Improving Access to Quality Medicines in the Greater Mekong Sub-region

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Manager, Asia Programs
Promoting the Quality of Medicines Program (PQM)
1. Access to quality-assured medicines (QAMs):
   a. Geographic and economic components
   b. Regulatory and technical framework
2. Issues, gaps, and challenges in access to QAMs
3. What has been done to address the situation
4. Examples of good practices and suggested solutions
Access to Quality-Assured Medicines Puzzle

Rational selection of products, suppliers and use

Sustainable financing

Affordable prices

GEOGRAPHICAL ACCESSIBILITY
[distance between services location and user location]

AVAILABILITY
[supply vs. demand]

SAFE EFFICACIOUS QUALITY COST-EFFECTIVE

ACCEPTABILITY
[Characteristics of products/services vs. user attitude, perception or expectations of products and services]

AFFORDABILITY
[Price, cost, value vs. user income or ability to pay]

Reliable health and pharmaceutical supply systems
Assured Medicines Quality

Documentation, monitoring, and evaluation

Pre-marketing quality assessment: marketing authorization, licensing, and registration

Regulatory elements: central administration, inspection, and official medicines labs services

Technical elements: quality specs, basic tests, GMP, GLP, GPP, GDP, and GSP

Post-marketing surveillance: quality monitoring, adverse events, supply chain inspection

Adequate legislation and law enforcement

Explanatory notes: GMP=Good Manufacturing Practice; GLP=Good Laboratory Practice; GPP= Good Pharmacy Practice; GDP=Good Dispensing Practice; GSP=Good Storage Practice


www.usp.org/worldwide/dqi/resources/technicalReports
Challenges in Filtering for Good Quality Medicines

- Pharmaceutical products available in the global market: 100,000 - 150,000
- Regulatory control measures, incl. registration and testing
- No. of meds approved for used in a country: 2000 - 35000
- Incl. EML up to 1,500

No. of meds approved for used in a country:
- 2000 - 35000
- Incl. EML up to 1,500
1. **Weak institutional capacity** to ensure access to good quality medicines are produced, procured, supplied, distributed to patients.

   - Ineffective legislation and regulations
   - Limited qualified human resources in QA/QC for MQ
   - Poor compliance with GMP, GLP, GD-SP, and GPP
   - Very limited awareness and advocacy activities
   - Inadequate border control — smuggling of medicines

2. Weak mechanism in **information-sharing, coordination in investigation, cooperation and collaboration** between regulators and other law enforcement agencies, resulting in ineffective enforcement.
Challenges to Addressing Medicines Quality Problems

1. Weak institutional capacity, e.g.,
   - Many non-GMP-compliant manufacturers exist
   - ≈ 100-150 establishments to inspect/year
     - Same inspector does both GMP and PMS
   - ≈ 80-120 samples tested/year/lab analyst
     - Poorly equipped lab with limited qualified personnel

2. Ineffective legislation and regulations, e.g.,
   - MRAs have no power to take action
   - No or minor punishment against violations
Compliance Gaps in GSP, GDP and GPP

Central level warehouse

Provincial level

Peripheral level

Source: Some photos courtesy of Associate Prof. C. Sooksriwong
Common Challenges: Compliance Gap in GLP

**National or Central level**
- Inadequate quality management system

**Sub-national or Provincial level**
- Non-ISO/IEC-17025:2005 and/or non-WHO PQ
- Lack of or inadequate quality management system and technical performance
Regulatory Challenge in Most Developing Countries

Business owner diagnoses, prescribes, dispenses

Informal and illegal markets

Uninformed consumer and patient
Possible Contributing Factors on Poor Access to Good Quality Medicines in Border Areas

1. Weak regulatory presence and enforcement at borders jeopardizes the assurance of product quality and safety in the market.

2. Very limited access to good quality medicines in remote and border areas could lead people to purchase and use expired, substandard, fake, and often counterfeit medicines, in part due to:
   - Long distance between the supplier/service provider and the user (geographical inaccessibility). Villagers in remote areas have to walk up to 2-8 hours to reach basic health services
   - Limited supply in both availability of selection and quantity of products
   - Limited availability of health facilities/services in borders and remote areas to meet the increasing needs
USP PQM Strategic Approach in the GMS

1. Strengthen capacity of regulators

2. Monitor Medicines Quality to support enforcement

3. Strengthen QC labs and manufacturers to meet international standards

4. Educate and raise awareness about medicines’ quality

5. Conduct operational research
Sample Data from USP PQM Medicines Quality Monitoring

Sampling Distribution By Therapeutic Indication 2003-2010

- Antibiotic: 35.2%
- Antimalarial: 49.1%
- Antituberculosis: 12.5%
- Antiretroviral: 2.7%
- Other: 0.4%
Poor-Quality Medicines Found in All Sectors

### Reasons for sample failure.

<table>
<thead>
<tr>
<th>Medication</th>
<th>Reason for failure</th>
<th>No. of samples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Artesunate</td>
<td>API comprises 86.96%.</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>API comprises 88.3% and related substances more than 2%.</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>API comprises 0% and disintegration in more than 60 minutes.</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Dissolution in less than 60% and related substances comprising more than 2%.</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Related substances comprising greater than 2%.</td>
<td>9</td>
</tr>
<tr>
<td>Artesunate + Mefloquine</td>
<td>Impurities in artesunate greater than 2%.</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Artesunate comprises 77.7% and related substances comprising more than 2%.</td>
<td>1</td>
</tr>
<tr>
<td>Artemisinin + Piperaquine</td>
<td>Artemisinin comprises 48.6% and piperaquine comprising 50.4%.</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Artemisinin comprises 4.8% and piperaquine comprises 50.7%.</td>
<td>1</td>
</tr>
<tr>
<td>Dihydroartemisinin</td>
<td>API comprises 87.0%.</td>
<td>1</td>
</tr>
<tr>
<td>Dihydroartemisinin + Piperaquine</td>
<td>Dissolution of DHA of 4.7% to 79.2% and PIP of 0.8-96.5%.</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Dissolution of DHA and PIP of 0% in 45 minutes.</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>Dissolution of DHA 0-82.5% and PIP 0-119.4% in 45 minutes.</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Dissolution of DHA 2-73.2% and PIP of 0.5-99.1% in 45 minutes.</td>
<td>1</td>
</tr>
<tr>
<td>Chloroquine</td>
<td>Dissolution of &lt;75% in 45 minutes.</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Disintegration in &gt;60 minutes.</td>
<td>6</td>
</tr>
<tr>
<td>Tetracycline</td>
<td>Dissolution of 1.04%-13.8% in 60 minutes.</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Dissolution of 25.3% -35.2% in 60 minutes.</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Disintegration in &gt;60 minutes.</td>
<td>1</td>
</tr>
<tr>
<td>Quinine</td>
<td>No API</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>46</td>
</tr>
</tbody>
</table>

## Sample Data from USP PQM

<table>
<thead>
<tr>
<th>Samples</th>
<th>Reasons for failure</th>
<th>No. of samples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primaquine phosphate</td>
<td>Identification test result: no active ingredient</td>
<td>1</td>
</tr>
<tr>
<td>Tetracycline hydrochloride</td>
<td>Dissolution test result: 0% - 0.8% for tetracycline hydrochloride</td>
<td>1</td>
</tr>
<tr>
<td>Chloroquine phosphate</td>
<td>Dissolution test result: 35.0% - 39.8% for chloroquine phosphate</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Identification test: no chloroquine, but contained quinine sulphate</td>
<td>1</td>
</tr>
<tr>
<td>Artesunate</td>
<td>Related substances: Above reference limit</td>
<td>1</td>
</tr>
<tr>
<td>Quinine sulphate</td>
<td>Identification test: no quinine, but contained chloroquine</td>
<td>1</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td></td>
<td><strong>7</strong></td>
</tr>
</tbody>
</table>

Sample Data from USP PQM: Progress in Reduction of Poor Quality Medicines

Conformed vs. Non-conformed Samples in GMS by Year of Sampling

<table>
<thead>
<tr>
<th>Year</th>
<th>Conformed to MQM Testing</th>
<th>Did Not Conform to MQM Testing</th>
</tr>
</thead>
<tbody>
<tr>
<td>2008</td>
<td>2807 (97.3%)</td>
<td>77 (2.7%)</td>
</tr>
<tr>
<td>2009</td>
<td>1442 (98.2%)</td>
<td>27 (1.8%)</td>
</tr>
<tr>
<td>2010</td>
<td>723 (98.6%)</td>
<td>10 (1.4%)</td>
</tr>
</tbody>
</table>
Examples of Awareness-Raising Tools and Activities

... Limited awareness activities to reach remote and border areas...
Pharmacide Series

PHARMACIDE: ONLINE

Pharmacide: Mekong Regional Documentary

... not cover remote and border areas...
Examples of Recent Progress: Enforcement

1. Educate distributors/retailers
2. Sign agreement not to purchase and/or sell CSMs
3. Close down outlets
4. Conduct fines, seize remaining stocks and destroy them
5. Blacklist/delist from registration

Key supporters/partners: Countries MOH, Police, Customs, and external assistance, including WHO, French Ministry of Foreign Affairs, USP PQM, and the INTERPOL
Main Focus Areas for Containing Artemisinin-resistant Malaria: Cross-border Sites
Examples of technical support of USP PQM to GMS

1. Technical assistance toward ISO-17025 accreditation and/or WHO PQ (VN NIDQC and Thailand BDN, achieved)

2. Essential equipment and facility design

3. Training in Analytical procedures and Quality Management Systems

4. Formation of NOMCOL-Asia
   - Inaugural meeting: Siem Reap, Feb 2013
   - Confirmed membership: Cambodia NHQC, HCMC IDQC, Laos FDQCC, Thailand BDN, Vietnam NIDQC
   - Others in process of joining
NOMCOL Main Objectives

- Harmonize methodologies to facilitate acceptance/recognition among countries and regions
- Enhance performance and technical skills of lab staff through proficiency testing and training
- Promote south-south collaboration in QC
Mechanism to strengthen regional cooperation and collaboration in monitoring quality of medicines and addressing counterfeit and substandard medicine products to support control of resistance of malaria, tuberculosis, and other infectious diseases

Regional “pool of experts” who specialize in medicines regulation, registration, post-marketing surveillance, and regulatory enforcement action
1. INTERPOL-led Storm Enforcement Network Initiative
2. ASEAN-PMAS and WHO RAS
3. WHO-led Working Group on Substandard/Spurious/Falsely-labeled/Falsified/Counterfeit Medical Products (SSFFC)
1. Strengthen MRA inspectors’ skills and experience in conducting GMP inspections

2. Support ATB manufacturers toward WHO PQ
   a. GMP aspect
   b. Dossier aspect

3. Support CROs in BA/BE toward WHO acceptance
Access Gaps in Health Services, including Medicines in Remote and Borders Areas

- Limited availability of quality products
- Low affordability
- Lack of objective information on quality, safety and efficacy, and rational use
- Inadequate quality of health and pharmacy services and information
- Geographical access in cross-border rural areas
1. Distance, cost, and limitation of medicines negatively influence utilization of public health services

2. Overall, the public sector was used in 20-40% of all illnesses and injuries

3. Retail pharmacy outlets are the first point of contact for 60-80% of the population
### Affordability: Example

#### Number of days worked to pay for treatment

<table>
<thead>
<tr>
<th></th>
<th>Private Facilities</th>
<th>Pharmacy/Drug Depots</th>
<th>Unlicensed Pharmacies</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pneumonia (pediatric 1-5 years)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amoxicillin 250mg</td>
<td>2.99</td>
<td>.97</td>
<td>1.4</td>
</tr>
<tr>
<td>Co-trimoxazole 80mg/400mg</td>
<td>2.89</td>
<td>.75</td>
<td>.84</td>
</tr>
<tr>
<td><strong>Dysentery (pediatric 1-5 years)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Co-trimoxazole 80mg/400mg</td>
<td>2.89</td>
<td>.75</td>
<td>.84</td>
</tr>
</tbody>
</table>

- Less than 1% of population is covered by any risk sharing scheme
- Payment for health care services, including medications, is a major cause of impoverishment; 46% of loss of farms was due to health care costs.

-- MOH/DDF Cambodia, 2008
The GMS Economic Corridors may contribute to the improved access to health care services, including medicines...

It may also facilitate the flow and supply of bad medicines given the weak regulation and control of MRAs at border crossing points...
Challenges in Rational Use of Medicines

1. Trainings are usually undertaken for prescribers; the impact is usually low and short-lasting.

2. Very limited system to monitor compliance of prescribers to treatment guidelines.

3. Compliance to treatment guidelines are usually low, e.g., a survey in Cambodia shows that appropriate prescription for treating malaria, diarrhea, and acute respiratory infections were 68 %, 3 % and 45 %, respectively (Chareonkul et al 2002).

4. Widespread misuse of medicines, including antibiotics and antimalarials

There is a need to monitor the use of medicines and to promote rational use of medicines/antibiotics among providers and consumers.
1. From 2003, active medicines quality monitoring sentinel sites established with the support of U.S. Pharmacopeia’s Promoting the Quality of Medicines program, funded by USAID/PMI:
   a. 2003 — 17 sites
   b. 2013 — 54 sites (2 inactive in Yunnan, and 1 in Cambodia)
   c. Focuses on antimalarials, antibiotics, and anti-TBs
   d. Quality testing with Minilab and confirmatory testing by reference laboratories
   e. Reduction of poor quality medicines from 30-40% to less than 10% in 2012

2. Factors for success: Effective coordination, partnering, and robust monitoring
Example of Good Practice: Operation STORM-Led by the INTERPOL

1. Collaborative actions
   a. MRAs, Customs, and Police of GMS countries
   b. INTERPOL, WHO, World Customs Organization

2. Simultaneous inspection/raids
   a. 15 April – 15 September 2008 (STORM I)
   b. January 2010 (STORM II).

3. Laboratory analysis by Singapore’s Health Science Authority

4. Seized 20 million pills of counterfeit/illega drugs

5. Success factors include collaboration and coordination between MRAs, customs, police, and private sectors within the country and between countries
Suggested Solutions to Improve Access to Good Medicines in Border Areas

1. In-country
   - Strengthening medicines management (supply, distribution, and storage) at provincial/district and village levels
   - Sustain/expand quality surveillance for medicines & products used for priority diseases
   - Improve legislation and regulation on licensing of manufacturers, distributors, and retail operators of medicines
   - Increase awareness of danger/risk in use of bad medicines
   - Provide incentive to healthcare providers to station at border areas
2. Inter-country borders action & collaboration

- Timely information-sharing on medicines quality, joint inspection/investigation, and collective enforcement —WHO-RAS, ASEAN-PMAS, BREMERE, INTERPOL-led Storm Enforcement Network initiatives

- Strengthening medicines regulatory authorities presence at border areas through networking, training and information support

- Enhance the official medicines QC labs’ capacity and participate in NOMCOL-Asia
LET US CHANGE OF PRACTICE FROM

“NATO - NO ACTION TALK ONLY”

TO

“ANTO - ACTION, NOT TALK ONLY”
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