Access to Quality Medicines and Other Technologies
Task Force

Regulation of Anti-Malarial Commodities with a focus on Artemisinin-Combination Therapy in Asia and Pacific region

Paul Lalvani, Andy Barraclough (Empower School of Health) and
Jody Tate (Health Resource Facility)
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### Acronyms

<table>
<thead>
<tr>
<th>Acronym</th>
<th>Description</th>
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<tbody>
<tr>
<td>ACCSQ</td>
<td>ASEAN Consultative Committee for Standards and Quality</td>
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<tr>
<td>ACTs</td>
<td>Artemisinin-based Combination Therapy</td>
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<td>ACTD</td>
<td>ASEAN Common Technical Dossier</td>
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<td>ACTR</td>
<td>ASEAN Common Technical Requirement</td>
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<td>ADDOs</td>
<td>Accredited Drug Dispensing Outlets</td>
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<td>ADR</td>
<td>Adverse Drug Reaction</td>
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<td>AFTA</td>
<td>The ASEAN Free Trade Area</td>
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<td>AMDR</td>
<td>Anti-Malarial Drug Resistance</td>
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<td>AMRH</td>
<td>The African Medicines Regulatory Harmonisation</td>
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<td>AMT</td>
<td>Oral Artemisinin-based Monotherapy</td>
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<td>APIs</td>
<td>Active Pharmaceutical Ingredients</td>
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<td>APLMA</td>
<td>The Asia-Pacific Leaders Malaria Alliance</td>
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<td>ASEAN</td>
<td>The Association of Southeast Asian Nations’</td>
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<td>BDN Thailand</td>
<td>Bureau of Drug and Narcotic, Thailand</td>
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<tr>
<td>BREMERE</td>
<td>Building Regional Expertise in Medicines Regulation, Information Sharing, Joint Investigation and Enforcement</td>
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<td>CDC</td>
<td>United States Centers for Disease Control and Prevention</td>
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<td>CDSCO</td>
<td>Central Drugs Standard Control Organization, India</td>
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<td>CTD</td>
<td>Common Technical Dossier</td>
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<td>CTR</td>
<td>Common Technical Requirements</td>
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<td>EFTA</td>
<td>European Free Trade Association</td>
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<td>ERAR</td>
<td>Emergency Response to Artemisin Resistance</td>
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<td>ERP</td>
<td>Expert Review Panel</td>
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<td>FDA</td>
<td>Food and Drug Administration</td>
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<td>FPPs</td>
<td>Finished pharmaceutical Products</td>
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<td>GMP</td>
<td>Good Manufacturing Practice</td>
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<td>GMS</td>
<td>Greater Mekong Subregion</td>
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<td>GPARC</td>
<td>The Global Plan for Artemisinin Resistance Containment</td>
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<td>HIV</td>
<td>The Human Immunodeficiency Virus</td>
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<td>ICH</td>
<td>International Conference on Harmonization</td>
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<td>INTERPOL</td>
<td>The International Criminal Police Organization</td>
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<td>ISO</td>
<td>International Organization for Standardization</td>
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<td>Lao PDR</td>
<td>Lao People’s Democratic Republic</td>
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<td>Laos FDQCC</td>
<td>Equipment for the Food and Drug Quality Control Center in Laos</td>
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<td>LSHTM</td>
<td>London School of Hygiene and Tropical Medicine</td>
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<td>MC</td>
<td>Malaria Consortium</td>
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<td>MFDA</td>
<td>The Myanmar Food and Drug Administration</td>
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<td>MoH</td>
<td>Ministry of Health</td>
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<td>MOPH</td>
<td>The Ministry of Public Health</td>
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<tr>
<td>MRA</td>
<td>Medicines Regulatory Authority</td>
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### Access to Quality Medicines and Other Technologies Task Force

<table>
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<th>Abbreviation</th>
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<tr>
<td>NDRAs</td>
<td>National Drug Regulatory Authorities</td>
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<td>NEPAD</td>
<td>The New Partnership for Africa's Development</td>
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<td>NHPCV</td>
<td>National Centre for Pharmacovigilance</td>
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<td>NIDQC Viet Nam</td>
<td>National Institute of Drug Quality Control of Viet Nam</td>
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<td>NMQCL</td>
<td>National Medicines Quality Control Laboratory</td>
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<td>NOMCoL</td>
<td>Network of Official Medicines Control laboratory</td>
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<tr>
<td>PIC/S</td>
<td>Pharmaceutical Inspection Convention and Pharmaceutical Inspection Co-operation Scheme</td>
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<td>PMI</td>
<td>President’s Malaria initiative</td>
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<td>PPWG</td>
<td>The Pharmaceutical Product Working Group</td>
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<td>POD</td>
<td>PosObatDesa/Village Drugs Post</td>
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<td>PQ</td>
<td>Prequalified</td>
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<td>PQM</td>
<td>Promoting the Quality of Medicines program</td>
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<td>PSI</td>
<td>Population Services International</td>
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<td>PvPI</td>
<td>The Pharmacovigilance Programme of India</td>
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<td>QA</td>
<td>Quality Assurance</td>
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<td>QC</td>
<td>Quality Control</td>
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<td>QMTF</td>
<td>Quality Medicine and Technology Task Force</td>
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<td>RDM-A</td>
<td>Regional Development Mission for Asia</td>
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<td>RDTs</td>
<td>Rapid Diagnostic Tests</td>
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<td>SRAs</td>
<td>Stringent regulatory authorities</td>
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<tr>
<td>UMC Sweden</td>
<td>The Uppsala Monitoring Centre, Sweden</td>
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<td>USAID</td>
<td>United States Agency for International Development</td>
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<td>USP</td>
<td>United States PharmacopeialConvention</td>
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<td>USP DQI</td>
<td>The United States Pharmacopeia Drug Quality and Information Program</td>
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<td>USP PQM</td>
<td>United States Pharmacopeial Convention Promoting the Quality of Medicines program</td>
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<tr>
<td>WHO</td>
<td>World Health Organization</td>
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<td>WHO WPRO</td>
<td>World Health Organization Western Pacific Regional Office</td>
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Executive Summary

This paper was prepared for the first meeting of the Access to Quality Medicine and Technology Task Force (QMTF) of the Asia-Pacific Leaders Malaria Alliance (APLMA) which is being held 12 – 13 March 2014 in Sydney. This paper focuses on the regulation of oral artemisinin-based combination therapy, vital for malaria control and elimination. The regulation of other anti-malarial commodities in the Asia-Pacific region is also critical but the challenges, effective strategies and stakeholders involved are so significantly different to those related to ACTs that they could not all be covered in this paper. It is hoped that the regulation of other anti-malarial commodities in the Asia-Pacific region will be the focus of future research.

Artemisinin plays a vital role in the treatment, control and elimination of malaria. As the safest and most effective anti-malarial medicine in the Asia-Pacific region, it is critical that its effectiveness and efficacy is sustained. However, malaria which is resistant to artemisinin has been identified in some countries of the Greater Mekong Subregion and has the potential to spread into neighbouring countries and beyond. The result of this spread of anti-malarial drug resistance would be severe, and represents a significant threat to malaria control efforts across the region.

Resistance to artemisinin is thought to have emerged due to poor treatment practices, inadequate patient adherence to prescribed anti-malarial regimens, the widespread availability of oral artemisinin-based monotherapies (AMTs), and substandard forms of anti-malarial medicines. These issues are exacerbated by the challenges in regulating the private sector and the pharmaceutical marketplace, which plays an important role in providing access to anti-malarial medicines in many countries in the region.

Regulating anti-malarial medicines is therefore vital to ensure that those with malaria can continue to be treated effectively, and that resistance is halted. The national drug regulatory authorities (NDRAs) of the countries which form the focus of this paper, whose mandate is to ensure access to safe, effective and quality-certified medicines, have variable capacity in carrying out their roles of drug registration, post-market surveillance, manufacturer and supply chain oversight, consumer protection including monitoring of adverse reactions and adverse events, controlling messaging from suppliers to consumers, and most importantly for the region, controlling the activities of the informal sector.

The nature of malaria in the Asia-Pacific region and the challenges faced in its control and elimination, demand an effective regulatory response, which is based on a harmonized and coordinated, national and regional approach. Only when countries develop adequate regulatory enforcement capacity, and work together, can regulatory challenges be effectively addressed.

1 WHO (2013a) World Malaria Report 2013
2 These are the countries which are key suppliers of artemisia annua (PRC and Viet Nam), the plant source of artemisinin, producers of artemisinin based medicines (India in addition to PRC) and the countries of the Greater Mekong Subregion (Cambodia, Lao PDR, Myanmar, Thailand, Viet Nam and Yunnan Province in PRC).
There are several ongoing global, regional and national regulatory-focused interventions, some of which have been catalogued and presented in Appendix 1. Drawn from this exercise, Section 5 of this paper presents four intervention options for strengthening and scaling up regulatory capacity. These range from global to regional initiatives; from public sector to private sector initiatives; and from the more standard approaches to the innovative. Drug regulation however is a function of the health system and should not target a specific vertical program such as malaria or HIV/AIDS. Interventions that benefit malaria will also benefit the entire health system and the region more broadly, not just malaria and not exclusively ACTs. The proposed interventions are:

1) establishing an Asia-Pacific prequalification program in coordination with the World Health Organization (WHO)

2) wiping-out the widespread distribution of sub-standard and counterfeit pharmaceutical products through advocacy and capacity building

3) strengthening private sector industry to attain higher quality manufacturing standards

4) phasing-out oral artemisinin-based monotherapies.

However, in order to identify which of these types of interventions will be most appropriate to invest in and scale up, it is recommended that first, an exhaustive inventory of all regulatory-linked activities should be developed. Each of these interventions should then be analyzed to determine their current and potential impact, return on investment, links to and leveraging of other initiatives, their potential for scaling up and lessons learnt in their implementation.

After this research and analysis has been completed, it is recommended that APLMA convene a consultation to bring together key stakeholders from policy, regulatory, public and private sector, manufacturing and downstream supply chain, and related technical partners. The research of potential interventions should be debated to determine which portfolio of activities are best suited for the challenges being faced in the different parts of the region, with a focus on region-wide approaches that leverage the strengths of partner countries. The consultation should end with a roadmap, which should include detailed strategies, workplans and budgets.

Finally, drawing on the findings of the paper four suggestions for policy recommendations are presented. These are:

1) promote the establishment of a ‘Regional Center of Excellence for Regulatory Sciences’ through inter-regional technical support, with more stringent regulatory authorities providing support to other national drug regulatory authorities in the region

2) build an Asia-Pacific regional prequalification center, in collaboration with WHO, European Medicines Agency, and United States Food and Drug Administration, all of whom are already collaborating closely with WHO’s prequalification program
3) make consumers the epicenter of the fight against poor quality drugs through leveraging of digital media, web and phone ‘apps’, and creating an ecosystem for real-time peer-to-peer and government-to-peer communications

4) allocate an appropriate level of funding for effective operations of an NDRA by encouraging governments to invest more internal funds in their national drug authorities, and also by accessing regional funds from development banks and donors. The investment in the NDRAs should be linked to the size of the country’s pharmaceutical market sector and its challenges.
1. Introduction and focus of research

The Asia-Pacific Leaders Malaria Alliance (APLMA) is holding the first meeting of the Access to Quality Medicine and Technology Task Force (QMTF) on 12 – 13 March 2014 in Sydney.

Several technical background papers are being prepared for the QMTF meeting to provide informative summaries for the task force members. This paper focuses on regulation of oral artemisinin-based combination therapy for the treatment of malaria.

*Oral Artemisinin-based Combination Therapy (ACTs) focus:* Anti-malarial commodities include a mix of preventative and treatment-focused products ranging from medicines, diagnostics, medical supplies, insecticides and bednets. Each one plays a critical role in the fight against malaria, and each commodity has unique regulatory challenges. The focus of this research is on oral ACTs, vital in malaria control and elimination. The regulation of other anti-malarial commodities in the Asia-Pacific region is critical for the control and elimination of malaria. The challenges, effective strategies and stakeholders involved in the regulation of these commodities however are so significantly different to those involved in the regulation of ACTs and are not covered in this paper. It is hoped that the regulation of other anti-malarial commodities in the Asia-Pacific region will be the focus of future research.

*Country focus:* APLMA member countries range from donors, artemisia growers (the plant from which the active ingredient is extracted), oral ACT manufacturers and consumers. The focus of this research is on countries that are oral ACT manufacturers, those with a high burden of malaria, and those with artemisinin-resistance. The focus countries are therefore Greater Mekong Subregion countries (including Cambodia, Lao PDR, Myanmar, Thailand, Viet Nam, and Yunnan Province in PRC), PRC more broadly and India. While the paper is focused primarily on a small group of countries, the challenges associated with the regulation of anti-malarial commodities can only be addressed through region-wide coordination and collaboration.

*Regulatory Focus:* This research focuses on regulatory challenges and solutions to promote access to quality-assured ACTs. However, the regulatory strategy needs to be considered in a global context and should support the global malaria action plan (GMAP). This paper provides a short summary GMAP and its linkages to regulatory issues. This is the basis on which regionally focused interventions should be developed. The paper then summarizes the context and key challenges of regulating ACTs in the Asia-Pacific. This is followed by a more detailed discussion of the regulatory approaches, challenges and several ongoing interventions. The research also includes four potential interventions and three case studies to provide more insight into possible options for regional action and concludes with some next steps and possible options for policy recommendations.

The structure of the paper is illustrated in Figure 1, which emphasizes that the most appropriate and effective strategy would be one that sits at the center of the three components.
2. Global Malaria Action Plan
The Global Malaria Action Plan provides a global framework for action around which partners can coordinate their efforts, and outlines the vision for a substantial and sustained reduction in the burden of malaria in the near and mid-term, and the eventual global eradication of malaria in the long term, when new tools make eradication possible.

ACTs play a vital role in the control and elimination of malaria with the total number of ACT treatments being scaled up from 11 million in 2005 to 331 million in 2012.\(^3\) The World Health Organization (WHO) recommends that ACTs are used for the treatment of uncomplicated \textit{P. falciparum} malaria and \textit{P. vivax} malaria which is resistant to other known effective drugs. Treatment should include one of the five recommended ACTs.\(^4\) The guidelines also state that artemisinin and its derivatives should not be used as oral mono-therapies in order to prevent the development of artemisinin resistance.

The GMAP highlights that anti-malarial drug resistance (AMDR) is a major public health challenge. Research has shown that ACT resistance is a result of poor treatment practices, inadequate patient adherence to prescribed anti-malarial regimens, the widespread availability of oral artemisinin-based monotherapies (AMTs) and substandard forms of anti-malarial medicines.\(^5\) In order to ensure early detection and inform and adapt treatment policy, continuous monitoring of ACT efficacy and resistance to ACT drugs is required.

\(^3\) WHO (2013a)
\(^4\) These are artemether plus lumefantrine, artesunate plus amodiaquine, artesunate plus mefloquine, artesunate plus SP, and dihydro-artemisinin plus piperaquine.
\(^5\) WHO (2013a)
As part of the global strategy to control AMDR, the World Health Assembly in 2007 endorsed that oral AMTs should be withdrawn and replaced with ACTs. Since then, the number of countries that still allow the marketing of AMTs has decreased from 55 in 2008 to only 9 countries in 2013, out of which only one country, Timor-Leste, lies in the Asia-Pacific region. The number of pharmaceutical companies marketing these oral AMTs reduced from 38 in 2010 to 30 in 2013—not a significant reduction; most of the AMT manufacturers are based in India.

3. Asia-Pacific region—context and challenges

The Asia-Pacific region is a major supplier of artemisia annua, the plant source for the anti-malarial medicine artemisinin, which is cultivated mainly in PRC and Viet Nam, and who together supply more than 80 per cent of global demand. It is estimated that 40-50 per cent of the oral ACT market is supplied by five leading Asian manufacturers based in India and PRC, countries which are also are significant producers of AMT. In addition, the region includes countries which are high-burden, high-risk, artemisinin-resistance countries (Greater Mekong Subregion [GMS] countries, including Cambodia, Lao PDR, Myanmar, Thailand, Viet Nam, and Yunnan Province in PRC).

The malaria landscape in the Asia-Pacific region varies from being an indoor-urban challenge in parts of India to being an outdoor-rural/forested-area problem along international borders of GMS countries. In the GMS in particular, the populations at risk are often ethnic minorities in remote areas and seasonal, migrant workers who move across international borders, and have limited access to the formal channels of health care, especially in areas where there is armed conflict or communal unrest. This points to the need to view this as a regional challenge requiring a regional solution.

There are four key critical regulatory-related challenges for malaria control and elimination in the Asia-Pacific region and especially across the GMS, which are described in more detail below.  

3.1 Increasing resistance to oral artemisinin-based combination therapies

Resistance to ACTs has now been detected in Cambodia, Myanmar, Thailand and Viet Nam. Even when a patient is resistant to artemisinin however, ACTs may still be used to treat malaria, as long as the partner drug is effective. However, in Cambodia’s Pailin province, resistance has been found to both of the components of multiple ACTs, and so a non-artemisinin-based combination has been introduced. This alternative drug is not as well tolerated and is at least ten times more expensive than ACTs; in addition, 

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7 The rational use of medicines refers to “Patients receive medications appropriate to their clinical needs, in doses that meet their own individual requirements, for an adequate period of time, and at the lowest cost to them and their community.” (WHO, 1985).


9 WHO (2013a).

10 WHO (2013a.)

there are very few quality-assured suppliers for this alternative drug, unlike ACTs which have many more high quality manufacturers.

Given the history of the spread of anti-malarial resistance from the GMS to the rest of the world for previously effective anti-malarial drugs such as chloroquine, there is a high degree of concern over the spread of artemisinin resistance. As there is no similarly safe and effective alternative anti-malarial medicine to ACTs, the importance of containing this drug resistance is therefore critical. In April 2013, WHO released the Emergency response to artemisinin resistance in the Greater Mekong Subregion: Regional framework for action 2013–2015. The document describes priority areas in which action is needed in the coming years to contain artemisinin resistance. In an initiative to combat artemisinin resistance, The Global Plan for Artemisinin Resistance Containment (GPARC) was developed by the WHO Global Malaria Programme through consultation with over 100 malaria experts. GPARC outlines various actions for containing artemisinin resistance, two of which can be supported with an effective national or regional drug regulatory strategy: the removal of 1) oral AMTs and 2) substandard and counterfeit anti-malarial medicines from the supply chain. Both of these key interventions can only be addressed effectively with strong regional collaboration and coordination.

The subsequent sections discusses various challenges faced in the region including the high prevalence of substandard and counterfeit anti-malarial medicines, weak health care service delivery for hard to reach populations and a lack of provider and consumer knowledge regarding the disease and the most appropriate way to use medicines.

### 3.2 High-prevalence of substandard and counterfeit anti-malarial drugs

Access to quality-assured malaria medicines is essential for an effective regional global response to malaria. However, the large-scale availability of sub-standard and counterfeit drugs is a major challenge to malaria control and elimination across the region, a challenge which must be addressed through collaboration and coordination.

Studies conducted over the last decade have pointed to an abundance of sub-standard anti-malarial medicines in the Asia-Pacific region. A study conducted in 2006 found a profusion of sub-standard artemisin in mainland South-East Asia, with 38 per cent to 52 per cent of artemisin blister packs not fully effective.

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12 WHO (2013a)
13WHO defines sub-standard medicines as “products whose composition and ingredients do not meet the correct scientific specifications and which are consequently ineffective and dangerous to the patient. Active ingredients may be completely absent in sub-standard drugs, which can lead to ineffective treatment, prolonged illness, or death. Alternatively, active ingredients may be present in sub-therapeutic concentrations leading to drug resistance” WHO (2003) Substandard and counterfeit medicines Factsheet, No 275.
14A counterfeit medicine refers to a product which is “deliberately and fraudulently mislabelled with respect to identity and/or source. Counterfeiting can apply to both branded and generic products and counterfeit products may include products with the correct ingredients or with the wrong ingredients, without active ingredients, with insufficient active ingredients, or with fake packaging”WHO webpage, What are Counterfeit Medicines? http://www.who.int/medicines/services/counterfeit/faqs/03/en/ accessed 1 March 2014
containing any active ingredient. Another study conducted along the Thai-Cambodia border showed an overall failure rate of 12 per cent for anti-malarial medicines. Even more worrying was the finding that the failure rate for AMTs was 60 per cent; other oral artemisinin-based drugs had a failure rate ranging from 12.5 to 35 per cent. It is important to emphasize that only two per cent of the failed samples were from the public sector, 26 per cent from the legal private sector and the majority, 72 per cent, were from the illegal private sector.

Some of the main regulatory-related reasons for the availability of sub-standard and counterfeit anti-malarial medicines in the market are linked to weak National Drug Regulatory Authorities (NDRAs), especially lack of post-market surveillance and drug testing due to weak National Laboratory infrastructure; and also a lack of consumer awareness and education, and weak coordination among NDRAs in the region.

3.3 Weak health care service delivery for hard-to-reach and mobile populations:
Patients in urban settings can generally access quality-assured ACTs through public sector and sometimes through the formal private sector. However, the hard-to-reach mobile populations, which form the ‘hot-spots’ of drug resistance, normally access health services from the predominately low-cost, poor quality, informal sector. A study on access to ACTs for malaria in Cambodia found that in remote areas, the coverage of rational diagnosis and treatment for malaria was very low, and there was widespread use of oral AMTs. The main reason for the low coverage of appropriate ACTs was the predominant use of the informal private sector for malaria services. Similarly another report highlighted the existence of unregulated private retail outlets to be the major source of sub-standard anti-malarial medicines in Laos, Cambodia and Myanmar. The risk is compounded by the fact that the private sector tends to be the first point of contact for over 70 per cent of people seeking malaria treatment. As a result, poor, hard to reach, and mobile populations are extremely important. This issue can only be addressed on a regional level, since an outbreak or exacerbation of artemisinin-resistant malaria among mobile and marginal groups will spread across national borders.

3.4 Lack of provider and consumer knowledge regarding the disease and rational use of medicines
In many parts of the GMS there is high degree of self-medication by a population that is generally not well informed (especially in remote areas) and which accesses low-cost, poor- quality anti-malarials from the informal private sector and the use of anti malarial medicines which does not align to established guidelines. Drug-use surveys have reported a high rate of malaria self-medication in many parts of the

17Phanouvong, S. (2013b) Presentation at the WHO Bi-regional Meeting on Healthy Borders in the GMS, August 2013, Bangkok.
GMS (53 per cent in a Lao PDR survey). These vulnerable populations do not have access to public sector health facilities, and often receive a ‘cocktail’ of drugs which may include antipyretics (used for fever), vitamins, anti-malarial medicines, antihistamines, and antibiotics, most of which are inappropriate for treating malaria.

Regulatory authorities have mechanisms through which they can address many of these challenges, as discussed in the next section. However, given the nature of malaria and the challenges of malaria control and elimination in the Asia-Pacific region, an effective regulatory response will require a harmonized and coordinated, national and regional strategy.

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21WHO (2010) Malaria in the greater mekong subregion: Regional and country profiles.
4. Regulatory Strategy and Challenges

4.1 Introduction to Pharmaceutical Regulation:

There are estimated to be more than 100,000 to 150,000 different pharmaceutical brands in the world.\(^2\) In the Asia-Pacific region, countries have registered from 3,000 to as many as 60,000 different brands.

WHO’s document titled Effective drug regulation: A multi-country study\(^3\) perfectly articulates that “drug regulation is a public policy response to the perceived problems or perceived needs of society. Consequently, drug laws need to be updated to keep pace with changes and new challenges in their environment”. In many instances the evolution of these policies and interventions have been a direct result of a crisis—either in their own country or in some other part of the world. The NDRA responses to the various crises have been to adopt regulations, structures and processes to “ensure the safety, efficacy and quality of drugs, as well as the accuracy and appropriateness of the drug information available to the public.”\(^4\)

Activities of a National Drug Regulatory Authority

The role of the NDRA is to register products based on need, quality, safety and efficacy. In addition to new product registration however, NDRA’s are involved in a full spectrum of drug regulatory activities that promote access to safe, effective and quality-certified medicines. Some typical activities include: authorization to conduct pre-market testing (clinical trials), product assessment and marketing authorization for new products and variation of existing authorizations, adverse drug reaction monitoring (pharmacovigilance), monitoring of drug utilization, provision of drug information, control of drug promotion and advertisements, quality control laboratory testing, Good Manufacturing Practice (GMP)\(^5\) inspections, licensing of manufacturers, wholesalers and other distribution channels.

Although the framework of an NDRA (see Figure 2) focuses on the structure of a single NDRA, it is important to emphasize the linkages and coordination between NDRA’s with regional structures (ASEAN Consultive Committee on Standards and Quality) and with the global structures, e.g. WHO’s prequalification program (WHO PQ). The WHO PQ assesses product dossiers, inspects manufacturing sites, approves drug testing laboratories and reviews protocols. Through these steps, the WHO PQ ensures that key health products meet stringent quality standards and are appropriate for international public health programs. The quality review conducted by WHO PQ can be leveraged by NDRA’s globally, who may not have sufficient regulatory capacity of their own to conduct their assessments. As a result of

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5 GMP, also referred to as ‘cGMP’ or ‘current Good Manufacturing Practice’ is the aspect of quality assurance that ensures that medicinal products are consistently produced and controlled to the quality standards appropriate to their intended use and as required by the product specification.
these efforts, many countries allow fast-track registration for products that have been approved by WHO PQ.

The components of an NDRA are illustrated in the framework presented in Figure 2 below:

**Figure 2- National Drug Regulatory Authority Framework.**

4.2 Regulatory environment and challenges for ACTs in Asia and Pacific

The regulatory framework (Figure 2) is broad in scope and covers the entire value chain from drug development to consumer protection. Unfortunately due to limited resources and capacity, several areas in drug regulation receive relatively less attention. For example, drug regulatory systems in most countries expend far more time and effort on pre-marketing than on post-marketing activities. WHO recommends that “no matter how thoroughly pre-marketing assessment is conducted, it is only one of the functions needed if the efficacy and, especially, the safety of drugs are to be assured. Post-marketing surveillance functions, such as adverse drug reaction (ADR) monitoring, quality control, testing and re-evaluation of registered products, should also be priority areas in drug regulation.”

Most of the focus-country NDRAs experience similar gaps, usually investing far more resources in pre-market activities vis-à-vis the oversight of post market surveillance, including regulation of the supply chain of importers, wholesalers, retailers and most notably, the informal sector. This is all the more significant given that most of the oral AMTs, sub-standard and counterfeit drugs are sold through the informal private sector.

Another key component of drug regulation that often receives less attention and funding than required is oversight of drug information being delivered by the suppliers to the providers and consumers—regulating this activity can significantly influence and promote rational drug use, and in the Asia-Pacific context, it could promote the use of quality-assured oral ACTs.\textsuperscript{27} Building awareness among consumers is therefore a vital area in need of strengthening. This could be encouraged by leveraging digital media and creating an culture of peer-to-peer and government-to-peer information sharing.

4.3 Regulatory Capacity in Asia-Pacific:
Across the globe, regulatory capacity varies significantly between countries. Broadly, the capacity of the various NDRAs can be segmented into three categories: stringent regulatory authorities (SRAs), which includes 35 countries which are members or affiliates of the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH). This includes Australia and Japan from the Asia-Pacific region. In addition are countries with regulated authorities, which includes 44 who participate in the Pharmaceutical Inspection Convention and Pharmaceutical Inspection Co-operation Scheme (jointly referred to as PIC/S), including Australia, Taiwan, Indonesia, Malaysia, New Zealand and Singapore, from the Asia-Pacific region; and others, which are generally felt to be less regulated authorities. The seven focus countries of this paper fall in to the last category and are considered to have varying levels of gaps in the regulatory policies, structures and capacity. Some countries in the wider Asia-Pacific region belong to the ICH and PIC/S categories and are therefore in a position to conduct technology transfer and capacity building across the region. The establishment of a Regional Center of Excellence for Regulatory Sciences for example which encourages inter-regional technical support could be an option. This would allow the SRA and PIC/S authorities in the region to provide technical support to other national drug regulatory authorities in the region, building capacity at the national level for the benefit of the region.

Reaffirming some of the previous statements and findings, United States Pharmacopoeial Convention (USP) conducted research in 2013,\textsuperscript{28} and concluded that the main causes for the presence of sub-standard and counterfeit drugs in the GMS countries are weak national drug regulatory capacity, which may include ineffective legislation and regulations, limited qualified human resource capacity, poor compliance by local manufacturers and importers, inadequate border control leading to smuggling of medicines and weak enforcement and prosecution. Weak coordination and collaboration with regional drug authorities, especially for cross-border challenges, was also considered to be a key gap. Building this capacity by allocating appropriate funding for NDRAs to allow for effective operations will be critical. These funds will primarily need to be invested in NDRAs by their governments but could be bolstered by regional and international financial support.

\textsuperscript{27} Ratanawijitrasin, S. and Wondemagegnehu, E. (2002)
\textsuperscript{28} Phanouvong, S (2013) Improving Access to Quality Medicines in the Greater Mekong Sub-region. WHO Bi-regional Meeting on Healthy Borders in the GMS August 5-7, 2013, Bangkok, Thailand
A brief comparison of some of the NDRA-linked characteristics of three focus countries is presented in the table below.

**Table 1- Comparative regulatory situation analysis of three countries (Myanmar, Thailand and India).**

<table>
<thead>
<tr>
<th></th>
<th>Myanmar</th>
<th>Thailand</th>
<th>India</th>
</tr>
</thead>
<tbody>
<tr>
<td>GDP per capita (nominal) (US$) (2011)</td>
<td>1,144</td>
<td>5,775</td>
<td>1,516</td>
</tr>
<tr>
<td>Pharma market size (domestic) (US$ billions) (2012)</td>
<td>0.25</td>
<td>4</td>
<td>16</td>
</tr>
<tr>
<td>Population (million) (2011)</td>
<td>53</td>
<td>67</td>
<td>1,237</td>
</tr>
<tr>
<td>Pharmaceutical consumption (US$) per capita</td>
<td>5</td>
<td>60</td>
<td>13</td>
</tr>
<tr>
<td>Technical staff at NDRA (central level)</td>
<td>42</td>
<td>96</td>
<td>119</td>
</tr>
<tr>
<td>Market size per technical staff (US$ million)</td>
<td>6</td>
<td>40</td>
<td>220</td>
</tr>
<tr>
<td>Number of drug samples tested (per year)</td>
<td>1,980</td>
<td>2,500</td>
<td></td>
</tr>
<tr>
<td>Market size per test conducted</td>
<td>$126,000</td>
<td>$1,600,000</td>
<td>$2,000,000</td>
</tr>
<tr>
<td>Percentage of drug products which fail quality control tests</td>
<td>8-10%</td>
<td>10%</td>
<td>6%</td>
</tr>
</tbody>
</table>

Besides the obvious differences in the country and market size, there is a huge variation in the number of NDRA staff relative to each country’s market size: in the case of Myanmar, one NDRA staff is available per $6 million; for Thailand, it is one person per $40 million and for India it is one person per $220 million. Similarly for the drug samples tested in each of the countries, Myanmar conducts one test per $126,000; Thailand conducts one per $1.6 million, and India conducts one test per $2 million. The percent of products that fail quality control testing vary significantly, but have been declining over a period of time. The failure rate in SRA countries is generally less than 1 – 2 per cent. More details on the regulatory systems and capacity of Myanmar, India and Thailand can be found in Appendix 3. These differences in NDRA capacity highlight the challenges many countries face in carrying out the full range of their regulatory functions (as highlighted in Figure 2). By working together to share resources and information however, regionally focused interventions may be able to address these differences in capacity to deal with this regional challenge.

A more detailed analysis of all the focus countries needs to be conducted with benchmarks to ICH and PIC/S countries, especially the countries that are in the Asia-Pacific region. The value of this study would be to inform policy makers regarding which areas are at risk and what actions need to be taken to strengthen the NDRAs across the region. A broader (more countries) and deeper (more indicators) analysis needs to be conducted, although not all of the data was available for the purposes of this paper.

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31 Several of the countries also have regulatory staff at the regional level, however, this has not been included in the calculation.
32 Central Drugs Standard Control Organization (Indian NDRA) data.
33 Central Drugs Standard Control Organization (Indian NDRA) data.
5. Options for interventions to improve the systems for the regulation of ACTs in the Asia-Pacific region

A rapid intervention-mapping exercise was conducted over a one-week period, primarily through secondary research, the results of which are presented in Appendix 1. The inventory showed that there are a range of ongoing interventions which are active in the Asia-Pacific region, aiming to strengthen regulatory systems. These interventions vary from regional, national or ‘hot-spot’ specific interventions; those which are either health-systems focused or activity specific; information-based market intelligence or operations and implementation-based interventions.

Based on this mapping exercise, four regionally-focused interventions are presented as illustrations of possible options for strengthening the regulations of anti-malarial medicines. These interventions range from global to regional; from public sector to private sector; and from the more standard approaches to more innovative interventions.\(^\text{35}\)

It should be emphasized that drug regulation is a ‘horizontal,’ health systems function; it cannot and should not target a vertical program, such as malaria or HIV/AIDS. As a result, NDRA linked interventions which benefit malaria will also benefit the broader health system, and even the region as a whole, not only malaria, and not exclusively ACTs.

**Intervention 1: Establishing an Asia-Pacific Prequalification Program in coordination with WHO**

WHO’s prequalification (PQ) programme has obtained high impact; it ensures that key health products are safe, appropriate and meet stringent quality standards for international public health programs. It does so by assessing product dossiers, inspecting manufacturing and testing sites. The quality review conducted by WHO PQ can be leveraged by NDRA’s globally, who may not have sufficient regulatory capacity of their own to conduct their assessments. Many countries allow fast-track registration for products that have been approved by WHO. In addition to improving access to quality-assured medicines, WHO’s PQ program has led to increased global competition by attracting new suppliers to compete for new market opportunities.

The success of the project has generated significant demand for WHO’s PQ services which are now involved in approving drugs, diagnostics, medical devices, vaccines, quality control testing laboratories, and even providing capacity building services. This has resulted in bottlenecks and presently there are over 150 medicines that are under first time assessment and another 44 prequalified medicines that are undergoing requalification review. In 2010, the median time to prequalify an innovator product was 4.3 months, and 31.6 months to prequalify a generic product.\(^\text{36}\) While the demand for WHO PQ services has

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\(^{35}\) Input into these interventions have been provided by Dr. Alasdair Breckenridge, the former Chair of UK’s Medicines and Healthcare Products Regulatory Agency.

\(^{36}\) WHO (undated) The WHO prequalification programme and the medicines patent pool: a primer
increased, resources for funding these activities has been declining, and it is believed that with available resources, prequalification will not be able to cover all of these needed products.\textsuperscript{37}

An alternative to WHO PQ that has been used by other public health organizations and manufacturers is to obtain regulatory approval from one of the stringent regulatory authorities (SRAs). For example, the United States (US) Food and Drug Administration (FDA) reviews the marketing applications using its normal standards for authorization. If the product still has marketing protection in the US, FDA issues a "tentative approval" rather than a "full" approval. The "tentative" approval signifies that the product meets all safety, efficacy, and manufacturing quality standards for marketing in the US, but cannot be marketed in the US because of legal market protection. USAID allows, under the President's Emergency Plan for AIDS Relief, purchase of any product that has either a "full" or "tentative" FDA approval.\textsuperscript{38}

The European’s Medicines Agency (EMA) has Article 58 of Regulation, which operates in co-operation with WHO to review product registration. The review is conducted at the same level as products for the European Union (EU), but the product is intended exclusively for markets outside of the EU. Medicines eligible for this procedure are meant to be only for public health, including drugs for malaria. This mechanism has already been applied for two ACTs already.\textsuperscript{39-40}

The initiatives and efforts being undertaken by the EMA can be deployed by other SRAs in the Asia-Pacific region, e.g. Australia’s NDRA, the Therapeutic Goods Administration (TGA), to establish a similar prequalification model for the Asia-Pacific countries. This would need to be developed in collaboration with WHO and other SRAs, and one approach could be to segment the products by therapeutic categories, or by type of health commodity (medicines, diagnostics, devices, etc.).

It will be important to link this activity with and to also support the ASEAN Consultative Committee for Standards and Quality, whose objective is harmonize and/or develop technical regulations for national application, strengthen cooperation within ASEAN countries in the area of capacity building, and convince Member States to consider modelling their technical standards and regulations after ASEAN harmonized technical standards and regulations. A short case study on the harmonization of pharmaceutical regulations for ASEAN member countries is provided in Appendix 2.

In the longer term however, a regional pre-qualification center could be established in the region which collaborates with WHO, the European Medicines Agency and the US FDA who are already working closely with the WHO PQ program.

\textsuperscript{37} WHO (2013c) WHO Prequalification: Progress report
\textsuperscript{38} US FDA International Programs webpage
http://www.fda.gov/InternationalPrograms/FDABeyondOurBordersForeignOffices/AsiaandAfrica/ucm119231.htm accessed 05.03.14
\textsuperscript{39} These are Pyramax\textregistered, (pyronaridine-artesunate) and Eurartesim\textsuperscript{®} (dihydroartemisinin-piperaquine).
\textsuperscript{40} Medicines for Malaria Venture webpage on Eurartesim http://www.mmv.org/achievements-challenges/achievements/eurartesim%C2%AE accessed 05.03.14
Intervention 2: Wipe-out the widespread distribution of sub-standard and counterfeit pharmaceutical products through advocacy and capacity building

As highlighted in this paper, the prevalence of sub-standard and counterfeit anti-malarials (ACTs and AMTs) ranges from 12 -50 per cent across some of the focus countries. This recommendation proposes to bring significant visibility across the region to this major public health challenge, by creating an easily understood pictorial measure dubbed a drug quality barometer’ similar to what environmentalists have used for air quality and the meteorologists have used for the weather. This will require the involvement of the media, NDRAs, police, private sector and most of all, the national policy makers and consumers.

The Global Fund’s Price and Quality Reporting mechanism (PQR) shares information about product quality failure rates at the global level on their website; countries in the region have also started to share information with each other using interactive tools like Post Marketing Surveillance Alert system which shares information relating to pharmaceuticals and health products. The ASEAN network has already adopted this system and more countries in the region have started to bring it into their regulatory functions, such as Philippines, which adopted the system in 2013. But gathering and sharing this data internally, with technical and regulatory organizations is not enough. The goal should be to bring this information to the public. A major component of this recommendation is to bring this information to the consumers through electronic channels including through ‘apps’, television, radio, and print media. Further, consumers should be engaged in helping to identify Substandard/ Spurious/ Falsely-labelled/ Falsified/ Counterfeit (SSFFC) medicine outlets, and refusing to buy suspect medicines, and especially anti-malarials. The drug quality barometer can act as a major public awareness raising initiative and help to drive this program forward.

However, the advocacy efforts should be coupled with WHO’s own SSFFC initiative. Some of SSFFC’s objectives are to identify major needs and challenges and make policy recommendations, and develop tools to counter SSFFC; to strengthen national and regional capacities in order to ensure the integrity of the supply chain; to exchange experiences, lessons learned, best practices, and information on ongoing activities at national, regional and global levels; and to strengthen regulatory capacity and quality control laboratories at national and regional levels. Some of countries in the region have already initiated efforts on SSFFC, but their efforts need to be scaled up.

A short case study on the efforts of USP to combat counterfeit drugs in five Mekong-country region is presented in Appendix 2.

Intervention 3: Strengthen private sector industry to attain higher quality manufacturing standards

Application of GMP during the manufacturing process of ACTs is critical as it ensures the quality of the products. The standards for cGMP were developed by WHO, and this has been replicated across the world.

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But the level of difference between the standard of WHO approval and the standard of individual NDRAs for GMP approval varies considerably. Some national authorities (SRA, PIC/S) have stringent standards and enforcement procedures, which are comparable to, or even exceed WHO standards. It is often the case however that in South-East Asia good standards (and policies) for cGMP exist, but enforcement by the NDRAs is weak and there is little assurance of product quality.

This proposed intervention has two components—manufacturer/private sector targeted interventions and NDRA targeted interventions.

The manufacturer interventions are again two-fold: first, is to strengthen capacity of the private sector to reach cGMP standards by providing technical assistance to them. UNITAID and the Gates Foundation provide funding through their market dynamics initiatives to incentivize and build capacity of manufacturers. The other part of the manufacturer intervention is to promote self-regulation within the industry, through lobbying and involvement of industry associations. Self-regulation in manufacturing is a strategy being deployed by the US FDA, which is helping to build industry capacity to conduct better internal audits and inspections on an ongoing basis.

The other part of the intervention involves building capacity of NDRAs in enforcement of cGMP standards. There are a few such initiatives conducted by WHO and USP (through funding from USAID), but they are under-funded and are operating at a much smaller scale than required.

This initiative will have both a regional and global impact as better quality products will become available to the focus countries, the rest of the Asia-Pacific region and other parts of the world.

**Intervention 4: Phase-out oral artemisinin-based monotherapies (as part of ‘Emergency Response to Artemisinin Resistance.’)**

There is continued availability and widespread use of oral AMT across several of the focus countries.

Many of the focus countries joined forces and have already started phasing-out AMTs from their market, by halting registration, importation, manufacturing, export and sale. But in spite of their efforts, AMT still exists in the market, adding to already growing drug resistance.

In some countries, the interventions include establishment of a taskforce of drug inspectors to wipe out all the monotherapies from the illegal market (confiscate, litigate, and destroy samples found in the market); intensified (global and national) post-marketing surveillance and inspection of drug outlets; training of public and private sectors on rational dispensing and the ban on oral AMTs.

Manufacturers should be further encouraged/instructed to discontinue the manufacture of oral. All countries in the region should make it illegal, and prohibit the export of oral AMT from their borders. The policy-makers should strengthen and scale up these efforts.

A short case study on important regulatory steps being taken in Cambodia to phase-out oral AMTs is presented in Appendix 2.
6. Concluding Remarks and Next Steps

ACTs have been a major advance in the control of malaria but their effectiveness is now under threat due to the prevalence of sub-standard and counterfeit products that are increasing parasitic resistance to ACT therapy. If this situation is not urgently addressed, ACTs may cease to be an effective treatment for malaria, with dire regional and global consequences. Few comparable alternatives are available for ACT-resistant malaria treatment, and all are far more expensive and not as well tolerated as ACTs.

Protecting the therapeutic efficacy and scaling up the use of quality-assured oral ACTs is a complex challenge that requires a comprehensive and regionally coordinated response.

As for interventions, which are the best interventions that should be scaled up? Which ones have the highest impact on saving lives and on improving the quality of drugs at the point of care? Which interventions are complementary or synergistic and therefore should be done together? Which ones will support NDRA system strengthening in general and also help the fight against malaria? And finally, should the focus be on regional and inter-country interventions or should it be at the country level?

While experimentation is good, it is probably not the best way to make long-term decisions on how to protect lives of people and the limited life of a highly effective drug molecule that is under threat.

Instead of investing in new interventions therefore, the recommended next step should be to immediately conduct an exhaustive inventory of all the regulatory-linked ongoing activities in the region, and add to it, other related global interventions. Each of these interventions needs to be understood through a detailed analysis to determine their impact, lessons learned, return on investment, and potential for scaling up.

After this research and analysis has been completed, which should take about six months, it is recommended that APLMA urgently convene a regional forum/consultation to determine which portfolio of activities are best suited for the challenges being faced in different parts of the region. The consultation should end with a roadmap, which should include regional and national strategies, detailed workplans and budgets.

Finally, at the policy level,\textsuperscript{42} there are some actions that country leaders may consider:

1. promote the establishment of a ‘Regional Center of Excellence for Regulatory Sciences’ through inter-regional technical support, with more stringent regulatory authorities providing support to other national drug regulatory authorities in the region.
2. build an Asia-Pacific regional prequalification center, in collaboration with WHO, European Medicines Agency, and United States Food and Drug Administration, all of whom are already collaborating closely with WHO’s prequalification program.

\textsuperscript{42} Input into these policy recommendations have also been provided by Dr. Alasdair Breckenridge, the former Chair of UK’s Medicines and Healthcare Products Regulatory Agency.
3. make consumers the epicenter of the fight against poor quality drugs through leveraging of digital media, web and phone ‘apps’, and creating an ecosystem for real-time peer-to-peer and government-to-peer communications.

4. allocate an appropriate level funding for effective operations of an NDRA by encouraging governments to invest more internal funds in their national drug authorities, and also by accessing regional funds from development banks and donors. The investment in the NDRA’s should be linked to the size of the country’s pharmaceutical market sector and its challenges.
# Appendix 1: Rapid inventory of ongoing regulatory interventions in the Asia-Pacific region

<table>
<thead>
<tr>
<th>Activity</th>
<th>Objective</th>
<th>Achievements</th>
<th>Stakeholders</th>
<th>Geographical Focus</th>
<th>Timeline</th>
<th>Source of information</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>Policy, product registration, Distributor and retailer license, targeted programs (counterfeit), pharmacovigilance, human resource management, coordination</td>
<td>Halt on registration, importation, manufacturing and sale of oral AMTs</td>
<td>Halt on the importation and sale of products from four “Ghost Companies” in Thailand, PRC; Decline in unlicensed drug outlets; Decline in counterfeit and substandard medicines; Decline in sale and distribution of oral monotherapies.</td>
<td>Ministry of Health of Cambodia, Ministry of health of Thailand, WHO, Bill &amp; Melinda Gates Foundation</td>
<td>Cambodia and Thailand</td>
<td>Year of initiation-2008 Ongoing</td>
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</tr>
<tr>
<td>5</td>
<td>Management Information System, coordination and pharmacovigilance</td>
<td>ASEAN Post Marketing Alert System</td>
<td>Increased sharing of drug alerts between countries More countries are adopting PMAS into their Pharmacovigilance system (e.g. Philippines have adopted this system in 2013)</td>
<td>Drug Regulatory Authorities – ASEAN region</td>
<td>South-East Asia</td>
<td>Year of Initiation – 2006 Ongoing</td>
</tr>
<tr>
<td>6</td>
<td>Human resource management, Quality control Product registration</td>
<td>Technical assistance in GMP to manufacturers for WHO prequalification of essential pharmaceuticals</td>
<td>7 Prequalified formulation manufacturers (Cipla-manufacturer for oral ACTs) 1 Prequalified API manufacturer</td>
<td>Concept Foundation Reproductive Health Supplies Coalition</td>
<td>India PRC</td>
<td>Year of initiation–2005 Ongoing</td>
</tr>
</tbody>
</table>
| 7 | Overall capacity building, human resource management | Capacity Building: USAID/USP technical assistance to Thailand’s Bureau of Drug and Narcotic laboratory to earn WHO prequalification status | Achievement of prequalification by Thailand’s Ministry of Public Health, Bureau of Drug and Narcotic laboratory following the technical support by USP/USAID via PQM programme. | Thailand FDA USP-Promoting the Quality of Medicines (PQM) (USAID) | Thailand | 2013 | [http://us.vocuspr.com/Newsroom/ViewAttachment.aspx?SiteName=uspharm&Entity=PRAsset&AttachmentType=F&EntityID=109942&Attac]
<table>
<thead>
<tr>
<th>Case</th>
<th>Description</th>
<th>Long term benefit: increase in availability of affordable, high quality medicines to patients.</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>8</td>
<td>Management Information Systems, Coordination and targeted programs (counterfeit)</td>
<td>Building Regional Expertise in Medicines Regulation, Information Sharing, Joint Investigation and Enforcement (BREMERE)</td>
<td>The programme has just started</td>
</tr>
<tr>
<td></td>
<td>Human Resource Management</td>
<td>Building HR capacity of National Drug Regulatory Authority</td>
<td>Establishment of WHO drug pre-qualification (PQ) program to evaluate a manufacturer's ability to consistently produce medicines of unified standards of quality, safety and efficacy. Building and transferring the capacity to NDRAs to assess these drugs.</td>
</tr>
<tr>
<td>---</td>
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<td>---</td>
</tr>
<tr>
<td>1</td>
<td>Pharmacovigilance, targeted programs (counterfeits), distributor and retailer license</td>
<td>Intensified post-marketing surveillance and inspection of drug outlets</td>
<td>Seizure of 19 tons of counterfeit medicines including 29 different products. Drastic decline in the number of unlicensed drug outlets distributing oral monotherapies and counterfeit drugs.</td>
</tr>
<tr>
<td>1</td>
<td>Targeted programs (counterfeit),</td>
<td>Closure of unlicensed drug outlets</td>
<td>Between 2001 and 2010 - 95% of unlicensed drug outlets have been closed by the government order,</td>
</tr>
</tbody>
</table>
| # | Monitoring drug utilizations | Creation of a Malaria Indicator Framework for accessing therapeutic efficacy of anti-malarial commodities. | Collaborating Partners: Mekong malaria programs, WHO, WPRO, USAID/PMI
MEASURE Evaluation, MMP
Technical partners: United States Centers for Disease Control and Prevention Malaria Consortium | Greater Mekong Subregion (GMS) | Year of initiation-1999
|---|-----------------------------|------------------------------------------------------------|--------------------------------------------------------------------------------|---------------------------------|-----------------|----------------------------------|
| 14 | Monitoring drug utilizations | Monitoring Drug Utilization (Anti-malarials) | Two household surveys, two outlet surveys and qualitative and quantitative supply chain research in Cambodia conducted. | Population Services International (PSI)
London School of Hygiene and Tropical Medicine | Cambodia, border area between Thailand and Cambodia | Year of initiation-2008
Appendix 2: Case studies of ongoing regulatory interventions in the Asia-Pacific region

A CASE STUDY ON THE HARMONIZATION OF PHARMACEUTICAL REGULATIONS FOR ASEAN MEMBER COUNTRIES

BACKGROUND

Efforts have been ongoing in South-East Asia over the last decade through the Association of Southeast Asian Nations’ (ASEAN) Consultative Committee for Standards and Quality (ACCSQ).

The Pharmaceutical Product Working Group (PPWG) was formed by the ACCSQ in 1999 to develop harmonization schemes of pharmaceutical regulations of the ASEAN member countries to complement and facilitate the objective of the ASEAN Free Trade Area, particularly the elimination of technical barriers to trade posed by regulations, however without compromising product quality, efficacy and safety.43

GEOGRAPHICAL FOCUS: Brunei Darussalam, Cambodia, Indonesia, Laos, Malaysia, Myanmar, Philippines, Singapore, Thailand, and Viet Nam.

ACTIVITIES

The PPWG's scope of harmonisation/cooperative activities includes:44

- Discussion of existing technical guidelines and regulatory requirements;
- Study of harmonised procedures and regulatory systems currently implemented in other regions relating to technical guidelines and regulatory requirements;
- Harmonisation of technical guidelines and regulatory requirements applicable to the ASEAN pharmaceutical industry;
- Development of Common Technical Documents with a view to arriving at Mutual Recognition Arrangement (MRAs).

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ACHIEVEMENTS: Areas of work undertaken by ASEAN and their status

<table>
<thead>
<tr>
<th>S.No.</th>
<th>Areas of work undertaken by ASEAN</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>ASEAN Common Technical Dossier</td>
<td>Approved &amp; Implemented</td>
</tr>
<tr>
<td>2</td>
<td>ASEAN Common Technical Requirement</td>
<td>Approved &amp; Implemented</td>
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<tr>
<td>3</td>
<td>Process Validation</td>
<td>Approved &amp; Implemented</td>
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<tr>
<td>4</td>
<td>Analytical Validation</td>
<td>Approved &amp; Implemented</td>
</tr>
<tr>
<td>5</td>
<td>ASEAN Glossary of Terms</td>
<td>Approved &amp; Implemented</td>
</tr>
<tr>
<td>6</td>
<td>Bioavailability/Bioequivalence Studies</td>
<td>Approved &amp; Implemented</td>
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<tr>
<td>7</td>
<td>Stability Study</td>
<td>Approved &amp; Implemented</td>
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<tr>
<td>8</td>
<td>Part II ACTR/ACTD Quality</td>
<td>Adopted &amp; Implemented</td>
</tr>
<tr>
<td>9</td>
<td>Safety Study</td>
<td>Adopted</td>
</tr>
<tr>
<td>10</td>
<td>Efficacy Studies</td>
<td>Adopted (ICH E1, E2A, E2C, E3, E4, E6, E7, E8, E9, E10, E11); Accepted as Reference Documents (ICH E2C(R1), E2D, E2E, E12)</td>
</tr>
</tbody>
</table>

A CASE STUDY ON THE EFFORTS OF USP DQI TO COMBAT COUNTERFEIT DRUGS IN THE FIVE-COUNTRY REGION OF MEKONG

BACKGROUND
In the South-East Asia/Western Pacific area, an estimated 10 to 35 percent of medicines are improperly or illegally produced and sold. In the Greater Mekong Subregion, these are sold primarily in the informal sector along international border areas for less than the price of standard anti-malarials. The inadvertent use of fake drugs has led to:
- Deaths from malaria
- Loss of confidence in malaria treatment and health systems
- Possible contribution to anti-malarial drug resistance in GMS

GEOGRAPHICAL FOCUS
Cambodia, Thailand, Lao People’s Democratic Republic (Lao PDR), Viet Nam, and Yunnan Province in PRC (across public and private sectors)

COLLABORATING PARTNERS
The USP DQI, United States Agency for International Development (USAID)/Regional Development Mission for Asia (RDM-A), the USAID/Cambodia Mission, each country’s Ministry of Health (MOH), medicines regulatory authority (MRA), national medicines quality control laboratory (NMQCL), national
priority disease control programs, surveillance site staffs, and, in some instances, community health care workers

ACTIVITIES

- USP DQI assessed the existing quality assurance/control systems of each country, including drug registration, quality control laboratories, procurement, storage and distribution, and post-marketing surveillance efforts. It then collected data from the field on specific anti-malarial drugs in order to determine the quality of medicines in the marketplace, present findings of gaps or weaknesses, and design individualized plans for improvement based on each country’s priorities. After assessments were completed, USP DQI launched the Anti-malarial Medicines Quality Monitoring Program in the Greater Mekong Sub-region.

- In Cambodia, Laos and Viet Nam, USP DQI supported the creation of inter-Ministerial committees consisting of MOH, Ministry of Finance/Customs, Ministry of Interior/Police, Ministry of Trade, and prosecutors to collectively work against counterfeit drugs and illegal outlets.

- The USAID Regional Development Mission for Asia (RDM-A) and the USAID/Cambodia Mission have all funded related medicine quality monitoring activities in Cambodia, Viet Nam, Lao PDR, and Thailand since the program began in 2003.

ACHIEVEMENTS

- USP DQI contributed to “Operation Jupiter,” which led to multiple arrests and the seizure of approximately $2.7 million worth of anti-malarial products.

- INTERPOL seized more than $6.65 million of counterfeit medicines for treatment of malaria, HIV, tuberculosis, and other common infections in Southeast Asia in 2008 and made 27 arrests.

- The quality assurance/quality control protocol that evolved has served as a model for activities in an additional 21 resource-limited countries in Africa and Latin America.

- Illegal outlets operating in Cambodia reduced from an estimated 1,100 in 2009 to fewer than 10 in 2011 (as per Ministry of Health Department of Drugs and Food data).

A CASE STUDY ON IMPORTANT REGULATORY STEPS BEING TAKEN IN CAMBODIA TO PHASE-OUT ORAL ARTEMISININ-BASED MONOTHERAPIES

BACKGROUND

The border area between Thailand and Cambodia is of interest because this is the area from which global anti-malarial drug resistance has originated over the past 30 years, and from which the first data on ACT resistance has emerged. There is an active and highly diverse market in anti-malarials in this area, including the use of drug cocktails in the private sector.
GEOGRAPHICAL FOCUS
Cambodia, border area between Thailand and Cambodia

COLLABORATING PARTNERS
Ministry of Health of Cambodia, Ministry of Health of Thailand, WHO, Bill & Melinda Gates Foundation, PSI

ACTIVITIES
The Cambodian Minister of Health\(^{47}\) used a multi-pronged approach with communications, meetings with stakeholders and stringent enforcement to implement a ban on oral AMTs:

\(\bullet\) In March 2009, the Cambodian Ministry of Health issued an official letter banning oral AMTs in Cambodia. One month later, a meeting of national stakeholders was held to disseminate the announcement to 54 private companies.

\(\bullet\) In July 2009, a provincial meeting was held to inform stakeholders at local level about the new ban and to raise awareness about the problems associated with use of monotherapies.

\(\bullet\) The Government has also conducted follow-up visits and confiscated illegal drugs\(^{48}\) through:

\(\quad\) Empowerment of drug inspectors to Judicial Police level (who can confiscate, litigate, and destroy samples found in the market)

\(\quad\) Intensified (global and national) post-marketing surveillance and inspection of drug outlets

\(\quad\) Training of public and private sectors on rational dispensing and use of AMT and the ban on oral AMTs

\(\quad\) Social marketing of related anti-malarial products by PSI, including training of private sector health worker on proper treatment for malaria

ACHIEVEMENTS

\(\bullet\) Ban on the importation and sale of products from four “Ghost Companies”

\(\bullet\) Withdrawal of market authorization for Oral Artemisinin-based monotherapies (March 2009)

\(\bullet\) Between 2001 and 2010, 95 per cent of unlicensed drug outlets have been closed by the government order, implemented by Drug Inspectors/Justice Police

\(\bullet\) Seizure of 19 tons of counterfeit medicines including 29 different products. Arrest and prosecution of two persons in Phnom Penh, along with destruction of the consignment

\(\bullet\) Since 2008, ACTwatch\(^{49}\) has conducted two household surveys and two outlet surveys as well as qualitative and quantitative supply chain research in Cambodia. Preparations are underway for the next outlet survey in the second half of 2013

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\(^{47}\) Sokea, V. (2010) Important regulatory steps being taken in Cambodia to phase out oral artemisinin-based monotherapies. Presentation given at the 14th International Conference of Drug Regulatory Authorities

\(^{48}\) WHO (2011) Global PLAN FOR artemisinin resistance containment (GPARC).

\(^{49}\) Launched in 2008, ACTwatch is a PSI research project in partnership with London School of Hygiene and Tropical Medicine (LSHTM). ACTwatch is intended to fill evidence gaps related to malaria diagnostics, antimalarial medicines and fever case management in the private and public sectors.
Appendix 3: Drug regulation systems in Myanmar, Thailand and India

Drug Regulation in Myanmar\textsuperscript{50}

[Population 53 million; estimated pharmaceutical market size: $250 million (based on a $5 per capita spend on pharmaceuticals); geographic size: 676,000 square km]

Despite the country’s size, the Myanmar Food and Drug Administration (MFDA) has only 42 technical staff to manage a sector consisting of 13,000 registered products, seven government manufacturers, more than 170 importers and/or wholesalers and 10,000 retail pharmacies.

Drug quality: The MFDA has its own drug testing laboratory and tests approximately 150 pre-market and 15 post-market drug samples per month. The estimated failure rate of the drugs tested was between 8 and 10 per cent. Currently, the lab is not able to do any bio-equivalence testing.

Pharmacovigilance: The MFDA does not undertake pharmacovigilance, leaving this to the Department of Medical Research, which reported three adverse drug reactions in 2010 but is unable to actively monitor pharmaceutical drug promotion due to resource constraints.

Drug registration: Registration of drugs does so manually as there is no electronic drug registration system.

In addition, there are currently there are no institutions monitoring drug consumption, carrying out prescription audits or drug promotion activities.

Drug Regulation in Thailand\textsuperscript{51}

[Population 67 million; estimated pharmaceutical market size: $4 billion;\textsuperscript{52} geographic size: 513,120 square km]

Thailand’s Food and Drug Administration (Thai FDA) under the Ministry of Public Health (MOPH) has only 96 staff members to manage a sector consisting of 17,424 drug stores, wholesalers and distributors, approximately 150 manufacturers and about 30,000 drug products.

\textsuperscript{50}Holloway, K. A. (2011)
\textsuperscript{51}Holloway, K. A. (2012)
Drug quality: The Thai FDA has its own drug testing laboratory which is accredited by ISO – 17025, the international accreditation which signifies competence of testing and calibration laboratories while also being WHO prequalified. It tests 2,500 drug samples per year, consisting of 1,000 samples for the Thai FDA post-marketing surveillance program focused mainly in pharmacy shops, 1,000 samples for their own post-marketing surveillance program of generic drugs in hospitals and 500 samples for operating an external quality assurance program for 12 public regional drug testing labs. The estimated failure rate of drugs was found to be 10 per cent with samples failing quality testing mainly due to poor dissolution and instability as per a study conducted in 2012.

Pharmacovigilance: The FDA’s National Centre for Pharmacovigilance (NHPCV) has nine pharmacists and six support staff. The national centre has a network of 12 regional centres that collect adverse event reports from the facilities which sit under them. Monitoring is based on spontaneous reporting, targeted spontaneous reporting (as used in a vertical disease control program), intensive cohort monitoring and cohort event monitoring. If there are serious safety concerns the product is referred for re-evaluation of the product registration and possible recall.

Drug Registration: The lack of any criteria to limit the registration of branded generic drugs has resulted in about 30,000 registered products and multiple brands. For example, in 2005, 101 brands of paracetamol (alone or in combination), 49 brands of chlorpheniramine and 41 brands of amoxicillin were found.

Drug Regulation in India

[Population 1,237 billion; estimated pharmaceutical market size: $26 billion; geographic size: 3,287,590 square km]

The Indian FDA, the Central Drug Standard Control Organization (CDSCO) does not manage the entire country by itself. Individual states have their own Drug Control Department, which is responsible for regulating the pharmaceutical industry in their respective state. CDSCO is responsible for controlling the registration of new drugs, pharmacovigilance activities, clinical trials and import of drugs. Given their remit, the CDSCO is understaffed with only 119 staff members out of 327 approved posts to manage a sector consisting of 600,000 drug stores, wholesalers and distributors, and approximately 10,000 manufacturers.

Drug quality: The CDSCO has seven drug testing laboratories, some of which are accredited by ISO – 17025 and can test around 8,000 samples in a year. None of the government laboratories are WHO PQ. Studies conducted by CDSCO in the year 2009 indicate that the level of sub-standard drugs on the market is around 6 per cent which is significantly lower than the previous decade.53

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Pharmacovigilance:54 The Pharmacovigilance Programme of India (PvPI) is managed by CDSCO in collaboration with Indian Pharmacopoeia Commission, which is the National Coordinating Centre and works closely with the global ADR monitoring centre in Uppsala Monitoring Centre (UMC) Sweden.

Drug Registration: Drugs can be registered at the centre with CDSCO (all new drugs and biologicals) or drugs can be registered at any of the states. There are an estimated 60,000 registered products in India, but the exact figure is not known.

54 The Pharmacovigilance Program of India (PvPI) website http://www.ipc.gov.in/PvPI/pv_about.html accessed 02.03.14.