strengthened the national medicine quality assurance system by providing technical assistance to conduct QA tests and by increasing awareness about medicine quality issues among regulators since 2005.

**Concerns:** To build the capacity of the national regulatory management system, further technical assistance with a more holistic approach is needed in areas of medicine licensing, GMP standards enforcement and compliance, supply chain inspection, import control, laboratory testing, and QA systems in procurement and distribution.

## **Gaps in Addressing Quality of Antimalarial Medicines**

### *Aspects That Need Addressing*

- **Regulatory capacity:** Budgeting for monitoring the quality of medicines is very limited. The total budget spent by DDF on improving the quality of antimalarials from 2011 to 2013 was less than USD 50,000 and funded by donors.<sup>104</sup> When monotherapy was banned in 2009, the budget for inspection was funded by the HSSP II budget and the inspection in 2011 was funded by the Global Fund.

The number of NRA permanent staff is only 38. Considering the total number (282) of importers and distributors of pharmaceuticals and the number (10,355) of registered pharmaceutical products, the human resources are very limited to perform the responsibilities NRA should undertake.

Transparency in drug registration and GMP inspection should be improved by addressing issues with government officers who own or possess shares of pharmaceutical companies or wholesalers.

GMP compliance of local pharmaceutical manufacturers needs improvement since only three of nine local manufacturers are GMP compliant. Good distribution practice should be implemented by enhancing inspections, by establishing guidelines, and by providing trainings for the designated responsible parties.

Although MOH announced that illegal drug outlets had been eliminated by the end of 2011, there is no documented evidence or reports on the complete eradication of illegal drug outlets, and counterfeit medicines are still reported. Pharmacovigilance activities are very limited to report adverse events or other side effects caused by counterfeit or substandard medicines.

- **Counterfeit/substandard medicines:** Sharing the information on identified counterfeit medicines with health care professionals and the public is very limited. Drug sellers often cannot distinguish between the authentic products and counterfeits because of the similarity of holograms and stickers. The public has very limited information about the impact of

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<sup>104</sup> According to key informant interview of this study.

counterfeit and substandard medicines and often seeks cheaper medicines due to financial burden.

The administrative response has not been timely because of the lengthy process of administrative approvals, which delays ability to take proper actions when suspicious counterfeit medicines are reported.

Key informant interviewees also pointed out that the level of punishment in Cambodia is not severe enough (e.g., people who trade in counterfeit and substandard medicines are sentenced to 5–10 years imprisonment, whereas in Vietnam, the violators are heavily sentenced to either life imprisonment or the death penalty).

- **National drug quality testing laboratory:** The limited availability of funding for the meeting of the interministerial committee at central and provincial levels and field inspection and sample collection has been an issue. Lack of monographs for medicines listed in the pharmacopeia and lack of primary standards have been identified as obstacles.

Current drug registration requirements for DDF marketing authorization do not request applicants to submit the complete dossier on specification of test methods. As a result, the NHQC does not have enough specification and test methods information to conduct the quality tests. USP/PQM (Promoting the Quality of Medicines) has assisted NHQC to improve the capacity of drug quality tests and compliance; however, the NHQC officer interviewed said they do not have monographs of newly approved medicines. Obviously, the poor drug registration review system at DDF affects NHQC's performance. Lack of relevant regulations and guidance on quality assurance of medicines has also added to poor capacity of the NRA.

- **Law enforcement:** Police enforcement is very limited in identifying and seizing counterfeit and substandard medicines. The key informant interviewee described the situation as follows: "Many illegal corridors along the country border without the presence of police, customs, and CAMCONTROL agency leave a big opportunity for smugglers to do as much illegal business as they can."

No policy or regulations are in place regarding the process to remove identified counterfeit medicines from the market. The only administrative actions taken by the government are to issue an official circular with the information of identified products to be recalled by a certain due date. After the cut-off date, the inspectors from both national and provincial levels carry out the actions to collect counterfeit products that are still displayed. Voluntary actions are needed by pharmaceutical companies and drug outlets to eliminate the products from the distribution channels.

#### *Access to Quality Antimalarials*

- **Availability of good-quality ACTs:** In border and remote areas, accessibility to quality ACT medicines is very limited because of poor transportation to public health care facilities or legitimate drug sellers. Affordability also leaves the poor to seek cheap medicines, which

are often poor-quality substandard or counterfeit medicines. Moreover, people tend not to complete the regimen because of the financial burden.

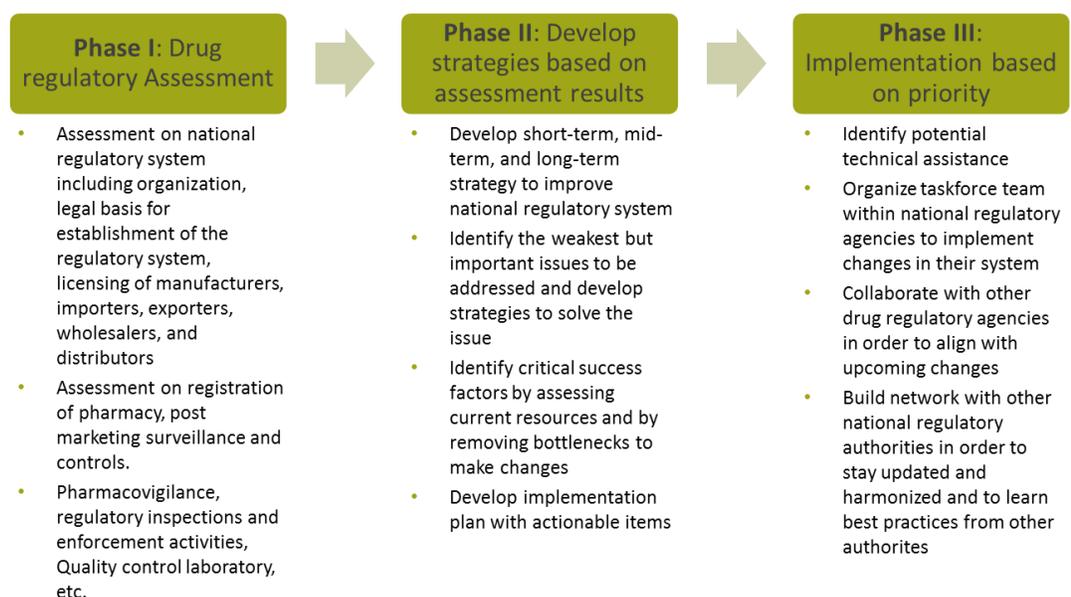
- **Public awareness and treatment-seeking behavior:** Drug sellers and health care professionals are not well informed regarding the presence of counterfeit medicines or banned medicines. Even when marketing authorization is cancelled, the information is not readily available.

Patients from marginalized groups are often illiterate and have limited access to information regarding the danger of poor-quality medicines. They often seek cheap medications, and drug sellers are not incentivized to recommend quality medicines.

### **Options for the Way Forward**

#### *Capacity Building of National Medicines Regulatory Authority*

- **Capacity building of drug regulatory governance:** By providing technical assistance based on thorough assessment, the NMRA can improve its capacity to ensure the quality of medicines. Through close collaboration between the Cambodian FDA and medicines regulatory authorities in neighboring countries, they can share information on how to improve the drug regulatory management system through harmonization of drug regulatory requirements and strengthening QA compliance across borders.



**Figure 2. National regulatory system strengthening process**

The WHO recommends strengthening the national drug regulatory authority by emphasizing the importance of assessing the current capacity to improve the capacity of the NMRA.<sup>105</sup> By identifying specific needs, appropriate technical assistance and training can be provided.

An example of technical assistance to strengthen the NMRA using the same approach as recommended by the WHO is provided by SIAPS, a USAID-funded program that has been providing technical assistance to the Bangladesh NMRA. The capacity-building strategy and implementation plan were developed based on a thorough assessment of the current regulatory system of the Bangladesh Director General of Drug Administration.<sup>106</sup> Now, the Director General of Drug Administration has agreed to adopt the Common Technical Document guidance for drug registration, and an internal taskforce team has been formed to launch an online drug registration review system to improve the transparency of drug registration and to strengthen the QA monitoring system for pharmaceuticals already marketed in the country. A similar type of technical assistance can be expanded to the DDF in Cambodia.

- **Monitoring the quality of counterfeit medicines in cross-border areas:** Through close cross-border collaboration in the Greater Mekong area, health ministries of participating countries can exchange information in a more effective way to contain the spread of counterfeit medicines in border regions. PMI has been supporting cross-border collaboration efforts between Myanmar, Cambodia, and Thailand. In March and August of 2012, PMI provided support for working group meetings to identify local needs, challenges, and opportunities at selected cross-border sites and to develop implementable action plans. To promote local ownership of cross-border coordination, participants were drawn from national programs; health administrations at the province, town, and district levels; nongovernmental organizations (NGOs); and other agencies from all three countries.<sup>107</sup>

However, it has been pointed out that political and financial commitment is a key success factor for effective collaboration on cross-border issues. To respond in a timely manner, capacity building of local health authorities is necessary in implementing coordinated regional malaria control efforts.

- **National drug quality testing laboratory:** The USAID-funded USP/PQM program has supported the Cambodian MOH to strengthen its QA/QC system in detecting poor-quality medicines; improving access to quality information; and raising medicine quality issues among regulators, health care providers, and the public. USP/PQM's medicine quality monitoring program can further assist Cambodia's National Medicine Quality Control

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<sup>105</sup> WHO. *WHO Data Collection Tool for the Review of Drug Regulatory Systems*. Geneva: WHO; 2007. [http://www.who.int/medicines/areas/quality\\_safety/regulation\\_legislation/assessment/en/](http://www.who.int/medicines/areas/quality_safety/regulation_legislation/assessment/en/).

<sup>106</sup> Nwokike J, Choi HL. *Assessment of the Regulatory Systems and Capacity of the Directorate General for Drug Administration in Bangladesh*. Submitted to the US Agency for International Development by the Systems for Improved Access to Pharmaceuticals and Services (SIAPS) Program. Arlington, VA: Management Sciences for Health; 2012. <http://siapsprogram.org/publication/assessment-of-the-regulatory-systems-and-capacity-of-the-directorate-general-for-drug-administration-in-bangladesh/>.

<sup>107</sup> PMI. Cross-border collaboration in the Mekong to combat drug-resistant malaria. October 2013. <http://www.pmi.gov/news/story-from-the-field/story-from-the-field---detail/cross-border-collaboration-in-the-mekong-to-combat-drug-resistant-malaria>.

Laboratory to expand its laboratory capacity at regional levels by providing professional training to improve capacity to conduct pharmaceutical analysis to confirm the results of testing in the field.

- **Police enforcement:** Interministerial collaboration has been initiated to strengthen police enforcement against illegal activities related to the production, importation, distribution, and sale of counterfeit pharmaceuticals in Cambodia. The USP/PQM program supported creation of an Interministerial Committee for Eliminating Counterfeit Drugs and Illegal Health Care Services and the national body authorized to take enforcement actions against counterfeit and substandard medicines.

However, strong political will and leadership will be needed to take actions on illegal importation and distribution of unapproved poor-quality medicines.

### *Access to Quality Antimalarials*

- **Accessibility to and affordability of good-quality ACT treatment in the private sector:** In Cambodia, the private sector has been the first point of contact for an estimated more than 70% of people seeking malaria treatment.<sup>108</sup> Expansion of the PSI subsidy program and the VMW program can be an option to improve the accessibility to quality ACTs by discouraging drug sellers to purchase cheap and poor-quality medicines. If the programs can be expanded on a large scale, a possibility exists to reduce the costs for purchasing prepackaged antimalarials, and economies of scale can be achieved through the existing infrastructure, such as warehouses and vehicles.
- **Supply chain management system to prevent the distribution of counterfeit medicines:** An effective recall system through strengthened police enforcement has to be established when counterfeit medicines are found, which should increase the awareness of the risks to the public health. An effective stock-out monitoring system will help improve the efficiency of use of available medicines. Training on supply chain management of antimalarials and commodities to private suppliers/distributors and outlets should be provided according to established guidelines and regulations. Accreditation of private suppliers/distributors and outlets by the MOH can help eliminate the presence of illegal drug outlets. A microfinance model can be used to encourage private suppliers/distributors and drug outlets, and the MOH can encourage them to comply with standards of supplying medicines. Utilization of the IT (cellular phone) system for communication between providers, suppliers, and outlets can also help reduce stock-outs and distribute available medicines in a more efficient manner.
- **Public awareness:** Key success factors for PSI to penetrate the antimalarial medicine market in a relatively short time were use of an extensive communication strategy to increase the public awareness of PSI's brand and to encourage the appropriate use of products. In this way, PSI was able to create demand by both consumers and providers.

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<sup>108</sup> WHO. *Malaria in the Greater Mekong Subregion: Regional and Country Profiles*. Geneva: WHO; 2010.

Key informants also expressed their opinions regarding the impact of broadcasting to disseminate information through TV and radio on the dangers to health and public security that are caused by counterfeit and substandard products.

More than 3,000 VMWs in 1,500 villages across Cambodia have been critical sources in delivering malaria treatments in remote areas. They launched a pilot project to report the incidence of new malaria cases by using mobile text messaging and web-based technology.<sup>109</sup> The Malaria Day Zero Alert System (funded by the Malaria Consortium) is a web-based application that enables health center staff and VMWs in provincial villages to report malaria cases via SMS text alerts to a centralized system.<sup>110</sup> This system can be used to report the cases on suspected counterfeit medicines if VMWs are trained to identify these medicines if they are used by village dwellers.

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<sup>109</sup> IRIN News. “Cambodia: Using text messaging as weapon in malaria war.” September 6, 2011. <http://www.irinnews.org/report/93662/cambodia-using-text-messaging-as-weapon-in-malaria-war>.

<sup>110</sup> The National Center for Parasitology, Entomology and Malaria Control (CNM), webpage information, <http://www.ilabsoutheastasia.org/network/cnm/>.

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## **Persons Interviewed**

<b>Organization</b>	<b>Type of organization</b>	<b>Interviewee</b>
Customs and excise agency	Government agency	Em Khim Vorac
Department of Drugs and Food (DDF)	Government agency	Dr. Heng Bun Kiet
National Health Product Quality Control (NHQC)	Government agency	Dr. Tep Keyla
National Drugs Inspector	Government agency	Dr. Khlaing Sameth
Pharmacist Association	Health professional organization	Dr. Yim Yann
AMFm Coordinator/National Malaria Control Program (CNM)	Government agency	Mrs. Mam Boravann
CAMCONTROL	Government agency	Dr. Hang Meun
USP/DQI	NGO	Pharm. Siv Lang

## ANNEX 12. COUNTRY REPORT: MYANMAR (BURMA)

### Summary

Myanmar has been reported to have 78% of the malaria cases and 75% of the malaria deaths in the GMS and has the most under-resourced health infrastructure.<sup>111</sup> Artemisinin-resistant parasites have been reported from the Thailand-Burma and Burma-China borders, caused by extensive migrant population and widespread use of oral artemisinin-based monotherapies. Heavy dependence on the private sector for health care services has also contributed to the widespread use of artemisinin monotherapies. Therefore, it is critical to control malaria resistance in the country to contain the spread of resistance in the region.

The use of counterfeit and substandard drugs and artemisinin monotherapy have been prevalent in Myanmar because of easy access and poor understanding of the risks among users. The national malaria treatment policy adopted ACTs as the principal treatment in 2002. However, the implementation to supply quality ACTs has not been sufficient because a large proportion of the population seeks treatment in the private sector where artemisinin monotherapies have been prevalent for many years.<sup>112</sup>

Although the legal framework has been established to prevent the production and importation of fake and substandard medicines, limited law enforcement in the country has not effectively controlled the presence of poor-quality antimalarial medicines.

To address the issues related to counterfeit medicines and the presence of artemisinin monotherapies, both short-term and long-term approaches are needed to effectively respond to the high occurrence of malaria cases in the country. Although highly subsidized, quality ACTs can replace the poor-quality antimalarials in the private sector in short term, the government should strengthen its capacity to control the quality of medicines in the country. PSI/Myanmar can use private health care providers to improve access to quality ACTs by providing highly subsidized medicines, but the government should be able to strengthen the roles of public health care facilities, especially in migrant populations, to monitor the spread of drug resistance among the mobile population.

Law enforcement also has to be strengthened by clearly defining the roles and responsibilities to share information with the public in an effective manner and to increase awareness of the risks of committing such crimes in the country. To protect the public from counterfeit and substandard medicines, the drug supply chain management system has to be improved to exercise recalls and dispose of the products found.

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<sup>111</sup> Christophel EM, et al. Joint Assessment of the Response to Artemisinin Resistance in the Greater Mekong Sub-Region Conducted November 2011 to February 2012, Summary Report. Draft for feedback. <http://malaria2012conference.com/cms/wp-content/uploads/2012/10/Joint-Assessment-of-the-Response-to-Artemisinin-Resistance.pdf>

<sup>112</sup> World Health Organization and Ministry of Health Myanmar. *Strategic Framework for Artemisinin Resistance Containment in Myanmar (MARC) 2011–2015*. April 2011. <http://www.searo.who.int/myanmar/documents/MARCframeworkApril2011.pdf>.

## Key Findings

### Regulatory Framework

#### Legislation

In Myanmar, the legislative framework consists of the National Drug Law 1992 in which the fifth paragraph states the need for quality assurance in respect of manufacture and for laboratory analyses of all pharmaceutical products, including raw materials and registered drugs.<sup>113</sup> The National Drug Law prohibits the manufacture, importation, exportation, storing, distribution, or sale of the following: a drug that has not been registered; a drug whose registration has been revoked temporarily or cancelled; a fake drug, drug differing from standards, deteriorated drug, or adulterated drug; a drug that has been manufactured with harmful substances; a dangerous drug that is determined by notification as not fit for use by the MOH.

#### Regulatory Functions

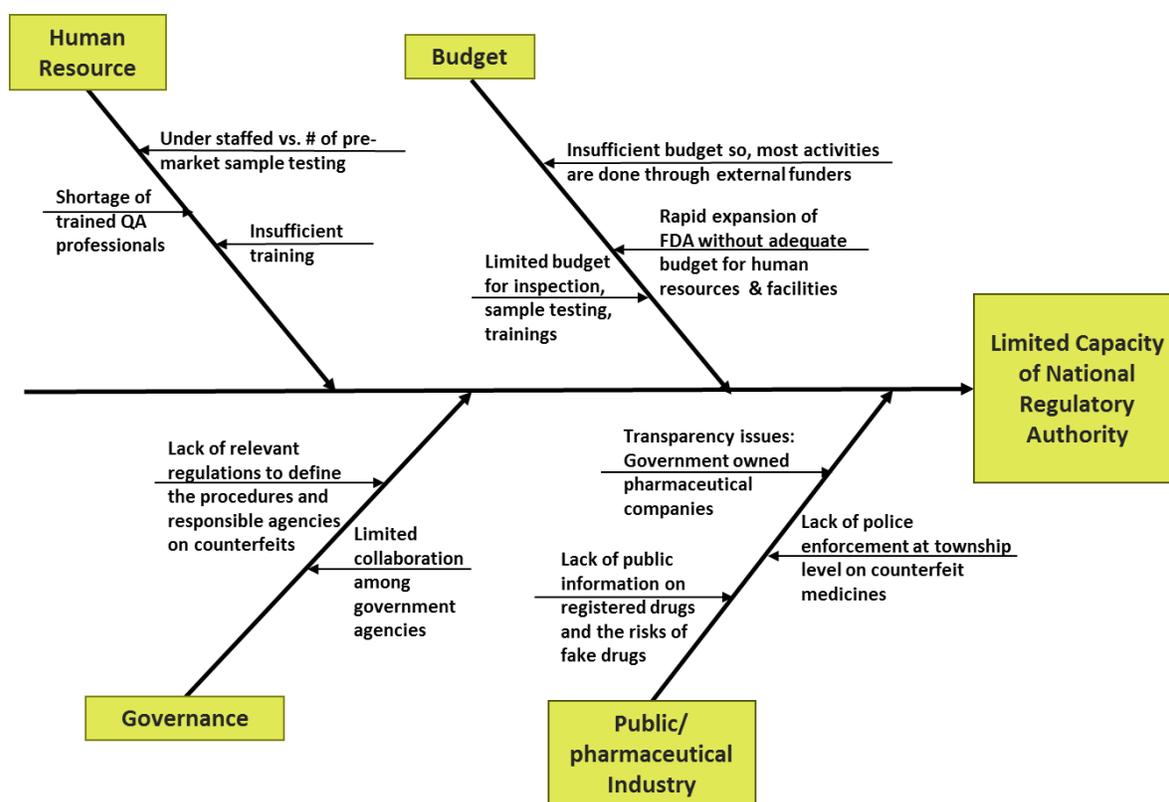
Three authorities are involved in drug regulation in Myanmar: the Myanmar Food and Drug Board Authority, the Myanmar Food and Drug Administration, and the Food and Drug Supervisory Committees at central, state/division, district, and township levels. The central Food and Drug Supervisory Committee issues licenses of drug wholesalers and retailers and conducts inspections. The Food and Drug Administrative Department (FDAD) through the Myanmar Food and Drug Board of Authority lays down the policy relating to registration of medicines, licensing health care professionals, GMP compliance of pharmaceutical manufacturers, and postmarket surveillance issues. FDAD branches at the Myanmar-China and Myanmar-Thailand borders check the quality of drugs imported through the border areas. Food and Drug Supervisory Committees in the states, divisions, districts, and townships function as implementing agencies for the FDAD to monitor and control the quality of foods and drugs at different administrative levels.

- **Drug licensing:** Myanmar FDAD issues drug marketing authorization and conducts inspections at pharmaceutical manufacturing facilities and importers and tests the quality of drugs. There are 650 permanent posts for National Medicines Regulatory Authority (NMRA). Among them, 60 are technical staff performing regulatory functions. Because the FDAD has recently become an independent agency, its roles have not been well defined yet and it is still recruiting more scientific staff.
- **Quality testing of medicines:** The FDAD conducts QA testing of drugs for registration and postmarketing surveillance. It has recently acquired basic testing equipment such as Minilabs (10 from WHO, 3 from USP/PQM) and a high-performance liquid chromatography (HPLC) and dissolution tester through USP/PQM and WHO. Staff interviewed from the Myanmar FDAD said they are overloaded with test requests for premarket QA tests while they are still suffering from limited trained staff and equipment. In 2013, the FDAD conducted 2,600 tests for product registration, and 5% to 7% of the tested samples failed.

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<sup>113</sup> WHO Regional Office for South-East Asia (SEARO). *Drug Testing Laboratories: Report of the South-East Asia Regional Meeting, Bangkok, Thailand, 27 April 2013*. New Delhi, India: WHO/SEARO; 2013.

- Regulatory capacity:** During military junta rule, the FDAD was just a name and its activities were very limited because of military governance, limited human resources, lack of financial resources, and lack of sophisticated or modern labs and equipment for testing of drug quality. However, in 2013 with the new government, the FDAD was upgraded to a separate department. In 2012, 69 drugs were rejected for registration from the aspect of quality, safety, and efficacy. According to the key informant interviews, drugs without the logo of Myanmar registration are rarely found at pharmacies, compared with past experience. Despite increased resources compared to the last decade, gaps in resources still exist—especially human resources to meet the demand for QA of drugs in the market. As illustrated in figure 1, shortage of technical staff, limited budget, lack of relevant legal framework, and lack of enforcement are the critical factors contributing to the NRA’s limited capacity in Myanmar.



**Figure 1. Factors contributing to the limited capacity of the Myanmar NRA**

- Drug licensing:** Myanmar has seven local pharmaceutical manufacturers, and all are owned by the government or a semi-public entity. All seven manufacturing facilities are GMP certified by the Myanmar FDAD. Three of these manufacturers produce antimalarials. Approximately 20 antimalarial medicines are available in the market.
- Quality testing of medicines:** The national drug testing laboratory is operated under the Myanmar Food and Drug Administration. It was originally established in 1995 and expanded

its branch laboratories in 2007. The national drug laboratory tests the quality of premarket and postmarket samples, including from the disease control programs.<sup>114</sup> The organization comprises six officers and 18 professionals, including lab technicians. On-the-job training has been provided by the USP/PQM program and WHO, but further technical assistance is still needed to address the imbalance between the testing workload and limited staffing.

- **Ban on artemisinin monotherapy:** Since the monotherapy treatment of malaria has been banned in Myanmar and monotherapy licenses were to expire by December 2012, all artemisinin monotherapy products were assumed to be phased out from the markets. However, according to interviews with pharmacists, artesunate monotherapy is still found in one of five pharmacies, and the product has been identified to have been manufactured by the military pharmaceutical factory for exclusive use of the military forces.
- **Pharmacovigilance of substandard and counterfeit medicines:** The number of tested premarket and postmarket drug samples was 1,799 at the drug quality control laboratory in 2012. Under MOH guidance, the FDAD regularly notifies the public as well as State and Regional Food Drug Supervisory Committees about alerts on counterfeit and illegal medicines. However, only three adverse drug reactions (ADRs) were reported in 2013, according to the interview with Department of Food and Drug Administration in Myanmar. In 2013, there were 63 cases of illegal medicines, including fake medicines.
- **Law enforcement on counterfeit and substandard medicines:** National law prohibits the manufacture, importation, exportation, storing, distribution, or sale of the fake drugs, drugs differing from standards, deteriorated drugs, adulterated drugs, and drugs that have been manufactured with harmful substances.

The Thai-Myanmar border area has been identified as a transit point for counterfeit drugs to be supplied to other countries. In 2008, during the IMPACT Operation in Myanmar, an Intensified Control Operation with 56 customs officers, conducted more than 150 checks across the country and seized three unregistered pharmaceuticals. The border area is also believed to produce precursors of counterfeits.<sup>115</sup> However, law enforcement on counterfeit medicines has not been well established or exercised because of undefined roles and responsibilities of relevant government agencies.

### ***Current Efforts That Support Country Capacity Building***

1. **M&E Plan-Malaria:** The Department of Vector Borne Disease Control (VBDC) with the WHO has developed a national M&E Plan-Malaria to effectively monitor malaria cases among people in high- and moderate-risk villages. Annual surveillance for antimalarial drugs is to be conducted with the FDAD. From the bilateral meeting with the WHO officer, the

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<sup>114</sup> Ibid.

<sup>115</sup> Interpol, IMPACT, and WHO. Operation Storm: final report. Undated. <http://www.interpol.int/Crime-areas/Pharmaceutical-crime/Operations/Operation-Storm>.

WHO provided Minilabs to the FDAD to central and region levels to test the quality of antimalarial medicines.<sup>116</sup>

- 2. Myanmar Artemisinin Resistance Containment (MARC) framework:**<sup>117</sup> A comprehensive national initiative was launched to control the spread of artemisinin-resistant parasite. It is a five-year strategic plan to contain the spread of malaria parasite resistant to artemisinin therapies. With technical support from the WHO, five international NGOs and four local NGOs have been collaborating on the malaria control program. Financial support has been secured from 3DF Three Diseases Fund (Australia, European Union, Netherlands, United Kingdom, Norway, Sweden, Denmark; USD 15.48 million for 2007–2010) and the Global Fund (USD 9.74 million for 2011–2015). The objectives include improving access to quality antimalarial medicines and to early diagnosis, which aligns with the national treatment guidelines. Also, the program aims to decrease drug pressure for selection of artemisinin-resistant malaria parasites by stopping the use of artemisinin monotherapies and substandard or fake drugs.

**Achievements:** The Malaria Technical Strategic Group and its task force were formed to provide overall guidance in planning, implementation, monitoring, and evaluation of MARC. Myanmar became the third country to initiate action against artemisinin resistance (in 2011) with support from the UK Department for International Development through 3DF and the Bill and Melinda Gates Foundation.

**Concerns:** The roles of the FDAD to ban and to recall the already registered artemisinin monotherapy products are very limited. The complexity of banning monotherapy products has become more complicated because the military uses the products.

- 3. Artemisinin monotherapy replacement project by PSI:** PSI has implemented artemisinin monotherapy replacement to substitute quality-assured ACTs in Myanmar. The project has been cofunded by the UK Department for International Development, the Bill and Melinda Gates Foundation, and Good Ventures. The program targets a switch from the widespread of availability of artemisinin monotherapies to quality ACTs.<sup>118</sup>

The program aims to increase the access to quality assured ACTs at private sector providers by providing financial subsidy to a small number of distributors who control the bulk of the country's wholesale market for anti-malarial drugs.

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<sup>116</sup> Disease Control and Prevention, Ministry of Health, Republic of the Union of Myanmar. *Monitoring - Evaluation Plan Malaria Prevention and Control, the Republic of the Union of Myanmar 2010–2015*. Revised September 2012. revised draft. [http://pr.org.mm/wp-content/uploads/2014/03/National\\_MnE\\_Plan\\_Myanmar-2010-2015\\_Malaria.pdf](http://pr.org.mm/wp-content/uploads/2014/03/National_MnE_Plan_Myanmar-2010-2015_Malaria.pdf).

<sup>117</sup> World Health Organization and Ministry of Health Myanmar. *Strategic Framework for Artemisinin Resistance Containment in Myanmar (MARC) 2011–2015*. April 2011. <http://www.searo.who.int/myanmar/documents/MARCframeworkApril2011.pdf>.

<sup>118</sup> UK Department for International Development. Intervention Summary: Replacement of malaria monotherapy drugs in the private sector to support the containment of drug-resistant malaria in eastern Burma. <http://files.givewell.org/files/DWDA%202009/PSI/Business%20Case%20and%20Summary%20202759.doc>.

**Achievements:** Artemisinin monotherapies have been replaced by quality ACTs in the market, and counterfeit medicines have been less frequently found in the private sector after the implementation of the program.

**Concerns:** Sustainable market supply of subsidized quality ACTs can be an issue in Myanmar.

4. **USP/PQM Program:** Since 2010, a USAID-funded USP/PQM program has provided hands-on training in collaboration with the VBDC, FDAD, and WHO on the establishment of a medicines quality monitoring program and compendia analysis of selected antimalarial medicines for FDAD labs. USP/PQM provided Minilabs and other essential laboratory equipment with reference standards.<sup>119</sup>

**Achievements:** Myanmar was the last country in the GMS that became part of PQM's medicines quality monitoring activities. In 2013, the USP/PQM program established its presence in Myanmar to provide a medicines quality monitoring program and provided trainings to establish sentinel sites. USP/PQM provided technical assistance for the FDAD to strengthen postmarketing surveillance to obtain evidence-based data to support actions on poor-quality medicines.

**Concerns:** FDAD has recently moved the entire laboratory to a new location; however, recalibration of all equipment and installation of the necessary system have not been completed because of budget and technical staff limitations. Among 45 tested samples in 2012–2013, 5 failed (11%).

5. **National Strategic Plan for Malaria Prevention and Control 2010–2015:** This is a five-year country-level strategic plan for malaria prevention and control. According to the plan, the quality of antimalarial drugs is to be tested regularly to ensure the availability of quality antimalarial medicine in the private sector. To improve the awareness of the risks of poor-quality medicines, messages to use quality antimalarial drugs are to be communicated to the community through mass media.

## **Gaps in Addressing Quality of Antimalarial Medicines**

### *Aspects That Need Addressing*

- **Regulatory capacity:** The Myanmar FDA has limited technical staff considering the number of registered medicinal products. Pharmacovigilance is not actively conducted, and only three or four ADRs were reported in 2010.<sup>120</sup>

Key informant interviewees identified that FDAD functions are still limited because of the shortage of trained staff and training opportunities. Furthermore, the process of drug

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<sup>119</sup> USP/PQM. PQM Support in Burma. Fact Sheet. 2013.

<sup>120</sup> Holloway KA. *Myanmar: Drug Policy and Pharmaceuticals in Health Care Delivery, Mission Report, 19–26 October 2011*. New Delhi, India: WHO/SEARO; 2011.

[http://www.searo.who.int/entity/medicines/myanmar\\_situational\\_analysis.pdf](http://www.searo.who.int/entity/medicines/myanmar_situational_analysis.pdf).

registration and monitoring is still done manually and would benefit from computerization to facilitate processing.

- **Counterfeit and substandard medicines and police enforcement:** Limited law enforcement on counterfeit and substandard medicines has created confusion and low ownership or leadership of the issue. For example, township medical officers are supposed to share the information regarding counterfeit medicines found at township level, but township medical officers are often too busy with other duties related to public health while FDAD does not have human resources or budget to have its own staff present at township level. Also, the role of FDAD is very limited in terms of exercising administrative measures because of the lack of regulations on seizing, confiscating, and disposing of counterfeits in the market.
- **National drug quality testing laboratory:** From 2011 to 2012, the national drug testing laboratory received 3,868 samples for testing. Among the tested samples, 13% to 15% of samples were collected for postmarketing surveillance.<sup>121</sup> Because more than 17,000 registered products are available in Myanmar, the national drug testing laboratory is overworked beyond its capacity. According to the key informant interview, among 2,600 tested samples for registration in 2013, 5% to 7% of those that applied failed tests.

#### *Access to Quality Antimalarials*

- **Availability of quality ACTs:** In Myanmar, the private health sector plays a major role in the health care system because most patients seek health care from private providers. Although public health centers provide ACT treatment free of charge, people prefer to use private clinics because of long and costly transportation to the nearest public health centers.

Widespread use of partial courses of oAMT has been reported in Myanmar. PSI has been working on the replacement of oAMTs with quality-assured ACT treatment.

PSI's baseline survey found that the private sector market share was dominated by oAMT (33%) and nonartemisinin therapies (38%): the private sector market share for ACT was 23%.<sup>122</sup> The oAMT market share ranged from 17% to 48% while quality-assured ACTs comprised roughly 40% to 60% of the market share in private health facilities and among health workers.

PSI has been supplying subsidized quality ACTs through a local distributor since 2011. The availability of quality ACTs has been improved rapidly, and the presence of artemisinin monotherapies has decreased in private sector (figure 2).

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<sup>121</sup> WHO Regional Office for South-East Asia (SEARO). *Drug Testing Laboratories: Report of the South-East Asia Regional Meeting, Bangkok, Thailand, 27 April 2013*. New Delhi, India: WHO/SEARO; 2013.

<sup>122</sup> PSI/Myanmar. *Outlet Survey: Baseline Study: The Republic of the Union of Myanmar 2012 Survey Report*. Yangon, Myanmar: PSI/Myanmar; 2012. <http://www.actwatch.info/countries/myanmar/outlet-reports/2012>.



Figure 2. Availability of ACT and artemisinin monotherapy in Myanmar, 2012–2013

- Public awareness and treatment-seeking behavior:** Key informant interviewees pointed out that the major driver of purchasing counterfeit antimalarial medicines is affordability of quality medicines. People who have limited access to public health care facilities often seek antimalarials in the private sector and prefer to purchase lower-price products because of their limited understanding of the risks of poor-quality medicines. Moreover, they often do not complete the full regimen. Difficult-to-reach groups such as migrant and mobile populations also need special attention to improve the access to quality medicines.

### Options for the Way Forward

#### Capacity Building of National Medicines Regulatory Authority

- Capacity building of drug regulatory governance:** Although the Myanmar FDAD has become an independent department with an extended organizational structure, the functions of the drug registration review process, postmarketing surveillance, preventive actions, and law enforcement on unregistered drugs in the market are still very limited. To improve access to quality medicines, the GMP compliance of pharmaceutical manufacturing facilities, including unregistered private small pharmaceutical producers, needs to be further addressed. Conflict of interest and transparency issues may continue to occur because government-owned pharmaceutical companies have advantages in registering medicines, especially because clear regulations and guidelines on medicines registration have not yet been established. Therefore, transparency of governance on medicines registration and GMP compliance needs to be improved to prevent any conflicts of interest among regulators wearing “two hats.”
- Monitoring the quality of counterfeit medicines in cross-border areas:** Close monitoring of the presence of artemisinin resistance is needed through cross-border collaboration in the Greater Mekong area. Close monitoring of the treatments of migrant workers is especially necessary to control the spread of resistance to artemisinin. Because fake medicines are more prevalent in cross-border areas due to the lack of control of distribution channels, close monitoring and law enforcement are needed to control counterfeit medicines.

- **National drug quality testing laboratory:** The USAID-funded USP/PQM program has supported the national drug testing laboratory to strengthen its capacity in conducting premarket and postmarket tests. However, systematic control and management of approved medicines are needed to manage approved medicines through a regular monitoring and surveillance program. The shortage of trained professionals to conduct compendia methods tests and the lack of equipment and expensive reference standards also need to be improved by securing budget funds.
- **Administrative measures:** Because of unclear roles of the FDAD and VBDC in taking administrative actions on detected fake and substandard medicines, the legal response to such crimes has been very limited and needs to be strengthened by establishing relevant regulations and by enhancing roles of responsible government agencies.

#### *Access to Quality Antimalarials*

- **Accessibility to and affordability of good-quality ACT treatment in the private sector:** In Myanmar, antimalarial medicines for the public sector have been procured through UNOPS with funding from the Global Fund and the Three Millennium Development Goal Fund. UNOPS has procured WHO-prequalified antimalarials through the UNOPS quality control system. However, the majority of the public still seeks antimalarial treatment in the private sector, which often provides poor-quality medicines. The expansion of socially marketed antimalarials (initiated by PSI in Myanmar) could further replace poor-quality antimalarials and artemisinin monotherapies by effective penetration of quality-assured ACTs at heavily subsidized prices.
- **Public awareness:** PSI has also been working through a public behavior change communication strategy to increase public awareness of the need to seek prompt treatment, use diagnostic tests, and complete full treatment courses. By leveraging efforts of NGOs, community health care volunteers, and health care providers such as the Myanmar Medical Association, case management can be also improved through private medical practitioners. PSI has also been working closely with private clinics by providing support such as treatment guidelines, rapid test kits, and quality ACTs to assist private clinics to charge patients lower prices for malaria treatments.

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## **Persons Interviewed**

<b>Organization</b>	<b>Type of organization</b>	<b>Interviewees</b>
National Malaria Control Program (Ministry of Health)	Government agency	Interviewee requested anonymity
Township Health Department	Government agency	Dr. Ei Ei Khin
Food and Drug Administration	Government agency	Dr. Theingi Zin
USP/PQM	International NGO	Dr. Soe Myat Tun Dr. Lu Lu Kyaw Tin Oo
University Research Co., LLC	International NGO	Dr. Saw Lwin
WHO Country Office national professional officer	WHO	Interviewee requested anonymity
PSI	NGO	Dr. Hnin Su Su Khin

## ANNEX 13. COUNTRY REPORT: THAILAND

### Summary

Because Thailand was the first GMS country to initiate artemisinin resistance containment programs, significant progress has been made in containing deaths caused by malaria. Antimalarial drugs in Thailand are managed under the integrated and vertical malaria program, which is managed by the Malaria Cluster of the Bureau of Vector-Borne Diseases (BVBD).

Artemisinin resistance on the western border of Thailand has been identified and confirmed in recent studies.<sup>123</sup> Counterfeit and substandard antimalarial drugs are still present despite progress made in this area. Recent surveys to detect substandard or counterfeit antimalarials in 2009–2011 found substandard antimalarials in all four countries surveyed (Cambodia, Lao PDR, Thailand, Vietnam). Thailand had fewer failing quality test cases (1%) than Cambodia (12%).

The use of artemisinin monotherapy for uncomplicated malaria in the public sector has been virtually eliminated. Antimalarial medicines are not allowed to be sold in the private sector, but artemisinin monotherapy is still available in border areas. Mefloquine and artesunate, which are the ACT regimen recommended by the national guideline, have been used for more than 20 years. However, in recent years the AS/MQ combination has shown an increasing failure rate.

In Thailand, mobile population across the borders with Myanmar and Cambodia and unrecorded migrants are the major contributors of counterfeit or substandard antimalarial medicines because these populations carry the medicines along from their countries and distribute them through private drug sellers. Because the issue of counterfeit or substandard medicines at pharmacies or in illegal drug markets has not been specifically targeted through the efforts of the BVBD Malaria Cluster, the problem still remains.

The country has a more advanced regulatory system compared with other GMS countries through more regular operation of drug quality testing for preapproval and postmarket surveillance. The Thai FDA has fully adopted ASEAN Harmonization of Pharmaceutical Product Registration, which has required the implementation of the ASEAN Common Technical Requirements and ASEAN Common Technical Dossier since 2008. The Thai FDA is also responsible for inspection of manufacturing sites for GMP compliance and postmarket surveillance to ensure the quality of medicines in the market.

Through decade-long technical assistance from external agencies including the WHO and USP/PQM program, the Thai national quality control laboratory (Bureau of Drugs and Narcotics; BDN) was selected as an international center for antimalarial drug testing and analysis in the Southeast Asia region as well as the WHO Collaborating Centre to perform drug QC testing of medicines from member countries of the South-East Asia Region and other countries in the Mekong Region. Therefore, the Thai FDA and BDN can play a significant role in advancing

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<sup>123</sup> WHO Global Malaria Programme. The status of drug-resistant malaria along the Thailand-Myanmar border. Revised May 9, 2012. [http://www.who.int/malaria/publications/atoz/drug\\_resistance\\_myanmar\\_thailand\\_border\\_may\\_2012.pdf](http://www.who.int/malaria/publications/atoz/drug_resistance_myanmar_thailand_border_may_2012.pdf).

national capacity of drug quality testing as a center of excellence to provide training and test samples for neighboring GMS countries.

## Key Findings

### *Regulatory Framework*

#### *Legislation*

In Thailand, the legislative framework consists of the Drug Act of B.E. 2510 (1967), the Drug Act of B.E.2546 (2003), and the Drug Act of B.E. 2530 (1987), which define the laws related to medicine licensing and GMP compliance. The laws are in the process of revision. When the revised law becomes effective, government-owned pharmaceutical companies will no longer be exempt from the requirements of licensing and product registration, and product liability will be implemented for the first time. Consumers will be able to directly sue and get compensation from drug manufacturers if any serious harm occurs to them after consumption, provided that product indications are strictly followed.<sup>124</sup>

The Drug Act 1967 (B.E. 2510), ministerial regulation of the Ministry of Public Health No. 20 (B.E.2525), and Notification of the Ministry of Public Health Subject regarding the GMP of modern drugs (B.E. 2554) describe laws and regulations related to defective medicinal products, including counterfeits and substandard medicines.

#### *Regulatory Functions*

The regulatory system has established mechanisms to ensure safety and quality of medicines both pre- and postmarketing periods. The Bureau of Drug Control under the Thai FDA is responsible for drug registration of locally manufactured products. Approval of importation of new medicines for clinical trials is granted by the Investigational New Drug Unit.

- **Drug licensing:** The Department of Medical Sciences conducts laboratory tests and certifies the quality of samples submitted prior to the approval of marketing authorization through the Thai FDA. All antimalarial drugs registered in Thailand after 1995 are under strict control for distribution and postmarketing surveillance by the Thai FDA to limit the availability to the public health care delivery system to minimize the misuses of drugs.
- **Quality testing of medicines:** The BDN was established in 1974 as an official medicine quality control laboratory of Thailand under the Ministry of Public Health. In 1986, the BDN was designated as a WHO Collaborating Centre for Quality Assurance of Essential Drugs. It functions as a regional laboratory to conduct sample testing for other countries with limited capacity and performs drug quality control testing for member countries of the South-East Asia Region and other countries in the Mekong region. The BDN has also organized

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<sup>124</sup> Thailand FDA: Laws and Regulations. <http://www.fda.moph.go.th/eng/drug/laws.stm>.

professional training courses upon request for WHO fellows from South-East Asian countries almost every year.

- **Regulatory capacity:** The Thai FDA has fully adopted ASEAN Harmonization of Pharmaceutical Product Registration, which requires the implementation of the ASEAN Common Technical Requirements and ASEAN Common Technical Dossier, since December 26, 2008. The Thai FDA has started accepting applications in the full format of ASEAN Harmonization since January 1, 2009. However, only 96 staff members (as of 2012) work at the central Thai FDA office dealing with a large number of products. The issue of having too many registered generic drugs has been pointed out. The lifelong product license and low requirements on drug registration documents have yielded too many “me-too” drugs in the market. The periodic review of registered drugs adopting re-registration has been proposed, but it has not been introduced yet.<sup>125</sup>
- **Drug licensing:** Local GMP-compliant pharmaceutical manufacturers have increased rapidly for the last decade as public procurement attracted the industry to supply quality medicines with GMP certificates. GMP has not been enforced as a mandatory requirement, but it has been discussed recently. The Government Pharmaceutical Organisation was established under the Ministry of Public Health by Parliamentary Act in 1966 to manufacture drugs to meet local needs. The Government Pharmaceutical Organisation manufactures 200 medicines and purchases both locally produced and imported medicines for public supply.

As of 2013, 172 pharmaceutical manufacturers and 1,090 manufacturers of traditional medicines are registered in Thailand. Among them 160 (93%) pharmaceutical manufacturers are GMP certified whereas 60 (5.5%) of 1,090 traditional medicine producers are GMP certified. According to the key informant interview, 830 medicinal products were newly registered by local manufacturers and 508 medicines were newly registered by importers in 2012. The total number registered to date is 25,778.

- **Quality check of medicines:** The BDN under the Department of Medical Sciences was established in 1974 as an official medicine quality control laboratory of Thailand under the Ministry of Public Health. The BDN tests chemical and biological pharmaceutical products, active substances, and drug containers for premarketing and postmarketing surveillance. The staff numbers 137, including 68 pharmacists, 14 scientists, and 12 laboratory assistants. Equipment includes high-performance liquid chromatography, gas chromatography, dissolution tester, and other spectrometers. The BDN annually conducts about 2,500 samples (of which 19% are illegal drugs). The BDN is internationally certified and maintains good practices through collaboration with other international bodies. The BDN is also collaborating with the USAID-funded PQM program as a confirmatory test laboratory.
- **Ban on artemisinin monotherapy:** Thailand registered oral artesunate in 1994 with a restriction in distribution regulated by the Ministry of Health, which resulted in very limited use, that is, as third-line treatment for quinine + tetracycline treatment failures. Artesunate

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<sup>125</sup> Holloway KA. *Thailand: Drug Policy and Use of Pharmaceuticals in Health Care Delivery, Mission Report 17–31 July 2012* New Delhi: WHO Regional Office for South East Asia; 2012.  
[http://www.searo.who.int/entity/medicines/thailand\\_situational\\_analysis.pdf](http://www.searo.who.int/entity/medicines/thailand_situational_analysis.pdf).

used in the national malaria vertical program must be prescribed as a component of ACT. However, artesunate that is available in the private sector is in the single artemisinin-based products not in the co-blistered products with mefloquine.

- **Pharmacovigilance on substandard and counterfeit medicines:** Post-Marketing Inspection Section, Drug Control Division, Thai FDA, is the office responsible for inspection of manufacturing sites for GMP compliance, monitoring advertisement, and products in the market for substandard, adulteration, counterfeiting, misleading, exaggerating, and hazard to the public. All promotional and advertisement materials and media as well as product package insert and labeling are subject to preapproval by the Thai FDA. According to the interview, 62,528 cases of ADRs or adverse drug events were reported in 2011 in Thailand.<sup>126</sup>
- **Administrative measures and police enforcement on counterfeit and substandard medicines:** The Consumer Protection Division, Royal Thai Police, and Thai FDA are responsible government agencies for law enforcement on defective medicines in Thailand.

### **Current Efforts**

1. **National Strategic Plan for Malaria Control and Elimination in Thailand 2011–2016:** A comprehensive national initiative was launched by the Thai government, and a national malaria treatment guideline was adopted to emphasize the correct use of ACT. The program aims to restrict incorrect use of antimalarial treatments by prohibiting sales of antimalarial medicines.

Since 1995, the Thai government has banned the sales of antimalarials in the private sector to control the unregulated use of antimalarials and to reduce the development of drug resistance. As a result, artemisinin is restricted for use only in health care facilities and not to be sold in private sector pharmacies or by drug sellers.<sup>127</sup>

**Achievements:** Quality and safe use of antimalarial medicines are emphasized in the national strategic plan for malaria, including systematic procurement of medical and nonmedical supplies, storage management to deliver drugs on time and avoid supply shortages, supporting a network for consistent surveillance of effectiveness of first-line drugs and surveillance of drug quality, and studies of factors that cause parasites to resist drugs.

Because all medications purchased in the national malaria program are procured centrally by the BVBD, the bureau ensures that all medications are supplied by GMP-certified manufacturers including the government pharmaceutical organization.

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<sup>126</sup> Health Product Vigilance Center Report [in Thai].

[http://thaihpvc.fda.moph.go.th/thaihvc/Public/News/uploads/hpvc\\_1\\_3\\_4\\_100412.pdf](http://thaihpvc.fda.moph.go.th/thaihvc/Public/News/uploads/hpvc_1_3_4_100412.pdf).

<sup>127</sup> Bureau of Vector-Borne Disease, Department of Disease Control.

*National Strategic Plan for Malaria Control and Elimination in Thailand 2011–2016.*

[http://www.nationalplanningcycles.org/sites/default/files/country\\_docs/Thailand/thailand\\_national\\_strategic\\_plan\\_2011-2016.pdf](http://www.nationalplanningcycles.org/sites/default/files/country_docs/Thailand/thailand_national_strategic_plan_2011-2016.pdf).

**Concerns:** The strategy does not specifically target containment of artemisinin resistance caused by the use of inappropriate artemisinin monotherapy. Also, the restriction of sales of antimalarial medicines may hinder access to malaria treatment among migrant populations who are afraid to seek care at public health facilities although malaria clinics offer treatment for illegal immigrants free of charge. Counterfeit or substandard antimalarial medicines are still found in the private sector in areas where mobile groups are predominant.<sup>128</sup>

- 2. Government's anticounterfeiting enforcement activities:** Through the government enforcement agencies, Consumer Protection Division, Royal Thai Police, and Thai FDA, the Thai government has been making efforts to identify counterfeits and publish the results. Random sampling QA tests are conducted by the Thai FDA and the results shared through the annually published Green Book.<sup>129</sup> However, the *Green Book* (figure 1) only publishes the products that passed the standards and tests. According to the key informant interviews, when an active ingredient is found to have lower than the minimum or higher than the maximum standards prescribed in the registered formula by more than 20%, the product is classified as a defective medicine.



**Figure 1. Green Book**

**Achievements:** Summaries of nationwide data on the quality of the medicines are published and shared through the *Green Book* so that the data can be used for procurement.

**Concerns:** Police enforcement on counterfeit medicines in border areas is still very limited. Although Operation Storm through collaboration with USP/DQI, INTERPOL and WHO was able to identify counterfeit medicines produced in neighboring countries, discontinuation of such activities has not been secured. The key informant interviewees pointed out that the current punishments are too weak compared to the profits perpetrators would make through the production and sales of counterfeit medicines.

- 3. USP/PQM Program:** Since 2005, USP/PQM (funded by PMI) has supported Thailand to collect samples and conduct QA tests. Working with the BVBD of the Department of

<sup>128</sup> Quality of malaria drugs still sale in drug stores in Tak province (in Thai).

<sup>129</sup> Website that publishes all the editions of the Green book, <http://dmsc2.dmsc.moph.go.th/webroot/drug/index.stm>.

Disease Control, the Thai FDA, and the BDN Quality Control Laboratory, PQM has provided technical assistance to scale up the antimalarial medicine quality monitoring system.<sup>130</sup> During the 2008–2009 operation, together with BVBD and the Thai FDA, USP/PQM also conducted a study on the quality of antimalarials in cross-border areas.



Figure 2. Sample test failure rate in Thailand, 2005–2009<sup>131</sup>

**Achievements:** Started in 1999, USP/DQI<sup>132</sup> followed by the USP/PQM program, USAID-funded drug quality monitoring programs provided technical assistance to enhance drug quality monitoring activities in GMS that Thailand participated in. Continuing efforts over a decade helped the Thai National Quality Control Laboratory (BDN) to be selected as an international center for antimalarial drug testing and analysis in the Southeast Asian region.

**Remaining Gap:** Because of the lack of a control system for poor-quality medicines, the test results are not shared with Health Product Vigilance Center when counterfeit or substandard medicines are identified by BDN or BVBD. Neither BVBD nor BDN has established a formal pharmacovigilance unit with experts.

### Gaps in Addressing Quality of Antimalarial Medicines

#### Aspects That Need Addressing

- **Regulatory capacity:** In 2012, there are 830 newly registered products by local manufacturers and 508 newly registered products from importers. The number of total registered products to date is 25,778<sup>133</sup> while the number of permanent staff is 304 (among

<sup>130</sup> USP/PQM, *Strengthening National Capacity in Medicines Quality: Five-year Summary (2005-2009)*. [http://www.usp.org/sites/default/files/usp\\_pdf/EN/PQM/RDMARReport.pdf](http://www.usp.org/sites/default/files/usp_pdf/EN/PQM/RDMARReport.pdf).

<sup>131</sup> USP/PQM, *Strengthening National Capacity in Medicines Quality: Five-year Summary (2005-2009)*. [http://www.usp.org/sites/default/files/usp\\_pdf/EN/PQM/RDMARReport.pdf](http://www.usp.org/sites/default/files/usp_pdf/EN/PQM/RDMARReport.pdf).

<sup>132</sup> USP/DQI, *Mekong Malaria Initiative Antimalarial Drug Quality Monitoring and Evaluation*. Rockville, MD: USP; 2003.

<sup>133</sup> Bureau of Drug Control, Thai FDA, [http://drug.fda.moph.go.th/zone\\_search/sea001.asp](http://drug.fda.moph.go.th/zone_search/sea001.asp).

them only a limited number are technical staff involved in drug registration review and GMP inspections).

However, drug quality issues still remain because medical doctors are suspicious about the quality of medicines produced by government-owned pharmaceutical companies.<sup>134</sup>

- **Counterfeit and substandard medicines and police enforcement:** Recent studies have reported that although the presence of counterfeit antimalarial medicines is less than in other GMS countries, a number of substandard antimalarial drugs were found in the market as well as certain drugs that are no longer recommended for malaria treatment.<sup>135</sup>
- **National drug quality testing laboratory:** Quality control tests at site are done using Minilab test kits while the confirmatory test is done by the BDN. The Thai FDA is the responsible entity for sampling antimalarials or other medicinal products in the market. Annually BDN analyzed 2,500 samples.<sup>136</sup> BDN conducted 12,027 samples collected from hospitals under the national universal health coverage scheme, and the Thai FDA collects samples from manufacturing, import, and other distribution sites to conduct postmarketing surveillance.

However, this sampling process by FDA has not been systematic. Also, strong government commitment through adequate budget has not been established. As a result, there is still dependence on donor funding in purchasing reference standard materials, hiring skilled technicians, and providing adequate professional training for staff.

### *Access to Quality Antimalarials*

- **Availability of good-quality ACTs:** In Thailand, antimalarial drugs are managed under the integrated and vertical malaria program led by the BVBD Malaria Cluster. Budget for the procurement of antimalarial medications comes from two sources: Department of Disease Control and the Global Fund. Budget from the Department of Disease Control is used to purchase the drugs that are used in the malaria clinics (under the Malaria Cluster of BVBD) and malaria posts (community clinics) under the Ministry of Public Health. The Principal Recipient Administrative Office purchases the antimalarials (funded by the Global Fund) for Shoklo Malaria Research Unit (SMRU) and temporary shelters along the Thai-Myanmar border. All antimalarial medications, including medications purchased from the Global Fund budget, are then distributed through the BVBD Malaria Cluster distribution channel.

According to the key informant interviews, inaccurate forecasting of demand for antimalarial medicines has been identified as a challenge for the BVBD Malaria Cluster. The procurement

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<sup>134</sup> Bate R. *Are Drugs Made in Emerging Markets Good Quality?* AEI Health Policy Working Paper 2010-02. Washington, DC: American Enterprise Institute for Public Policy Research; 2010. <http://www.aei.org/wp-content/uploads/2011/10/20101222-Bate-WP.pdf>.

<sup>135</sup> Vijaykadga S, Cholpol S, Sitthimongkol S, et al. Strengthening of national capacity in implementation of antimalarial drug quality assurance in Thailand. *Southeast Asia Journal of Tropical Medicine and Public Health* 2006;37(suppl. 3):5–10.

<sup>136</sup> WHO Regional Office for South-East Asia (SEARO). *Drug Testing Laboratories: Report of the South-East Asia Regional Meeting, Bangkok, Thailand, 27 April 2013*. New Delhi, India: WHO/SEARO; 2013.

of antimalarial medicines is done only once a year, and inaccurate forecasting has resulted in the overstock and expiration of purchased antimalarial medicines for several years.

- **Public awareness and treatment-seeking behavior:** Recently, partially artemisinin-resistant *P. falciparum* malaria has emerged on the Cambodia-Thailand border. Exposure of the parasite population to artemisinin monotherapies in subtherapeutic doses for more than 30 years and the availability of substandard artemisinins have probably been the main driving force in the selection of the resistant phenotype in the region.<sup>137</sup> The National Strategic Plan for Malaria Control and Elimination in Thailand 2011–2016 includes preventing use of artemisinin-based monotherapy, fake drugs, and inappropriate treatment in the private sector.<sup>138</sup>

### **Options for the Way Forward**

#### **1. Capacity Building of National Medicines Regulatory Authority**

- **Capacity building of drug regulatory governance:** The key informants pointed out that to address the issues with substandard medicines in the country, drug regulatory governance needs to be improved in the areas of transparency in approving drug marketing authorizations and in exercising administrative measures when substandard medicines are identified.

As an effort to improve GMP compliance and to reach the global standard of GMP practice, the government can gradually implement mandatory GMP compliance in local manufacturers. For example, government-owned pharmaceuticals can lead the pharmaceutical industry in improving the quality assurance management system as a benchmark model for the rest of pharmaceutical manufacturers by providing training on site and by sharing their know-how.

- **Monitoring the quality of counterfeit medicines in cross-border areas:** Key informants have pointed out that the Thai drug regulatory authority still needs to improve its drug monitoring system to detect defective products more effectively and take actions to remove the identified products from the market. For example, the Thai government does not have clear regulations or guidance on how to exercise administrative measures in confiscating products from the market or preventing such cases by enhancing site inspections.

To develop and improve more systematic drug monitoring system, the relevant regulatory bodies need to define clearly their roles and responsibilities. Then, they can develop the system (e.g., web-based management system) to track down records of QA test failures and take necessary actions regarding the registered medicines in a more effective and timely manner. Regular monitoring of pharmaceutical plants can be systematically

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<sup>137</sup> Dondorp AM, Yeung S, White L, et al. Artemisinin resistance: current status and scenarios for containment. *Nat Rev Microbiol* 2010;8(4):272–80.

<sup>138</sup> Bureau of Vector-Borne Disease, Department of Disease Control. *National Strategic Plan for Malaria Control and Elimination in Thailand 2011–2016*.

recorded to trace a history of noncompliance and improvement efforts as an inspection result. The system will also allow the responsible government agencies to share the information among stakeholders, including health care professionals and the public.

- **National drug quality testing laboratory:** As a WHO Collaborating Centre, the Thai national drug testing laboratory (BDN) can play a significant role as a regional hub through collaboration with neighboring GMS national regulatory authorities.<sup>139</sup> While other neighboring countries develop and improve their own capacity to strengthen the drug quality testing laboratory, the Thai BDN can conduct confirmatory tests to share the results with other regulatory authorities so timely actions can be taken to prevent widespread use of counterfeit or substandard medicines.

By continuing collaborative activities with ASEAN, PIC/S, and the USP/PQM program, BDN can strengthen its capacity while assisting other neighboring countries by providing trainings on what it has learned from more advanced organizations.

- **Police enforcement:** The Thai NDRA took appropriate action against violators in country to ensure that antimalarial drugs are of good quality. However, the key informant interviewee noted that the risks of prosecution and penalties levied for counterfeiting are inadequate because the current penalty for producing counterfeit medicines is only a small fine. Therefore, clearer and heavier penalties may need to be considered to reduce the production of counterfeit or substandard medicines in the country.
2. **Access to quality antimalarials:** Although antimalarial treatment is available at public health care facilities at no cost, demand still exists for supply of antimalarial medicines in the private sector. To reduce inappropriate use of antimalarial medicines in the private sector, public education needs to be strengthened through mass communication, trainings, and other media to improve the awareness of risks of substandard medicines and to increase the awareness of the availability of quality antimalarial medicines at public health centers at no cost even among illegal migrants.

The Ministry of Public Health and malaria partners have been exploring nontraditional ways to reach hard-to-reach areas such as factories, plantations, and border areas to raise awareness on identifying symptoms of malaria and on how to seek proper treatments.<sup>140</sup> To increase access to malaria treatment in migrant populations, several interventions have been suggested in the past. Approaching leaders of immigrants to encourage immigrant patients to receive care from malaria clinics can be considered to raise awareness while hiring local health volunteers from immigrants at malaria treatment posts.

Operating mobile malaria treatment posts (units) can also serve hard-to-reach populations with active screening activities on malaria. By coordinating among GMS countries, mobile

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<sup>139</sup> WHO Regional Office for South-East Asia (SEARO). *Drug Testing Laboratories: Report of the South-East Asia Regional Meeting, Bangkok, Thailand, 27 April 2013*. New Delhi, India: WHO/SEARO; 2013.

<sup>140</sup> USAID PMI. *President's Malaria Initiative: Greater Mekong Sub-Region, Malaria Operational Plan FY 2013*. [http://www.pmi.gov/docs/default-source/default-document-library/malaria-operational-plans/fy13/mekong\\_mop\\_fy13.pdf?sfvrsn=6](http://www.pmi.gov/docs/default-source/default-document-library/malaria-operational-plans/fy13/mekong_mop_fy13.pdf?sfvrsn=6).

malaria posts at the border areas can be possible if funding is secured from international donors.

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(<http://www.thaivbd.org/>)  
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## Persons Interviewed

Organization	Type of organization	Interviewees
National Malaria Control program, Malaria cluster of BVBD, Department of Disease Control, Ministry of Public Health	Government agency	Dr. Apinya Niramitsantipong, Country Program Manager Ms. Surawadee Kitchakarn, Focal point for antimalarial medicines quality monitoring Mrs. Saowanit Vijaykadga (former Officer in Charge of Malaria Cluster of BVBD)
WHO country office	International organization	Dr. Deyer Gopinath, Medical Officer Dr. Martin Eisenhower, Technical Officer
Bureau of Drugs and Narcotics (National QC Lab), Department of Medical Sciences, MOPH	Government agency	Dr. Wiyada Akarawut, Acting Director
Chulalongkorn University – ANEQAM QC Lab	Academic institution	Dr. Vorasit Vongsutilers, Director of Pharmaceutical Technology Service Center
Kenan Institute (former Officer in Charge of Malaria Cluster of BVBD)	Nonprofit global health organization	Mrs. Saowanit Vijaykadga

## ANNEX 14. COUNTRY REPORT: VIETNAM

### Summary

Malaria-epidemic areas in Vietnam are remote forest and border areas where the majority of dwellers are marginalized groups, including migrant workers and ethnic minorities. Vietnam reduced malaria death cases from 142 to 21 from 2000 to 2010.<sup>141</sup> However, artemisinin resistance has been identified and confirmed in Vietnam (figure 1), and delayed parasite clearance was detected after treatment with dihydroartemisinin-piperaquine in Bu Dang in 2009. Dihydroartemisinin-piperaquine was reported for reduced susceptibility to artemisinins in Gia Lai province in 2010 and in Dak Nong and Quang Nam in 2012.<sup>142</sup>

Summary of the status of artemisinin resistance in the Greater Mekong Subregion

	artemisinin resistance		containment activities started	AL		AS-MQ		DHA-PPQ	
	suspected year of emergence	detected		D3+	TF	D3+	TF	D3+	TF
Cambodia	2001*	2006	2009	◆	◆	◆	◆	◆	◆
Laos	2013	2013	2014	◆	–				
Myanmar	2001*	2008	2011	◆	–	◆	–	◆	–
Thailand	2001*	2008	2009	◆	◆	◆	◆		
Viet Nam	2009	2009	2011					◆	–

Legend: ■ first-line treatment; \* detected retrospectively using molecular markers or retrospective data;  
 ◆ observed to be > 10%; – observed to be < 10%; blank = undetermined

Figure 1. Status of artemisinin resistance in the Greater Mekong Subregion<sup>143</sup>

In 2011, Vietnam began containment activities based on the Global Plan for Artemisinin Resistance Containment (GPARC) with support from the WHO Western Pacific Regional Office and WHO Country Office.<sup>144</sup> Other measures by the National Institute of Malariology, Parasitology and Entomology (NIMPE) include risk management through early detection and vector control; improving public awareness on the risks of counterfeits and substandard drugs through information, education, and communication trainings in high-burden malaria zones through village malaria workers; improving access to antimalarials by providing medicines free of charge at public health centers; strengthening antimalarial quality monitoring activities in 23 provinces; and sharing information on the dangers of counterfeit and substandard medicines through mass media.

<sup>141</sup> USAID PMI. *President's Malaria Initiative: Greater Mekong Sub-Region, Malaria Operational Plan FY 2013*. [http://www.pmi.gov/docs/default-source/default-document-library/malaria-operational-plans/fy13/mekong\\_mop\\_fy13.pdf?sfvrsn=6](http://www.pmi.gov/docs/default-source/default-document-library/malaria-operational-plans/fy13/mekong_mop_fy13.pdf?sfvrsn=6).

<sup>142</sup> Global Malaira Programme, WHO. Status report on artemisinin resistance, January 2014. [http://www.wpro.who.int/topics/malaria/Update\\_on\\_artemisinin\\_resistance.pdf](http://www.wpro.who.int/topics/malaria/Update_on_artemisinin_resistance.pdf).

<sup>143</sup> Ibid.

<sup>144</sup> Ministry of Health of Vietnam, National Malaria Control and Elimination Programme and National Institute of Malariology, Parasitology and Entomology. National Strategy for Malaria Control and Elimination for the Period of 2012–2015. Hanoi; December 2011.

The government budget for drug quality monitoring and surveillance is very limited. Most monitoring activities, such as conducting screening analysis by collecting samples in the market, are funded by donors. The sample size varies each year depending on the availability of funding from donors.

Although antimalarials are provided free of charge at public health facilities, people still purchase antimalarial medicines at community pharmacies or drug stores, partly because of the limited accessibility in remote areas but also because of the cost for diagnosis testing at public health facilities in urban areas.

To address issues related to the presence of counterfeit and substandard antimalarial medicines in Vietnam, continued efforts are required in monitoring the quality of medicines in the market and taking appropriate actions to recall and remove falsified products from the market by strengthening law enforcement.

To contain the spread of artemisinin resistance especially among the migrant population, it is recommended to improve the access to quality antimalarial medicines in the remote border areas by providing mobile malaria health posts for rapid diagnosis and quality treatment.

To change health care-seeking behavior of patients in general and to encourage use of public health care centers, user fees should be waived for diagnosis of malaria because many patients residing in urban areas still seek antimalarials in private community pharmacies and unlicensed drug stores. Mass communication can be a good option to educate the public on the dangers of counterfeit and substandard medicines while encouraging them to seek health care at public health centers.

## **Key Findings**

### ***Regulatory Framework***

#### *Legislation*

In Vietnam, the legislative framework consists of the Pharmaceutical Law (2005), the Law on People's Health Protection (Chapter VI), the Criminal Law (Article 156 and 157), and other Ordinance on Private Medical and Pharmaceutical Practices.

#### *Regulatory Functions*

Under the MOH, the Drug Administration of Vietnam (DAV) is responsible for the regulation of pharmaceuticals. The DAV evaluates drug applications for their compliance with the 2005 Pharmaceutical Law and issues marketing authorizations accordingly.

- **Drug licensing:** To receive pharmaceutical product marketing authorization in Vietnam, one must obtain a Drug Trading Certificate (for locally manufactured drugs) or a Certificate of Operating in Medicinal Products and Raw Medicinal Materials in Vietnam (for imported

drugs). Annually, the product license holder should report to the DAV on registered drugs that are no longer manufactured or imported.

- **Quality testing of medicines:** In Vietnam, a Certificate of Satisfaction of Principles and Standards of Good Manufacturing Practices (GMP Certificate) is a prerequisite to obtain a manufacturing license. The DAV issues the GMP Certificate if the manufacturer is in compliance with GMP standards. Currently 178 pharmaceutical manufacturers are registered, 121 of which are GMP certified. In Vietnam, 29,541 pharmacies are licensed by the DAV and regularly monitored by economic police and trade supervisors.

Responsibilities for drug inspection are divided into central and provincial levels. Quality control of pharmaceuticals is carried out by the National Institute of Drug Quality Control (NIDQC) in Hanoi, the Sub-Institute of Quality Control in Ho Chi Minh City at central level, and the drug quality control and the provincial laboratories of the provincial health departments at provincial level.<sup>145</sup>

- **Regulatory capacity:** Vietnamese regulations on drug registration are in line with the ASEAN Common Technical Dossier and ASEAN Common Technical Requirements because Vietnam joined the ASEAN Pharmaceutical Regulatory Harmonization efforts.
- **Drug licensing:** Manufacturers are required to provide pharmaceutical regulatory data in compliance with ASEAN Common Technical Dossier guidance, relevant pharmacopoeia information, references for testing, and samples for pharmaceutical marketing authorization.
- **Quality testing of medicines:** USP/PQM has provided technical assistance to establish sentinel sites for the Medicines Quality Monitoring (MQM) program in six provinces in collaboration with NIMEP and DAV and the NIDQC since 2003.<sup>146</sup> When DAV receives information on medicine quality issues from NIDQC, DAV conducts inspections and takes necessary administrative actions to remove products from the market through recalls.
- **Ban on artemisinin monotherapy:** In 2008, the government delisted oral artemisinin-based monotherapies from the national antimalarial treatment policy in Vietnam.<sup>147</sup> In 2013, the government issued an official letter to ban the oAMT products. Although Vietnam has issued a decision to withdraw, stop production, and cancel the registration of artemisinin monotherapies, it has not yet explicitly banned the export of these drugs, which thus become available in neighboring countries.<sup>148</sup> It has been reported that artemisinin monotherapy products are still found in the market.

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<sup>145</sup> WHO Essential Drugs and Other Medicines. *Theme Paper for Discussion: Effective Drug Regulation: What Can Countries Do?* Geneva: WHO; 1999. <http://apps.who.int/medicinedocs/en/d/Js2216e/>.

<sup>146</sup> Ministry of Health of Viet Nam. Medicines Quality Monitoring Program 5 Year Report Viet Nam 2005–2010. Supported by USAID through USP DQI/PQM. Hanoi; 2010.

<sup>147</sup> WHO Global Malaria Programme. The World Health Organization (WHO) urges regulatory measures to stop marketing of oral artemisinin-based monotherapies and to promote access to artemisinin-based combination therapies (ACTs). Last updated November 5, 2010. [http://www.who.int/malaria/publications/who\\_measures\\_to\\_stop\\_monotherapies.pdf](http://www.who.int/malaria/publications/who_measures_to_stop_monotherapies.pdf).

<sup>148</sup> World Health Organization Office of the Representative in Viet Nam, Production and cross-border transport of Artemisinin monotherapies: Incident report and proposed actions. 2012.

- **Pharmacovigilance on substandard and counterfeit medicines:** Health care providers, pharmaceutical manufacturers, and distributors are required to report ADRs to the government. The MoH is responsible for monitoring ADRs. The DAV and the National Drug Information and Adverse Drug Reaction Monitoring Center are responsible for pharmacovigilance in the country.
- **Administrative measures and law enforcement on counterfeit and substandard medicines:** In Vietnam, the Pharmaceutical Law strictly prohibits acts related to conducting drug trade without certificates, trading in drugs of unclear origin, counterfeit drugs, substandard drugs, and expired drugs. However, it has been reported that unregistered and counterfeit drugs are still found in the private sector.

### **Current Efforts That Support Country Capacity Building in Vietnam**

1. **National Monitoring and Evaluation Plan for Malarial Control and Elimination 2011–2020:** A national monitoring and evaluation plan for malaria control and elimination for 2011–2020 was recently developed to assess progress in strategy implementation and evaluate program outcomes and their impact. The national guidelines on malaria epidemiological surveillance were also developed to improve the monitoring system. Through the Global Fund’s support, an electronic management information system for monitoring malaria was implemented.<sup>149</sup> The program is expected to improve the supervision and management of the quality of medicines in the private sector to ensure the quality of the drugs used.<sup>150</sup>
2. **National Strategy for Malaria Control and Elimination 2011–2020:** Objectives of the program include ensuring all people have better access to early diagnosis and prompt and effective treatment at public and private health facilities.

Antimalarial drugs are given free of charge to malaria patients and suspected cases through public sector outlets. A new drug policy was introduced in late 2009, by which ACT was adopted to be the first-line drug for *P. falciparum* malaria. It has been reported that about 80% of early treatment is provided at the commune and village levels through village health workers, while approximately 10% of cases are treated by mobile teams and only 10% to 15% in hospitals in Vietnam.<sup>151</sup> Village workers play an important role in detecting and providing first-line treatment for the migrant and marginalized groups in the country.

3. **PQM program:** The PQM program, funded by USAID through PMI, has been active in providing technical assistance to Vietnam to improve the management of drug quality in the country. USP/PQM provided technical assistance to strengthen the capacity of NIMPE, DAV, and NIDQC to improve the drug regulatory system and postmarketing surveillance.

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<sup>149</sup> The Global Fund, Audit of Global Fund Grants to the Socialist Republic of Viet Nam. 2013 Feb.

<sup>150</sup> National Monitoring and Evaluation Plan for Malaria Control and Elimination in Viet Nam for the Period 2011–2020. Hanoi, March 2011.

<sup>151</sup> WHO/Southeast Asia Region and Western Pacific Region. *Malaria in the Greater Mekong Subregion: Regional and Country Profiles*. New Delhi, India: WHO; 2010.

USP/PQM supported the country to strengthen quality control laboratories through training and provision of essential lab equipment, reference substances, and chemical reagents.<sup>152</sup>

**Achievements:** USP/PQM has helped strengthen the drug quality management system by coordinating different stakeholders to combat the prevalence of counterfeit medicines in Southeast Asia.

**Concerns:** Because of limited budget and skilled technicians, needs remain to be filled, such as providing Minilabs to provincial laboratories for prompt testing on counterfeit or substandard medicines in a highly endemic region.

### **Gaps in Addressing Quality of Antimalarial Medicines**

#### *Aspects That Need Addressing*

- **Regulatory capacity:** According to the key informant interview, currently 10,692 locally produced pharmaceutical products and 11,923 imported products are registered at DAV. Among them, 8 products are antimalarial medicines. However, active surveillance on registered medicines and a good drug registration review process do not seem to be in place and need further investigation to understand the drug regulatory capacity of DAV. According to the key informant interview, only two negative administrative decisions (refusals or suspensions) were made on drug applications in the past three years.

The effectiveness of GMP inspections has been pointed out as problematic during the key informant interview because the number of inspectors is limited in the provinces.

- **Counterfeit and substandard medicines and police enforcement:** Prevailing self-treatment practice and health care-seeking behavior have worsened the failure of effective treatment. Poor-quality antimalarials or monotherapies are often purchased in the private sector because many patients were not aware of risks of poor-quality medicines and they prefer private community pharmacies where they can purchase what they want instead of purchasing a full course of treatment.
- **National drug quality testing laboratory:** According to the key informant interview, premarket sampling tests on imported and exported pharmaceutical products should be improved because currently only limited numbers of products are tested. During the interview, it was also pointed out that the coverage of sentinel sites should be expanded by hiring more staff. The sustainability of operations also has to be addressed because a high turnover rate of technical staff at sentinel sites has been observed. Political commitment by securing government budget is needed to improve the sustainability of the drug quality surveillance operation. In this way, NIDQC will be able to plan the size of sample collection regularly instead of changing the scope of operation depending on the size of outside funding received.

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<sup>152</sup> USAID/USP PQM. Fact Sheet: Promoting the Quality of Medicines Program in Vietnam. July 2013. [http://www.usp.org/sites/default/files/usp\\_pdf/EN/fact\\_sheet-vietnam\\_july\\_2013-final.pdf](http://www.usp.org/sites/default/files/usp_pdf/EN/fact_sheet-vietnam_july_2013-final.pdf).

Domestic manufactured drugs			Imported drugs		
Total amount of samples	Amount of samples failed	Ratio of samples failed	Total amount of samples	Amount of samples failed	Ratio of samples failed
33,905	762	2.30%	5,577	186	3.50%

**Figure 2. Number of tested samples at NIDQC in 2013**

- **Pharmacovigilance on substandard and counterfeit medicines:** Although an active antimalarial QA monitoring system has been established, the current system covers only limited areas of the country. The most difficult-to-reach areas such as border areas with a high transmission rate are not currently covered because of limited budgetary and human resources.

#### *Access to Quality Antimalarials*

- **Availability of good-quality ACTs:** Although antimalarial drugs are provided free of charge to malaria patients through the public sector, limited access to quality medicines is still reported in the private sector. The fee for diagnosis tests at public health facilities is also identified as a contributing factor for patients' tendency to prefer private community pharmacies or clinics.
- **Public awareness:** Although efforts have been made to improve the public awareness of the dangers of counterfeit and substandard medicines through mass media such as broadcasting *Pharmacide: Mekong* on the Vietnamese Health TV channel, hard-to-reach populations are still at risk because they do not have TVs or radios and reside in remote areas.

#### **Options for the Way Forward**

##### **1. Capacity building of NMRA**

- **Capacity building of drug regulatory governance:** Relevant regulations and drug policies are in place to regulate and manage the quality of medicines in Vietnam. However, the level of execution of administrative measures to control the quality of medicines in the market seems weak and needs to be strengthened. As drug quality surveillance data show, the issues of substandard medicines should be addressed by DAV by improving the drug registration review process and by strengthening the roles of inspection on both premarket and postmarket sample tests.
- **National drug quality testing laboratory:** The USAID-funded USP/PQM program has supported the national drug testing laboratory to strengthen its capacity in conducting premarket and postmarket product sample tests. According to the key informant interview, 13% of samples were not tested (mostly biological products) because of lack of equipment and limited capacity in 2013. Strengthening the capacity of the national drug quality test

laboratory is still needed to ensure proper testing equipment, provide proper trainings and increase budget to purchase samples and reference standard materials.

- **Police enforcement:** Police enforcement has not been strongly implemented because of lack of collaboration among relevant government agencies. However, the administrative measures should be strengthened to prevent the production, importation, and circulation of inferior-quality medicines. Through active collaboration with law enforcement agencies, public law enforcement should be strengthened while DAV can improve the public awareness of the dangers of counterfeit and substandard medicines.

## 2. Access to quality antimalarials

- **Accessibility to and affordability of good-quality ACT treatment in private sector:** Affordability of good-quality ACT treatment in the private sector has been reported as a major obstacle for patients to access medicines. Because the majority of patients still seek treatment in the private sector, a new approach needs to be considered to improve the affordability of quality ACT treatment in the country.
- **Public awareness and care-seeking behavior:** To change the care-seeking behavior, the government should be able to supply free malarial diagnosis service at least at public health centers. A new communication method should be introduced for hard-to-reach populations to guide them to seek proper antimalarial care.

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## Persons Interviewed

<b>Organization</b>	<b>Type of organization</b>	<b>Interviewees</b>
National Drug Information and ADR Center Hanoi University School of Pharmacy <a href="http://canhgiacduoc.org.vn/">http://canhgiacduoc.org.vn/</a>	National pharmacovigilance center	Nguyen Hoang Anh (Vice Head)
National Institute of Malariology, Parasitology and Entomology (NIMPE)	Institution that runs the national malaria control program (though the NMCP is administratively distinct)	Nguyen Thi Minh Thu (Pharmacist, MSc., PhD) Dr. Duong Tran Thanh (NIMPE Director)
Drug Administration of Vietnam (DAV)	National medicines regulatory authority	Nguyen M Phar. Van Vien (Director, Drug Quality Control Unit)
National Institute for Drug Quality Control (NIDQC)	National drug quality control laboratory	Dr. Doan Cao Son (Director) Dr. Tran Viet Hung (Vice Director)
Provincial Center for Malaria Control, Binh Phuoc Province	Binh Phuoc province malarial control program	Vice Head of the Provincial Center for Malaria Control
Institute of Malariology, Parasitology and Entomology, Ho Chi Minh City (HCM – IMPE)	Institution that runs the national malaria control program in Ho Chi Minh City/southern Vietnam	Trinh Ngoc Hai (Head of a HCM – IMPE’s Laboratory)
World Health Organization, Ho Chi Minh City Office	WHO Vietnam branch office	VanTuan Le (Acting Officer in Charge of HMCM Office / National Professional Officer)
Institute of Drug Quality Control Ho Chi Minh City	National drug quality control laboratory – Ho Chi Minh City branch (responsible for Ho Chi Minh City and southern provinces)	Nguyen Thanh Ha (Head of Research and Training Department)