FRAMEWORKS AND PROCESSES FOR MALARIA CONTROL, DRUG QUALITY AND ARTEMISININ RESISTANCE IN ASIA

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Frameworks and Processes for Malaria Control, Drug Quality and Artemisinin Resistance in Asia

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ACRONYMS
A2S2 Assured Artemisinin Supply Service (UNITAID)
ACCSQ ASEAN Consultative Committee on Standards and Quality
AMR Anti-microbial resistance
ANEQAM Asian Network of Excellence in Quality Assurance of Medicines
APLMA Asia Pacific Leaders Malaria Alliance
APMEN Asia-Pacific Malaria Elimination Network
AQMTF Access to Quality Medicines and Other Technologies Taskforce
ASEAN Association of Southeast Asian Nations
BA/BE Bioavailability/bioequivalence (BA/BE)
BREMERE Building Regional Expertise in Medicines Regulation, Information-Sharing, Joint Investigation, and Enforcement
DOT Directly observed therapy
ERAR Emergency Response to Artemisinin Resistance
GFATM Global Fund for AIDS, Tuberculosis and Malaria
GMP Good Manufacturing Practice
GPARC Global Plan for Artemisinin Resistance Containment
IMPACT International Medical Products Anti-Counterfeiting Taskforce
INTERPOL International Criminal Police Organization
MARC Myanmar Artemisinin Resistance Containment
MRA Medicine Regulatory Authority
NRA National Regulatory Authority
oAMT  Oral artemisinin monotherapy
OMCL  Official medicine quality control laboratories
PIC/S  Pharmaceutical Inspection Convention and Pharmaceutical Inspection Co-operation Scheme
PMAS  Post Market Alert System
PMI   President’s Malaria Initiative
PPWG  Pharmaceutical Product Working Group
PQM   Promoting Quality Medicines
RAI   Regional Artemisinin Initiative
RAS   Rapid alert system
SOMHD Senior Officials Meeting On Health Development
SSFFC Substandard/Spurious/Falsely-Labelled/Falsified/Counterfeit
USP   United States Pharmacopeia
WWARN Worldwide Artemisinin Resistance Network
Executive Summary

This paper has been prepared for the Second Meeting of the Access to Quality Medicines and Other Technologies Taskforce and focuses on frameworks and programs to improve drug quality. It provides reference points for the intense work already underway but also identifies areas where effectiveness and efficiency might be improved. The emphasis throughout is on quality rather than quantity and on the ways in which drugs are supplied rather than how they are used. An appendix links to organizations which promote drug quality.

Frameworks

A framework may be defined as “an underlying set of ideas, principles, agreements, or rules that provides the basis or outline for something to be more fully developed at a later stage.” ¹ This paper describes the most relevant frameworks for the control and improvement of drug quality for malaria control in Southeast Asia, but also discusses the “later stage” developments required for implementation – specifically, the operational processes required and the organizations and programs which support them. Broadly speaking, four types of framework influence efforts to control artemisinin resistance:

- Frameworks for controlling anti-microbial resistance (AMR) in general, including for bacterial infections, tuberculosis, and malaria;
- Frameworks targeted specifically to artemisinin resistance, especially in Asia;
- Quality control frameworks for essential medicines of all kinds;
- Quality control frameworks for drugs in Southeast Asia.

WHO's 2014 Global Report on Antimicrobial Resistance² summarizes broad AMR concerns and provides a backdrop for our work; the principles of accurate diagnosis, intense case management, and assured drug quality articulated there are as important for malaria as they are for tuberculosis and bacterial infections, and there may be much to learn from counter-ARM efforts. WHO’s “Regional Framework for Action 2013-15, Emergency Response to Artemisinin Resistance in the Greater Mekong Subregion”³ elaborates these principles for this region.

Observations: Existing frameworks are mutually supportive and reflect basic public health principles; however, they do not fully reflect the motivations and needs of private stakeholders and others outside the health sector. Those primarily focused on malaria may

¹ Bing Dictionary, www.bing.com
² http://apps.who.int/iris/bitstream/10665/112642/1/9789241564748_eng.pdf?ua=1
³ http://www.who.int/malaria/publications/atoz/9789241505321/en/
neglect the potential value of links with other disease control programs and essential medicine quality assurance.

**Recommendation**: Efforts should be made to broaden malaria control frameworks to reflect the needs of all groups including integrated systems development, multiple private sectors, industry leaders, and the full range of government units (including military, police, customs agents, decentralized political representatives and others).

**Strategies**

The principles expressed in frameworks are of little value if not further embodied in operational strategies and eventually work plans and donor grants. Since frameworks emphasize the regional nature of both malaria control and drug quality assurance, implementing strategies should do so as well. Frequent updates are required in areas of rapid epidemiological and programmatic change, especially as artemisinin resistance is further documented and donor resources shift.

**Observations**: This paper does not concentrate on implementation strategies except to note that many are national in scope and focus on geographically and program-limited funding envelopes rather than inter-country public health zones (e.g., eastern Myanmar-western Thailand; Laos-Viet Nam-Cambodia development areas). Strategies to engage the military, private employers and other key groups are often lacking.

**Recommendation**: To fully implement regional frameworks, donors and organizations with multi-country funding should encourage strategies that focus on people at risk, i.e., not limited to specific funding envelopes and projects. Inter-country strategies may be especially necessary for drug treatment policies, procurement and distribution of malaria commodities, surveillance, operations research and M&E, behavior change communication (BCC), and efforts to reach people who move freely along international borders.

**Recommendation**: Malaria program staff should cooperate with, and even promote, development of integrated disease control and systems development strategies. Donors should relax vertical funding restrictions to facilitate integrated programming and health systems development.

**Operational processes**

This paper succinctly summarizes a number of processes through which programs implement drug quality strategies, including:

- Registration and licensing
- Pre-qualification of suppliers
- Import and export controls
Drug testing and post-market surveillance
Alert systems and enforcement.

**Observations:** These processes are largely implemented by national programs, but harmonization of approaches and sharing of resources and findings is desirable to enhance efficiency. There have been significant advances to strengthen international cooperation for these processes, as for example the May 2014 meeting of Malaria Medicine Regulators. However, human and technical resources remain inadequate. Rules may be less stringently applied, moreover, in the case of pharmaceutical products purchased with national and/or private sector resources.

**Recommendation:** Malaria Medicine Regulators have made an important first step to harmonize regulations and minimize duplication of efforts. AQMTF should endorse and further support these efforts.

**Programs to coordinate processes and strengthen capacity**
Development of supportive systems and human/technical capacity-building are both essential and generally cut across disease categories (although donor-funding is often vertical). Organizations described here include:

- Pharmaceutical Inspection Convention and Pharmaceutical Inspection Co-operation Scheme (PIC/S)
- WHO “hub” for the Emergency Response to Artemisinin Resistance (ERAR)
- Association of Southeast Asian Nations (ASEAN)
- United States Pharmacopeia (USP)
- Asian Network of Excellence in Quality Assurance of Medicines (ANE/QAM)
- Medicines regulatory authorities (MRAs)
- Building Regional Expertise in Medicines Regulation, Information-Sharing, Joint Investigation, and Enforcement (BREMERE).

**Observations:** Programmatic resources to support resistance management and drug quality are greater than ever, but funding tends to sit in fragmented donor and national budgets and to focus on specific diseases and activities. One result is frequent and potentially duplicative meetings; another is substantial time spent coordinating what should be integrated activities. Overlap and duplication reduces efficiency and probably efficacy. The

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4 Malaria Medicine Regulators recommendations, 2014.
need for capacity development and sustainability of regional implementing organizations may be neglected in project design and funding.

**Recommendation:** APLMA should promote efforts to build Asian leadership and funding for regionally-based organizations and inter-country programs. They should encourage donors (especially the Global Fund and President’s Malaria Initiative) to support integrated strategies rather than “projectized” activities.
Frameworks and Processes for Malaria Control, Drug Quality and Artemisinin Resistance in Asia

This paper summarizes frameworks, guidelines and resources for controlling malaria and controlling drug quality in Southeast Asia, focusing on rapidly evolving resistance to artesunate. It serves as a reference point for APLMA’s Access to Quality Medicines and Other Technologies Task Force (AQMTF), for its second meeting in Manila, June 9-10, 2014. It also raises issues for discussion at regional leadership level.

Three questions motivate this discussion:

- Do the existing frameworks for malaria control and drug quality provide adequate guidance for action; is greater harmonization needed?
- How can existing organizations contribute more effectively to drug quality control? What can be done to strengthen inter-country collaboration and political support for these organizations?
- What is needed to make quality control processes more transparent and effective, especially at the regional level?

Discussions about access have usually focused on supply rather than demand, but problems are multi-dimensional and bear as much on provider and client preferences and use as on procurement and distribution. In brief: poor quality drugs exist in part because uneducated and impoverished users want them and will pay for them; and even high quality drugs will contribute to artemisinin resistance if users abuse them - without parasitological diagnosis, completion of prescribed dosages, and recommended follow up. Thus, behavior change of treatment providers, drug sellers, and individuals with fever is as important as access to quality drugs. This paper will focus on the regional frameworks and programs involved in supply, but with frequent references to behavior change and case management.

Government- and donor-financed commodities are primarily distributed through public sector channels; yet a very substantial proportion of care-seeking occurs outside the public sector, from private clinicians, pharmacists and drug sellers. Efforts to improve private-sector quality range from voluntary training to compulsory (but often poorly enforced) regulation and “control;” but access to quality drugs may be particularly problematic. This Taskforce, with membership beyond the usual public health authorities, may provide
greater opportunity to influence private health care, potentially with an eye to positive incentives for improvement as well as to restrictive regulation.

Frameworks relevant to drug quality and artemisinin resistance
A framework may be defined as “an underlying set of ideas, principles, agreements, or rules that provides the basis or outline for something to be more fully developed at a later stage.” Broadly speaking, four types of framework influence efforts to control artemisinin resistance:

- Frameworks for controlling anti-microbial resistance (AMR) in general, including for bacterial infections, tuberculosis, and malaria;
- Frameworks targeted specifically to artemisinin resistance, especially in Asia;
- Quality control frameworks for essential medicines of all kinds;
- Frameworks for medicines in Southeast Asia.

Frameworks for controlling anti-microbial resistance
While this Taskforce focuses on artemisinin resistance, its work is part of a broader effort to manage growing resistance to antibiotics, tuberculosis medications, and other essential medicines. WHO’s 2014 Global Report on Antimicrobial Resistance\(^5\) summarizes broad AMR concerns and provides a backdrop for our work; while specific problems and strategies vary by disease and location, the principles of accurate diagnosis, intense case management, and assured drug quality are as important for tuberculosis and bacterial infections as they are for malaria. Though programs differ substantially, efforts to improve access to, and appropriate use of, quality medicines have much to share across disease categories.

Frameworks for responding to artemisinin resistance
Even before the first framework written specifically for artemisinin resistance, the World Health Organization (WHO) identified a core principle, that oral artesunate should only be used in combination with a partner drug (so-called artemisinin combination therapy or ACT).

- WHA60.18 (2007) urged Member States to cease progressively the provision in both the public and private sectors of oral artemisinin monotherapies and to promote the use of ACTs.

\(^5\) [http://apps.who.int/iris/bitstream/10665/112642/1/9789241564748_eng.pdf?ua=1](http://apps.who.int/iris/bitstream/10665/112642/1/9789241564748_eng.pdf?ua=1)
Two years later, WPR/R60.R5 (2009), a resolution of the WHO Regional Committee for the Western Pacific, urged that region’s Member States to prohibit the marketing of artemisinin-based monotherapies.

In January 2011, WHO launched The Global Plan for Artemisinin Resistance Containment (GPARC)\(^6\), to:

- Define priorities for the containment and prevention of artemisinin resistance;
- Motivate action and describe responsibilities by constituency;
- Mobilize resources;
- Define governance mechanisms and indicators for continuous assessment of progress.

As resistance intensified and became evident in additional locations, the global sense of urgency increased, resulting in WHO’s Regional Framework for Action 2013-15: Emergency Response to Artemisinin Resistance in the Greater Mekong Subregion (ERAR)\(^7\). ERAR endorsed GPARC principles but further elaborated 15 priority actions to achieve:

- Full coverage with high-quality interventions in priority areas;
- Tighter coordination and management of field operations;
- Better information for artemisinin resistance containment;
- Regional oversight and support.

Quality control frameworks for essential medicines

The frameworks cited above assume the availability of efficacious drugs, a condition which members of this Taskforce know to be uncertain. WHO, and Member States working through WHO, lead several initiatives aimed specifically at drug quality. In 2006, WHO formed the International Medical Products Anti-Counterfeiting Taskforce (IMPACT), with working groups on Communications, Legislative Regulatory Infrastructure, Regulatory Implementation, Enforcement, and Technology. As described at the Taskforce’s website\(^8\), this group has published a number of reference documents and guides, of relevance to the AQMTF, though not specifically so far on malaria medicines. Starting in 2011, Member States formed a working group and then a “mechanism” on

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8 [http://www.who.int/impact/](http://www.who.int/impact/)
“Substandard/Spurious/Falsely-Labelled/Falsified/Counterfeit” (SSFFC) drugs.\(^9\) (Medicines in this category may include products with either correct or incorrect ingredients, or with no active ingredients at all. Some ingredients may be insufficient or even excessive, possibly with false packaging.) One of several SSFFC working groups focuses on Actions, Activities and Behaviors that result in SSFFC products.

Perhaps most important for malaria products, WHO has established a framework for **Quality Assurance of Pharmaceuticals**\(^{10}\) and specific operational procedures for confirming producer adherence to Good Manufacturing Practices (GMP). Companies wishing to qualify for donor-financed malaria procurement must obtain GMP certification and – for Global Fund - apply for prequalification.\(^{11}\) While these processes provide some assurance of quality and ability to meet production deadlines, they are also time consuming and costly for small producers and those with limited market potential outside home countries. (As discussed later in this paper, several Asian drug producers do not qualify for GMP certification.)

WHO has developed a framework for assessing national capacity in regulating drug quality, embodied in a self-assessment questionnaire.\(^{12}\) While perhaps never applied within Asia, this questionnaire provides useful ideas about what should be in a national plan for drug quality assurance.

**Quality control frameworks for pharmaceutical products in Southeast Asia**

Within the Greater Mekong Subregion, all countries have promulgated frameworks intended to guide both public and private health care, including malaria treatment. Some, such as Viet Nam’s, deal specifically with pharmaceutical supplies, whereas others focus on broader health systems and human resources. Some have been issued by Ministries of Health and apply specifically to public services; whereas others emanate from the Head of Government’s office or other leadership levels and are intended to cover all sectors related to health care services.

\(^9\) [http://apps.who.int/gb/SSFFC/](http://apps.who.int/gb/SSFFC/)
\(^{11}\) See list at [www.theglobalfund.org/documents/psm/PSM_ProductsMALARIA_List_en/](http://www.theglobalfund.org/documents/psm/PSM_ProductsMALARIA_List_en/)
The Medicines Policy for the Kingdom of Cambodia, for example, aims to maximize:

- **Access**: equitable availability and affordability
- **Quality**: including safety and efficacy
- **Rational use**: therapeutically sound and cost-effective use of medicines by health professionals and consumers.

The main approaches within the Medicines Policy of Cambodia are:

- to maximize partnership between the major players: the Government (economy and finance, foreign affairs, commerce, the customs, ministry of health); academics, community leaders, private sector and development partners;
- to increase coordination within the health sector: public, private, international agencies and development partners;
- to maximize collaboration with vertical programs
- to promote cooperation with other sectors such as Legal, Transport, Education, Personnel and Training Departments
- to enhance technical cooperation with other countries and international agencies such as WHO and other development partners.

These objectives and approaches have almost certainly been applied elsewhere as well.

**Observations**: Existing frameworks are mutually supportive and reflect basic public health principles; however, they do not fully reflect the motivations and needs of private stakeholders and others outside the health sector. Those primarily focused on malaria may neglect the potential value of links with other disease control programs and essential medicine quality assurance.

**Strategies for implementing frameworks**

The principles expressed in frameworks are of little value if not further embodied in operational strategies and eventually work plans and donor grants. Since frameworks emphasize the regional nature of both malaria control and drug quality assurance, implementing strategies should do so as well. Every country receiving Global Fund resources has a national malaria control strategy, but some national strategies require almost annual adjustment because of rapid epidemiological and ecological changes. Strategies for Cambodia, Viet Nam and Thailand aim for malaria elimination, while those for Myanmar and Laos aim for control. Perhaps the best known malaria control strategy in
In addition to general strategies for malaria control, some countries have developed specific strategies for pharmaceutical products.\textsuperscript{14}

\textit{Observations:} This paper does not concentrate on implementation strategies except to note that many are national in scope and focus on geographically and program-limited funding envelopes rather than inter-country public health zones (e.g., eastern Myanmar-western Thailand; Laos-Viet Nam-Cambodia development areas). Groups not fully engaged in strategic planning for malaria control and drug quality may include:

- Military and police
- Drug producers, importers and sellers
- Private employers, especially those employing mobile workers
- Immigration authorities
- Decentralized government authorities.

\textbf{Processes to control and improve drug quality}

“Processes” are the operational actions through which frameworks and strategies are implemented. Ideally, they ensure that only high quality commodities are produced, procured, distributed, and ultimately used. In practice, implementation falls short of ideals, because human resources are inadequate or poorly motivated, or because the processes themselves are poorly designed. In other domains, “continuous quality improvement” techniques have generated significant process adjustments, but these require transparent and respectful communication among all parties and have not been fully applied to drug quality issues.

Key processes to be discussed below include:

- Drug registration and licensing of producers
- Pre-qualification of suppliers
- Import and export controls
- Drug testing and post-market surveillance
- Alert systems to notify sub-standard and counterfeit drugs
- Enforcement actions for unlicensed and sub-standard drugs.

\textsuperscript{13} http://www.searo.who.int/myanmar/documents/MARCframeworkApril2011.pdf.

\textsuperscript{14} See for example the Medicines Policy for the Kingdom of Cambodia, 2010.
Registration and licensing

One of the first tasks for implementing malaria drug frameworks has been to withdraw authorization for marketing and/or producing oral artemisinin monotherapy (oAMT). According to WHO, only 30 factories worldwide retain licenses to produce oral monotherapy, of which 19 are in Asia. In the past, a number of countries, most notably Myanmar, allowed importation of oAMT, but as of late 2013 only Timor Leste does so.

National or state regulatory authorities (NRA) license specific pharmaceutical manufacturers, generally requiring renewal every five years. Many NRAs are empowered to inspect producers before and after licensing, but may not always do so because of the typical resource constraints. The potential quality benefits of frequent inspection, especially for small-scale producers, were shown by a 2010 review.

Prequalification of suppliers

WHO’s certification process for Good Manufacturing Practice sets a global standard for quality and may motivate medicine producers to aspire for export markets. The certification process can be time-consuming and costly, however, and may discourage producers with existing national markets.

The Global Fund’s prequalified list, now including nine ACT suppliers, is based on GMP requirements but also reflects dependability of production processes and ability to respond to procurement deadlines. Most international agencies and donors restrict procurement to GF prequalified products and producers, but private wholesalers and governments using national budgets may opt for national producers.

Import and export controls

Import/export controls are managed by national authorities, often based within the ministry of commerce. These authorities can block some sub-standard commodities, but they may be only partially effective for private sector movements. (And of course not at all for illegal drugs.) Donors generally require factory-level pre-testing of individual batches

16 http://www.who.int/malaria/monotherapy_NDRAs.pdf?ua=1
18 See list at www.theglobalfund.org/documents/psm/PSM_ProductsMALARIA_List_en/
for bio-availability/bio-efficacy (BA/BE) prior to shipping since the quality of individual batches may vary. Most MRAs lack capacity to conduct inspections of the facilities of the exporting countries, nor do they have the effective means to verify the GMP certificates and/or certificates of analysis of the products.

Drug exports sometimes pass through fewer controls than imports; thus, countries which bar imports of artemisinin monotherapy may have fewer tools for restricting exports. Export controls may be particularly awkward from designated free trade zones. In addition, MRAs in some countries, due to demand for artemisinin monotherapies in some countries outside Asia, still allow local manufacturers to produce for exports.

Post market testing
Anecdotes abound of artemisinin monotherapy and counterfeits available in local markets, but with substantial reductions over the past several years. Prevalence of counterfeits is difficult to quantify precisely because sampling requires scarce human resources and lab capacity, and because drug sellers may hide unapproved anti-malarials from untrusted clients. Consumer demand for “cheap” drugs will continue to pull in sub-standard or counterfeit products as long as they are available, and in some countries artemisinin may be purchased and used for conditions other than malaria.

Chemical testing is an essential adjunct of every quality assurance program, using both mobile mini-labs and national facilities. Virtually every country in the region attempts to inspect and test drugs after they reach the market, but Official Medical Quality Labs (OMQLs) must also inspect TB drugs and antibiotics and are universally understaffed and equipped. They may be discouraged as well, since the political will and international cooperation required to enforce quality control has been weak in the past.

Alert systems and enforcement
Some drug production and distribution is criminal in intent and must be addressed swiftly and without regard to national borders, before it moves elsewhere. Producers in particular are very often in different countries than users; and in some cases the reputation of certified GMP suppliers may be jeopardized by deliberate falsification of brand names or packaging.
Both ASEAN and WHO/Western Pacific Regional Office have established rapid alert systems:

- ASEAN Post-Marketing Alert System (PMAS)
- WHO Rapid Alert System (RAS)\(^{19}\).

The objective of both is to facilitate rapid information sharing and guide responses; it also serves as a longer-term tool for developing a regional database of incidents. As stated at the WHO website: “Rapid communication, organized information exchange and efficient modes of reporting are crucial to combat counterfeiting. RAS provides rapid communication and a mechanism for alerting member countries and areas and other concerned parties to minimize the adverse impacts of the distribution and use of counterfeit medicine.”

ASEAN PMAS covers cosmetics and traditional medicines as well as ethical drugs, but an early report\(^{20}\) highlighted problems likely to affect all types of products:

- Illicit products may be marketed with multiple names and packaging, complicating efforts to remove them from shops.
- Contact persons for rapid alerts may change frequently or be difficult to reach when needed.

Both USP-PQM and the Worldwide Antimalarial Resistance Network maintain online databases of reports of sub-standard and counterfeit medicines.\(^{21}\) Beyond information-sharing, responses to documented sub-standard and counterfeit drugs must include rapid product removal from supply and circulation, including distributors, and retail shops and efforts to prevent any future importation or sale. In some cases, legal prosecution may be appropriate and feasible. At the international level – again beyond alerts – efforts may be necessary to identify drug sources and potentially close down and prosecute unregistered producers.

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\(^{19}\) [http://www.counterfeitmedalert.info/default.asp](http://www.counterfeitmedalert.info/default.asp)

\(^{20}\) [Progress report on the implementation of ASEAN Post-Marketing Alert (PMA) System](http://www.counterfeitmedalert.info/default.asp)

Within countries, cooperation between medicine regulatory authorities, police and customs is essential. Across borders, collaboration between producing countries, consuming countries and international enforcement agencies (especially INTERPOL) must also occur. Political will to cooperate and to take necessary enforcement measures may need to come from senior levels of government.

**Destruction of outdated medicines**
While the extent of the problem is not known, anecdotal evidence suggests that expired drugs may be re-labeled and remain on the market. Some may originate with public programs which fail to dispose properly of expired products. Thus, prompt removal and destruction of expired stocks is an essential element of quality control.

**Efforts to strengthen appropriate use**
As noted earlier, even high quality medicines used inappropriately may generate resistance; thus, efforts to improve diagnostics and treatment are very important for maintaining drug efficacy. These efforts are beyond the current scope; however, deficiencies are common and feature in all of the operational frameworks cited earlier. Undiagnosed self-treatment may be particularly common among the mobile and forest-based populations most at risk for malaria.

**Continuous quality improvement**
Drug quality assurance is sometimes seen as a “control” activity, to “enforce” standards, yet it may also be approached as a positive intervention to improve manufacturing capacity and provide a price incentive for marketing higher value products. USP, for example, has technical capacity to assist producers to meet WHO GMP requirements, but has not yet done so for malaria medications. Population Services International in Myanmar uses donor funds to subsidize artemisinin combination therapy and thereby replace monotherapy. Other positive means of improving quality need to be identified and supported.

*Observations:* These processes are largely implemented by national programs, but harmonization of approaches and sharing of resources and findings is desirable to enhance efficiency. There have been significant advances to strengthen international cooperation for these processes, as for example the May 2014 meeting of Malaria Medicine Regulators. However, human and technical resources remain inadequate. Rules may be

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22 Malaria Medicine Regulators recommendations, 2014.
less stringently applied, moreover, in the case of pharmaceutical products purchased with national and/or private sector resources.

**Programs and organizations which promote access to quality medicines and other technologies**

Many groups and activities aim to strengthen quality, both nationally and at the regional level. Some have been mentioned earlier as sponsors of specific frameworks; others are highlighted here for their role in promoting harmonization, information sharing, capacity development, and implementation of specific processes. This partial list includes:

- Pharmaceutical Inspection Convention and Pharmaceutical Inspection Co-operation Scheme (PIC/S)
- WHO “hub” for the Emergency Response to Artemisinin Resistance (ERAR)
- Association of Southeast Asian Nations (ASEAN)
- United States Pharmacopeia (USP)
- Asian Network of Excellence in Quality Assurance of Medicines (ANEQAM)
- Medicines regulatory authorities (MRAs)
- Building Regional Expertise in Medicines Regulation, Information-Sharing, Joint Investigation, and Enforcement (BREMERE)

The chart below lists many of these organizations and the processes which they support:

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**PMAS**  |  **Regionally traded products**  |  **Alert system**  
---|---|---
ANEQAM | Essential medicines | Regional centers of expertise  
National regulatory authorities | MRA, OMCL | Essential medicines | Registration, licensing, inspection  
BREMERE | Essential medicines | Development of regional expertise, information sharing, collaboration  

**PIC/S**

The **Pharmaceutical Inspection Convention and Pharmaceutical Inspection Co-operation** Scheme (jointly referred to as PIC/S) are two international instruments between countries and pharmaceutical inspection authorities, which cooperate for GMP. As described in the PIC/S website23, “PIC/S’ mission is "to lead the international development, implementation and maintenance of harmonised GMP standards and quality systems of inspectorates in the field of medicinal products. This is to be achieved by developing and promoting harmonised GMP standards and guidance documents; training competent authorities, in particular inspectors; assessing (and reassessing) inspectorates; and facilitating the co-operation and networking for competent authorities and international organisations.” A long list of publications24 provide guidance for individual GMP and inspection activities.

**WHO “hub” for the Emergency Response to Artemisinin Resistance (ERAR)**

WHO’s recently established “hub” for the **Emergency Response to Artemisinin Resistance** (ERAR) includes "increasing access to quality antimalarial treatment as one of its core mandates". Its affiliated staff of 17 professionals includes specialists on drug access and quality, efficacy testing, monitoring, surveillance and operations research, migrant health, BCC/advocacy, and support for certain national programs. The hub provides overall technical coordination for national programs but does not directly implement field activities.

**ASEAN Consultative Committee on Standards and Quality (ACCSQ) and Pharmaceutical Product Working Group**

ASEAN, the **Association of Southeast Asian Nations**, provides an “umbrella” platform for many discussions affecting member states (listed in appendix), but relies on national governments to ensure follow up. As early as 1992, ASEAN created a Consultative

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Committee on Standards and Quality (ACCSQ) with a broad mandate to enhance intra-regional trade. In 1999, this committee further created a Pharmaceutical Product Working Group (CCSQ/PPWG) to harmonize pharmaceutical regulations in Member States and to eliminate technical barriers to trade, without compromising on drug quality, safety and efficacy. Work has subsequently proceeded on Common Technical Requirements, a Common Technical Dossier, and a Mutual Recognition Agreement for GMP inspections. These work groups develop recommendations for the Senior Officials Meeting On Health Development. ASEAN also set up the Post-Market Alert System (ASEAN/PMAS) for counterfeit drugs, discussed above.

United States Pharmacopeia (USP)

**United States Pharmacopeia** (USP), an American not-for-profit and scientific organization responsible for much pharmaceutical quality assurance in that country, has helped to strengthen national and regional capacity in Asia. The key areas of technical support provided by USP include strengthening the medicines regulatory agencies’ post-marketing surveillance through medicines quality monitoring to obtain evidence data and regulatory inspection in the supply and distribution chains to support enforcement actions; building the quality control laboratories toward international standards; and raising awareness on counterfeit medicines. With funding from the US President’s Malaria Initiative (PMI), USP’s “Promoting Quality Medicines” project now works to:

- Accredit national quality control laboratories to ISO/IEC-17025 or WHO Prequalification
- Support selected manufacturing facilities to attain WHO Prequalification status
- Facilitate and expedite development of ASEAN reference standards
- Continued education and training for personnel of medicines regulatory authorities (MRAs) and quality control labs
- Strengthening the capacity of MRAs to conduct post market surveillance and obtain evidence data to support enforcement actions.

Asian Network of Excellence in Quality Assurance of Medicines (ANEQAM)

In 2006, USP helped establish the **Asian Network of Excellence in Quality Assurance of Medicines** (ANEQAM) to strengthen existing national institutions and link them together to form a network. ANEQAM aims to achieve three objectives:

- To build up local capacities in various fields of medicine quality assurance;
- To facilitate South to South cooperation by increasing access to technical experience and skills through a collaborative technical and information sharing mechanism; and
• To promote financial and technical sustainability of network members.

After some technical support from USP, the following institutions have been providing technical expertise through ANEQAM:

• Pharmaceutical Technology Services Center of Chulalongkorn University's Faculty of Pharmaceutical Sciences (Bangkok) for quality control and development of analytical methods and procedures for antimalarials that do not have public monographs; and
• Faculty of Pharmacy of Mahidol University (Bangkok) for Good Manufacturing Practices

Medicines regulatory authorities (MRAs)
At the national level, two bodies usually bear primary responsibility for drug quality. One is the medicines regulatory authority (MRA), commonly identified as the “food and drug administration.” While MRA functions obviously vary from country, their common responsibility is to ensure that all medicines, including vaccines, are safe, effective and of good quality. Their role in drug registration and licensing was noted earlier. A subset of Malaria Medicine Regulators met recently in Bangkok. The second national body is the Official Medicines Quality Control Laboratory or OMQL, primarily empowered to test the quality of specific pharmaceutical products. In most countries, the OMCL is a sub-unit of the MRA.

Building Regional Expertise in Medicines Regulation, Information-Sharing, Joint Investigation, and Enforcement (BREMERE)
While efforts to strengthen individual institutions are essential, there is general recognition that quality control requires regional collaboration, including both producing and consuming countries. It also requires collaboration within countries - between medicine regulatory authorities (MRAs), official medicine quality control laboratories (OMCL), and a variety of enforcement agencies (police, customs authorities, others). “Coordination,” moreover, implies joint action, not simply meetings and routine information-sharing (vital those these are), but remedial activities to upgrade production, share technical resources, and block illicit flows.

One effort to achieve this is an organization entitled **Building Regional Expertise in Medicines Regulation, Information-Sharing, Joint Investigation, and Enforcement**, established in August 2012. This group links regulatory, testing, and enforcement representatives from eight countries: Cambodia, People’s Republic of China, Laos, Myanmar, Thailand, Viet Nam, Philippines and Indonesia. Its aims are to:

- Create a regional “pool of experts,” both through locally-managed training and sharing of expertise, especially in medicines regulation, registration, post-marketing surveillance, and enforcement.
- Strengthen collaboration between political and technical bodies—MRAs, WHO at the country, regional, and central levels—within each country and the region.
- Improve processes among regulatory/technical agencies and other involved sectors (e.g., customs, police/Interpol, prosecutors) at the national and regional levels for information-sharing, collective investigation and enforcement.
- Engage enforcement agencies in timely information sharing and alert other countries to complement the ASEAN PMAS and WHO-led SSFFC mechanism.

**Observations:** Programmatic resources to support resistance management and drug quality are greater than ever, but funding tends to sit in fragmented donor and national budgets and to focus on specific diseases and activities. One result is frequent and potentially duplicative meetings; another is substantial time spent coordinating what should be integrated activities. Overlap and duplication reduces efficiency and probably efficacy. The need for capacity development and sustainability of regional implementing organizations may be neglected in project design and funding.
SUMMARY: Critique and Challenges

This paper has described the frameworks, organizations and processes in Asia within which regional malaria programs operate in efforts to control artemisinin-resistant malaria, including several which are much broader than any single disease. The fact that sub-standard and counterfeit drugs still circulate is not surprising since this is a global problem affecting developed as well as developing countries; yet protection of antimalarial drugs requires extra urgency because health and development in Asia and Africa are at great risk. There is no viable replacement for artemisinin should our efforts fail; and businesses, governments and drug producers should be as concerned as public health authorities.

Strengths

We have already made good progress in our work on malaria, although significant challenges remain. The principles of good malaria control are well-accepted:

- While both preventive measures and early diagnosis and treatment (EDAT) are required universally, give highest priority to prevention in high transmission areas and to intense case management (100% diagnosis and directly observed therapy) in areas with documented artemisinin resistance;
- Use artemisinin “only” in combination with effective partner drugs (injectable artesunate is appropriate in certain cases);
- Procure drugs from GMP-certified producers only, and test each batch before use;
- Strengthen regional and border area collaboration for all aspects of malaria control.

Malaria programs, moreover, also benefit from:

- The strengths of numerous regional and global organizations dedicated to “rolling back malaria” and controlling artemisinin resistance; the almost weekly regional meetings to share technical updates and reports;
- Resources such as GMP certification, pre-qualification, international and local expertise guide procurement and build capacity.

Weaknesses

The greatest weakness of all these efforts, though, is that malaria transmission is driven by economic, political and ecological factors outside health sector control; but frameworks and strategies have largely been developed without full engagement of stakeholders with other interests and mandates. Public health specialists must, of course, articulate effective disease control approaches and convince others to respect them, but they are likely to achieve greater impact needs of quality assured programs, but they are likely to achieve
greater impact if they take account of the legitimate interests of other public and private stakeholders. Political endorsement is likewise essential, not just in the capital but in decentralized regional structures as well. There is a need to understand all stakeholder motivations and try to develop joint action plans that recognize and consider non-health factors.

A second major weakness in local malaria strategies is that pre-defined funding envelopes encourage country-specific and “projectized” thinking, even as mosquitoes, people, drugs and money move without regard to manmade boundaries. Touring national and district program offices in the Greater Mekong Subregion, one rarely sees maps without large white spaces exactly where our actions should be most intense – just across international borders. Some countries, moreover, make weaker efforts to oversee and control drug exports than imports, even though the artemisinin resistance that may evolve just across the border will threaten their own program as well as their neighbor’s. Public health specialists may be very aware of inter-country ecological zones and the importance of cross-border trade and population movements, but lack the political “clout” to develop joint programs. Political leaders’ support of these initiatives is essential.

**Recommendations**

1. Efforts should be made to broaden malaria control frameworks to reflect the needs of all groups including integrated systems development, multiple private sectors, industry leaders, and the full range of government units (including military, police, customs agents, decentralized political representatives and others).

2. To fully implement regional frameworks, donors and organizations with multi-country funding should encourage strategies that focus on people at risk, i.e., not limited to specific funding envelopes and projects. Inter-country strategies may be especially necessary for drug treatment policies, procurement and distribution of malaria commodities, surveillance, operations research and M&E, behavior change communication (BCC), and efforts to reach people who move freely along international borders.

3. Malaria program staff should cooperate with, and even promote, development of integrated disease control and systems development strategies. Donors should relax vertical funding restrictions to facilitate integrated programming and health systems development.
4. Malaria Medicine Regulators have made an important first step to harmonize regulations and minimize duplication of efforts. AQMTF should endorse and further support these efforts.

5. APLMA should promote efforts to build Asian leadership and funding for regionally-based organizations and inter-country programs. They should encourage donors (especially the Global Fund and President’s Malaria Initiative) to support integrated strategies rather than “projectized” activities.
Appendix: Brief descriptions of Frameworks and Organizations

**Asian Collaborative Training Network for Malaria (ACT Malaria):** Formed in 1996, ACT Malaria promotes collaborative training and networking among member Southeast Asian countries (Bangladesh, Cambodia, People’s Republic of China, Indonesia, Laos, Malaysia, Myanmar, Philippines, Thailand, Timor Leste and Viet Nam). Its best known course is Management of Malaria Field Operations (MMFO), but it has recently moved into microscopy quality assurance.

**Asia-Pacific Malaria Elimination Network (APMEN):** APMEN’s long-term aim is to eliminate malaria in member countries (Bhutan, Cambodia, People’s Republic of China, Democratic People’s Republic of Korea, Indonesia, Laos, Malaysia, Nepal, Philippines, Republic of Korea, Solomon Islands, Sri Lanka, Thailand, Vanuatu and Viet Nam). APMEN conducts annual meetings, offers fellowships for advanced training, and provides research grants.

**ASEAN Consultative Committee for Standards and Quality (ACCSQ)/Pharmaceutical Product Working Group:** Originally formed in 1992 to promote regional trade, ACCSQ created the Pharmaceutical Product Working Group (CCSQ/PPWG) in 1999 to harmonize pharmaceutical regulations and eliminate technical barriers to trade. Work has subsequently proceeded on Common Technical Requirements, a Common Technical Dossier, and a Mutual Recognition Agreement for GMP inspections.

**Association of Southeast Asian Nations (ASEAN):** Originally formed in 1967, ASEAN promotes trade and political cooperation among Member States (Brunei, Cambodia, Indonesia, Laos, Malaysia, Myanmar, Philippines, Singapore, Thailand, and Viet Nam).

**Building Regional Expertise in Medicines Regulation, Information-Sharing, Joint Investigation, and Enforcement (BREMERE):** Regional association, formed in 2012; membership includes regulatory, testing, and enforcement representatives from Cambodia, People’s Republic of China, Laos, Myanmar, Thailand, Viet Nam, Philippines and Indonesia.

**Emergency Response to Artemisinin Resistance (ERAR):** Both a framework (Emergency Response to Artemisinin Resistance in the Greater Mekong Subregion (ERAR) (http://www.who.int/malaria/publications/atoz/9789241505321/en/) and a “hub,” with a staff of approximately ten professionals. The framework and the hub guide WHO’s response to what is widely seen as a public health emergency.

**Global Fund Regional Artemisinin Initiative (RAI):** A special Global Fund allocation of $100m (http://portfolio.theglobalfund.org/en/Country/Index/MER) for combatting artemisinin resistance in Cambodia, Myanmar, Thailand, Laos and Viet Nam, including a $15m allocation for inter-country activities.


**International Medical Products Anti-Counterfeiting Taskforce (IMPACT):** WHO formed this taskforce in 2006, with working groups on Communications, Legislative Regulatory Infrastructure, Regulatory Implementation, Enforcement, and Technology. The Taskforce has published a number of reference documents and guides, of relevance to the AQMTF, though not specifically so far on malaria medicines.

**Mechanism on Substandard/Spurious/Falsely-Labelled/Falsified/Counterfeit (SSFFC) drugs:** A WHO working group, intended to bridge the diverse definitions of sub-standard and counterfeit.


**President’s Malaria Initiative (www.PMI.gov):** A joint endeavor by the United States Agency for International Development (USAID) and the Centers for Disease Control and Prevention (CDC) to reduce malaria morbidity and mortality by 50% in 19 high burden countries. PMI now includes the Greater Mekong Subregion, focusing on management and control of artemisinin resistance.

**Senior Officers Meeting on Health Development (SOMHD):** Annual ASEAN meeting of health officials.
