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Improving Antimalarial Medicines Quality in GMS: Data from the Promoting the Quality of Medicines (PQM) Program

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Presentation Outline

1. Background and Rationale
2. Methodological Framework
3. Highlights of Findings
4. Actions Taken
5. Selected Data on Antimalarial medicines (AML) Quality from a Thailand-Cambodia Cross-border Study
6. Looking Forward

Background and Rationale

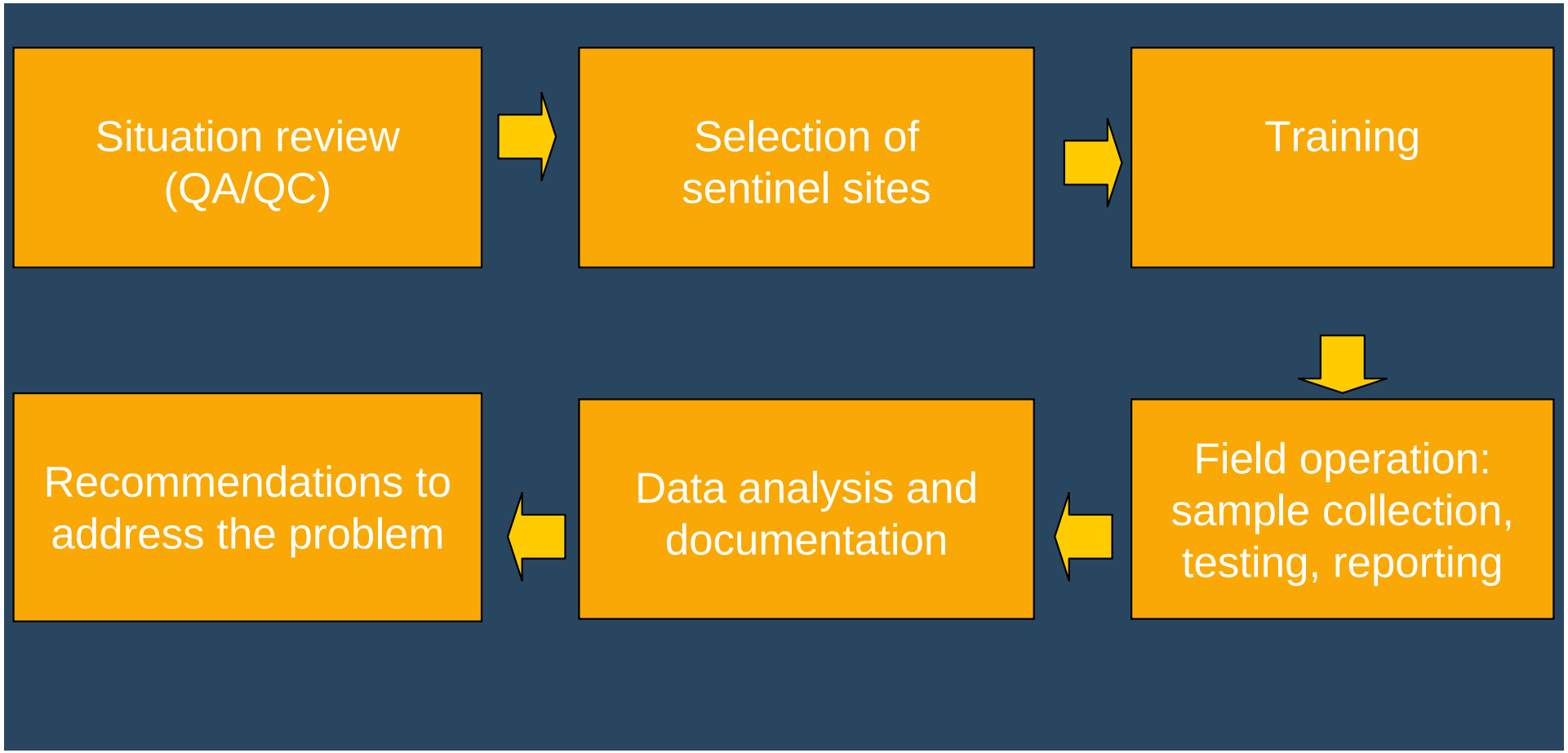
In late 2002, WHO, Roll Back Malaria Initiative, USP DQI, and other partners identified three key areas that required action:

1. Establish a strategic approach for early detection of counterfeit and substandard medicines
2. Enhance the technical capacity of QC labs
3. Strengthen national medicines regulatory authorities (MRAs)

Establishing Medicine Quality Monitoring (MQM) in GMS

- Aim: Strengthen medicines quality assurance programs and systems (QA/QC) at national and program levels
- Objectives:
  - Obtain evidence-based data from the field on the quality of selected anti-infective medicines
  - Present data to MRAs and other appropriate agencies to address the problems

Methodological Framework



Training on basic medicines testing, sampling and compendial analysis was provided to participating countries

Establishing MQM: Sampling

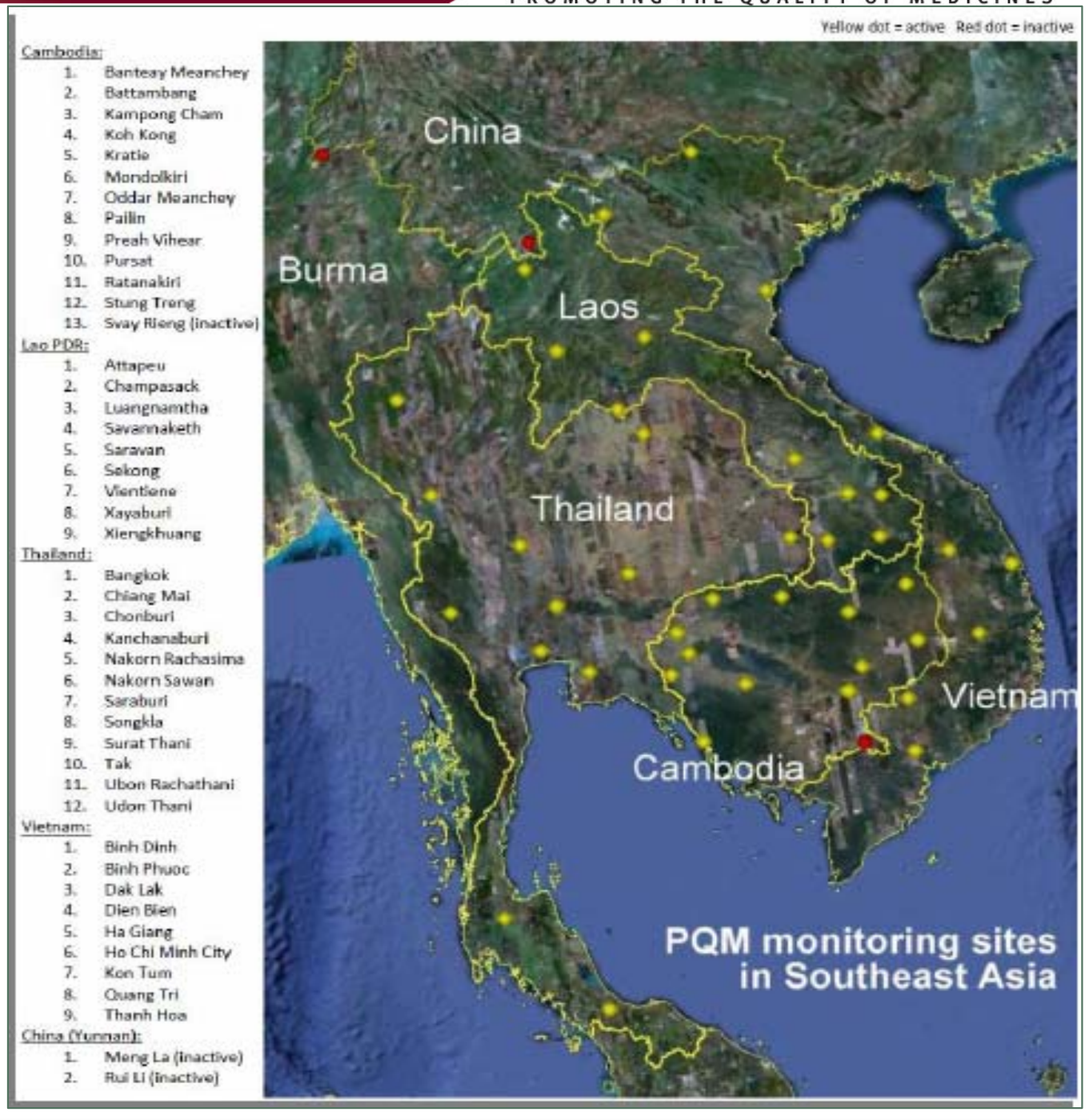
Sampling team collecting samples and recording details

Two-level Testing Approach

Where	Level	Purpose
National/or reference QC laboratory	Compendial Testing (pharmacopeial specifications, validated industry methods)	Determine legal compliance, regulatory support, impurities
Sentinel site	Basic Testing (PV-inspection, TLC, simple disintegration)	Screening

Monitoring Sites

Increased # of sites:
2003: 17
2006: 28
2009: 45
(42 active; 2 in Yunnan China and 1 in Cambodia)



GMS MQM Results July 2003-Sept 2006

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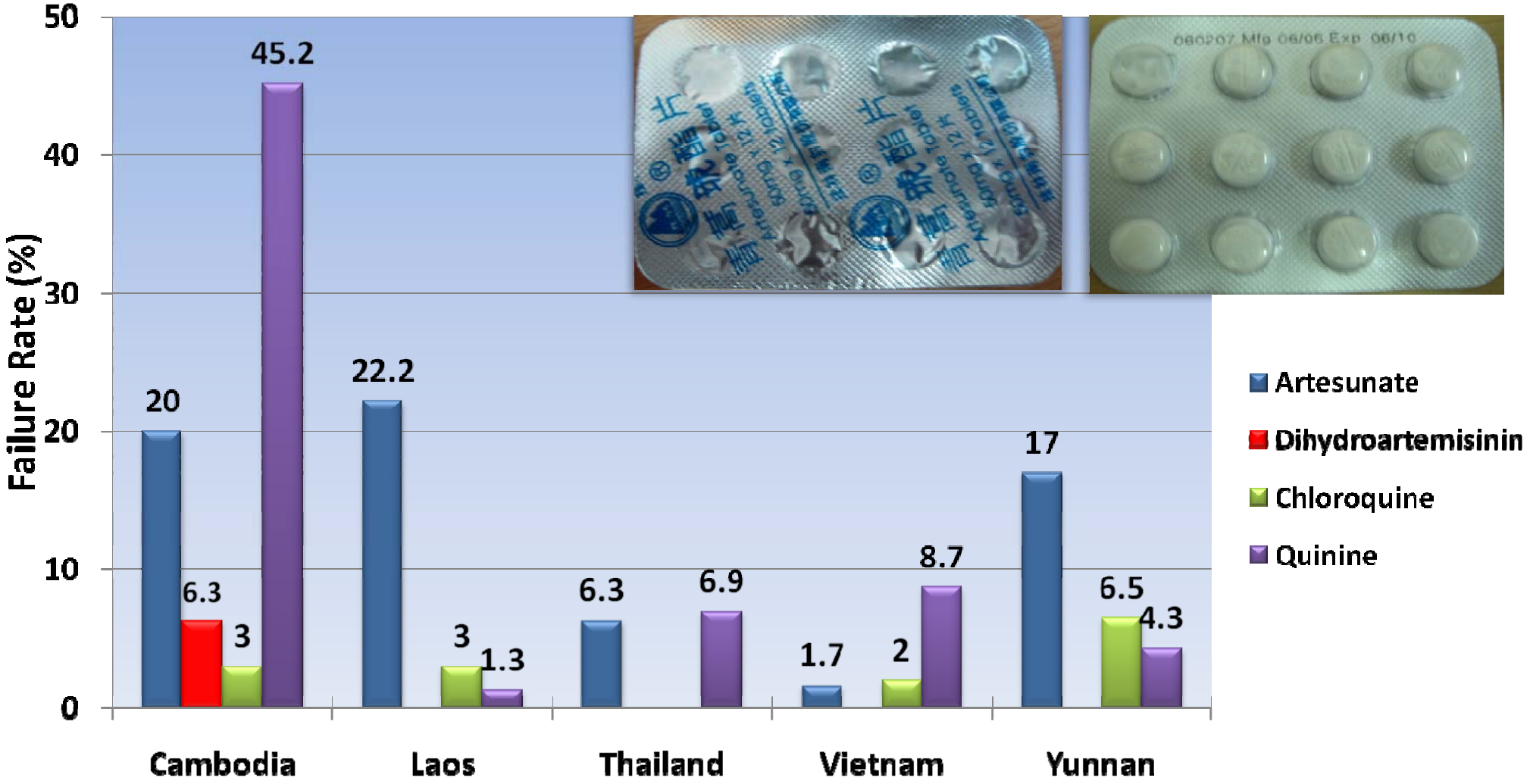
Fig 1: Failure rate (%) by product and country



Highlights of MQM Findings

Fig 2: Total No. (11534) of Samples Collected and Tested in Cambodia, Lao PDR, Thailand and Vietnam: 2005-2010 by therapeutic indication

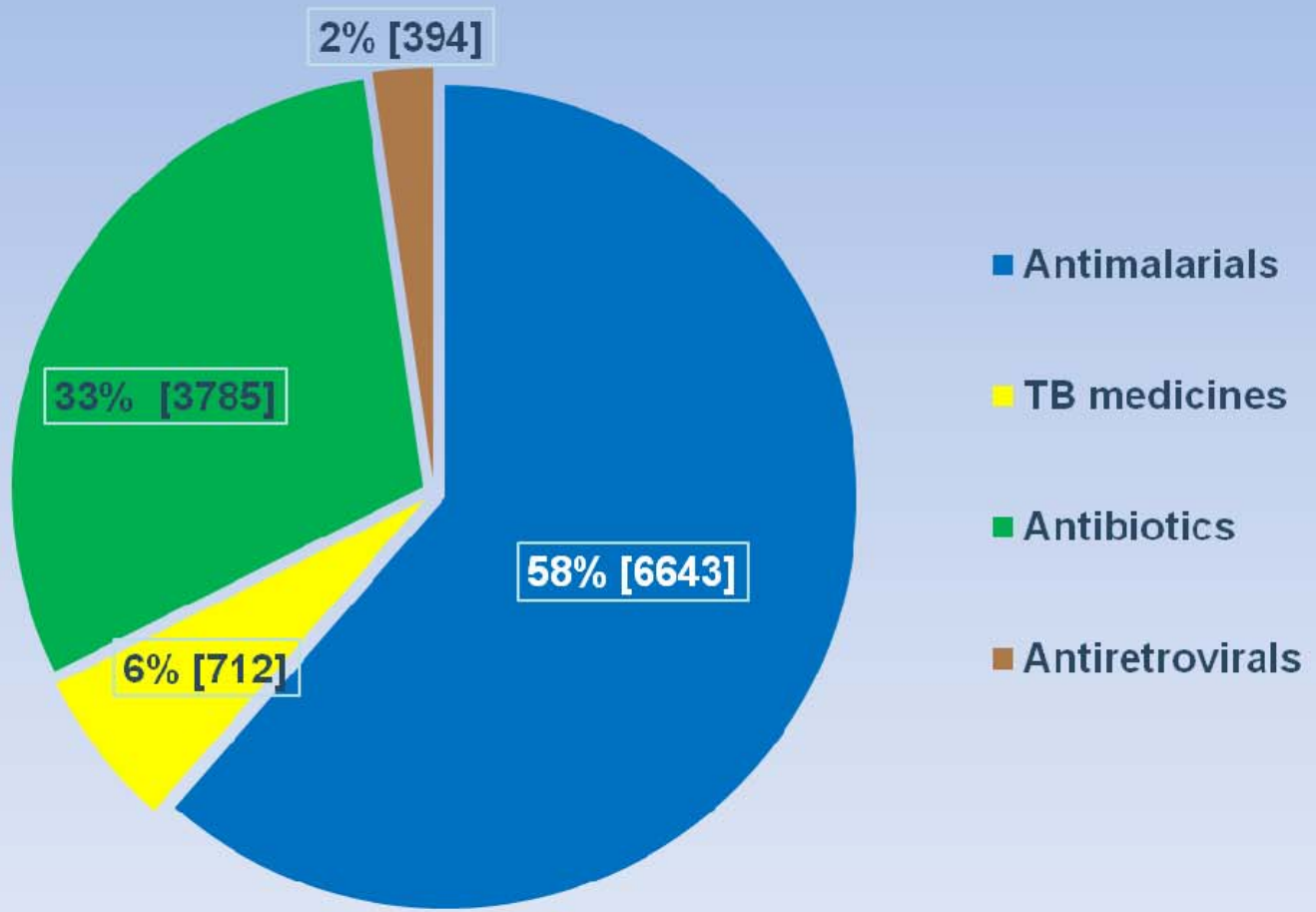


Figure does not include samples collected/tested from TH-KH cross-border study on AMLs quality in 2009.

Highlights of MQM Findings

Fig 3: Total Number (6643) of Antimalarial Samples Collected/Tested 2005-2010, by Country

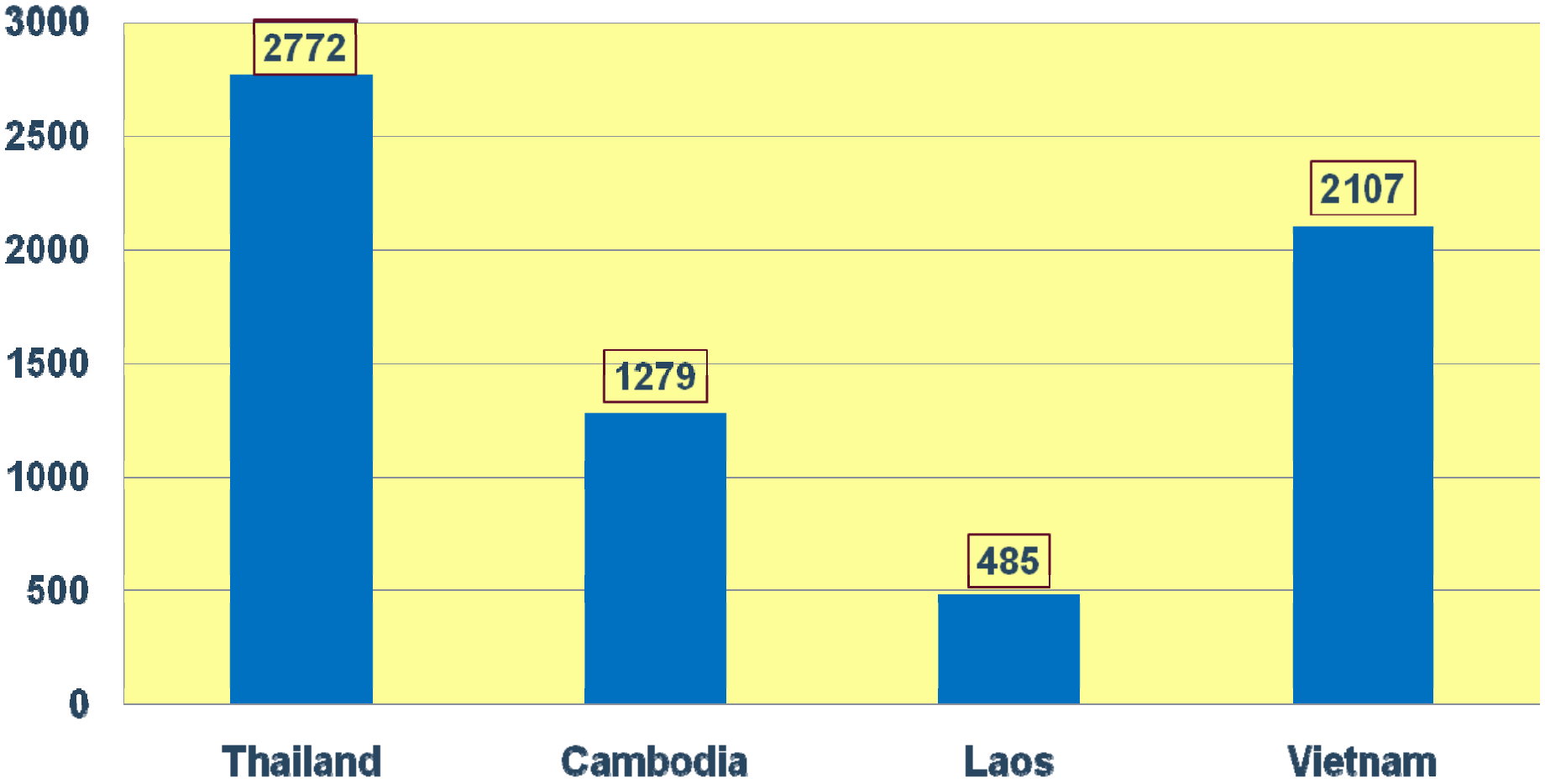


Figure does not include samples collected/tested from TH-KH cross-border study on AMLs quality in 2009.

Highlights of MQM Findings

Fig 4: Of 51 Total Antimalarial Samples Failed Quality Testing 2007-2010 in Thailand, Vietnam, Laos and Cambodia

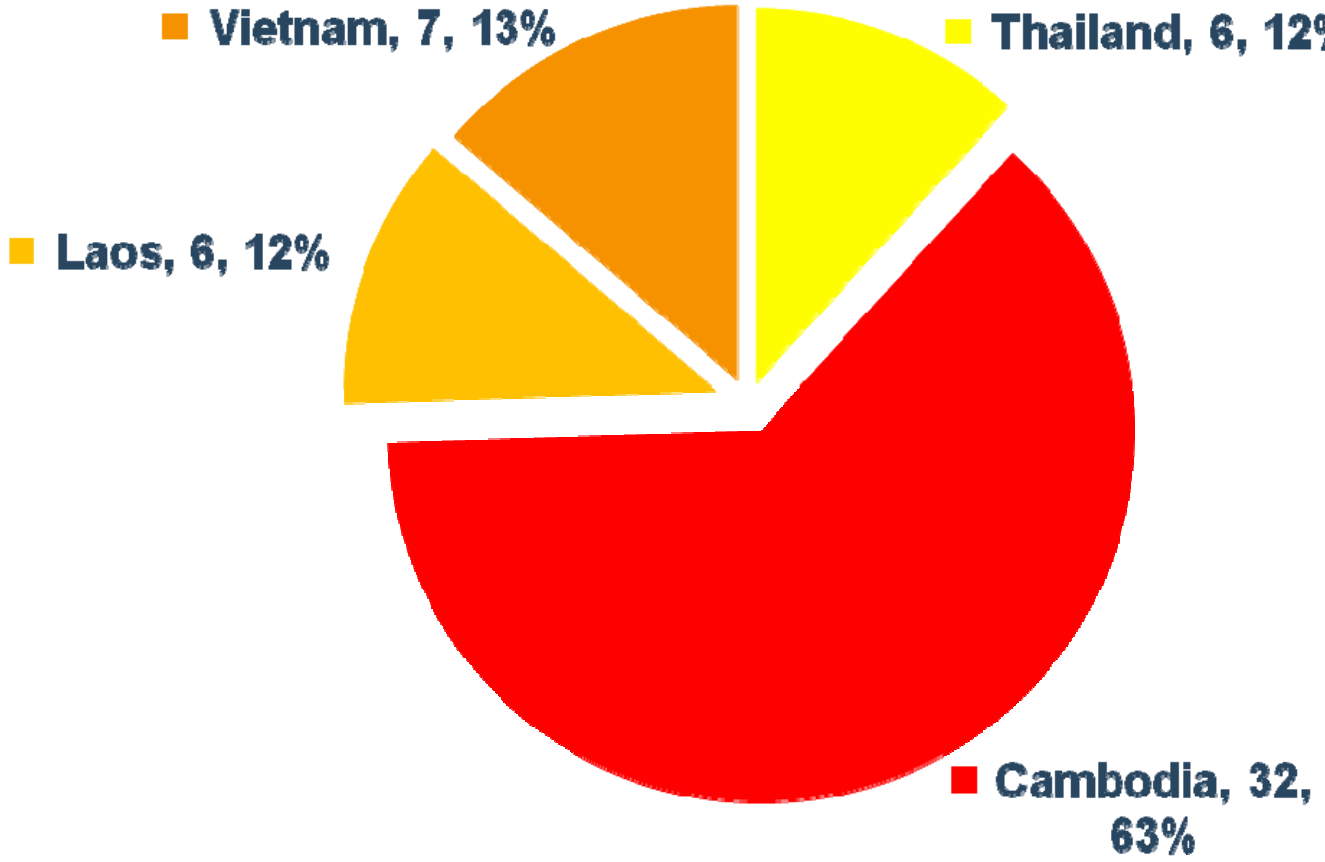
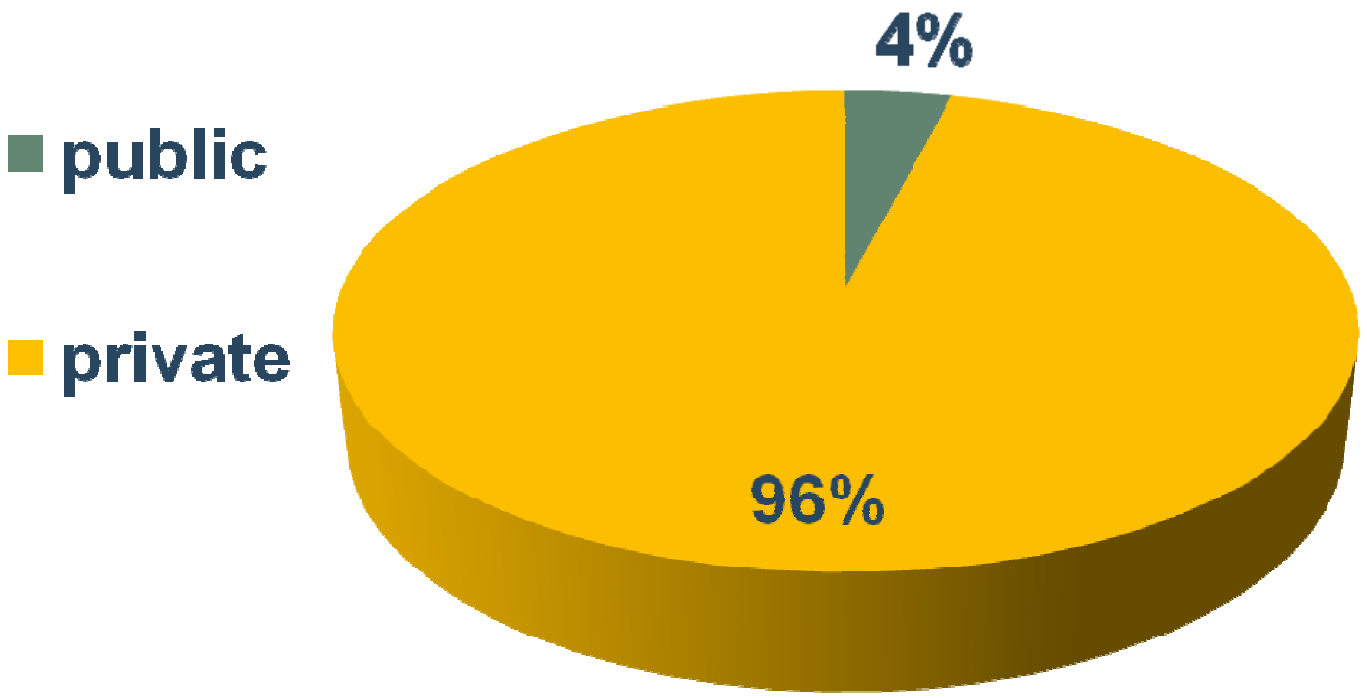


Figure does not include samples collected/tested from TH-KH cross-border study on AMLs quality in 2009.

Highlights of MQM Findings

Fig 5: Sector Where Failed AMLs Were Found: in Cambodia, Vietnam and Laos 2007-2010



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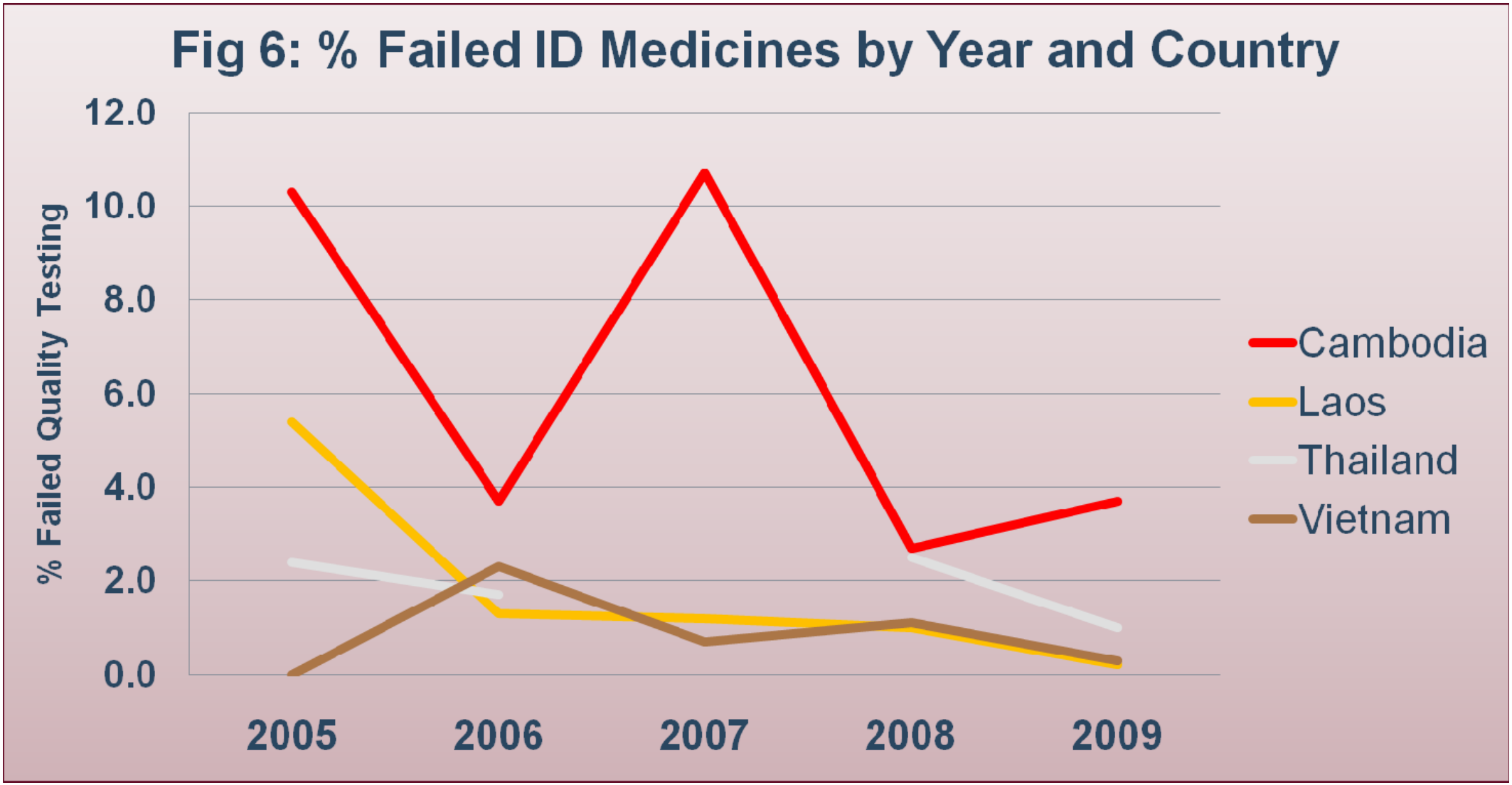
Highlights of MQM Findings



Thailand was on hold in 2007: no data was collected

Figure does not include samples collected/tested from TH-KH cross-border study on AMLs quality in 2009.

Highlights of MQM Findings

Most Commonly Found Poor Quality Antimalarials: Data from Medicines Quality Monitoring

Cambodia, Vietnam, Thailand and Laos 2007-2010

Products by API	Number Failed Quality Testing
Chloroquine phosphate	23
Artesunate	14
Tetracycline	8
Quinine Sulfate	5
Primaquine phosphate	1
Total	**51**

Figure does not include samples collected/tested from TH-KH cross-border study on AMLs quality in 2009.

Highlights of MQM Findings

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Of 51 Most Commonly Found Poor-quality Antimalarials 2007-2010: Data from Medicines Quality Monitoring, by Country

Cambodia	
Product by API	No.Failed Quality Testing
Chloroquine phosphate	20
Artesunate	6
Tetracycline	3
Quinine Sulfate	3
Total	32

Vietnam	
Antimalarial	No.Failed Quality Testing
Tetracycline	4
Quinine Sulfate	2
Artesunate	1
Total	7

Laos	
Product by API	No.Failed Quality Testing
Artesunate	6
Total	6

Thailand 2008-2009	
Product by API	No.Failed Quality Testing
Artesunate	1
Chloroquine phosphate	3
Primaquine phosphate	1
Tetracycline	1
Total	6

Figure does not include samples collected/tested from TH-KH cross-border study on AMLs quality in 2009.

Enforcement by MRAs

- **Fines**
- **Seizures**
- **Retail Outlet Closures**
- **Arrests**

- Issued regulatory warnings/notices to alert health professionals and public (Vietnam, Laos)
- Fined and closed outlets (Laos and, recently, Cambodia)
- Reported to WHO Rapid Alert System (Cambodia)
- Investigated further with manufacturers (All countries)

Enforcement Action Taken in Cambodia

PROMOTING THE QUALITY OF MEDICINES

រោងចក្រ៥ត្រូវបានរកឃើញថា ផលិតឱសថក្លែងក្លាយ!

សេចក្តីប្រកាសព័ត៌មានរបស់ក្រសួងសុខាភិបាល ស្តីពី ការរកឃើញឱសថក្លែងក្លាយនៅលើទីផ្សារកម្ពុជា

ថ្មីៗនេះក្រសួងសុខាភិបាលបានរកឃើញថា រោងចក្រផលិតឱសថចំនួន៥ បានទីងកំពុងចរាចរលើទីផ្សារកម្ពុជានូវផលិតផលឱសថក្លែងក្លាយ ដែលគ្មានចុះលេខបញ្ជីកាពីក្រសួងសុខាភិបាល រោងចក្រទាំង៥ នោះគឺ:

1- VKP Pharmaceutical Co., Ltd. Thailand
2- Shen Wei Pharmaceutical Co., Ltd. China
3- China Southern Da Zhong Pharmaceutical Co., Ltd. China
4- Fu Li Pharmaceutical. China
5- SG. Pharmaceutical. China

អាស្រ័យហេតុនេះ សូមឱសថការី គ្រូពេទ្យព្យាបាល អាជីវករ និងសាធារណជនទាំងអស់ជៀសវាងដាច់ខាតនូវការនាំចូល ការចែកចាយ និងការប្រើប្រាស់ផលិតផលឱសថ ដែលផលិតចេញពីរោងចក្រទាំង ៥ ខាងលើ ។

VKP Pharmaceutical Co., Ltd. Thailand

Fu Li Pharmaceutical Co., Ltd. China

AMPIMEX Capsule SP 500mg
Manufactured by:
Fu Li Pharmaceutical Co., Ltd. China

AMOXYMEX Capsule SP 500mg
Manufactured by:
Fu Li Pharmaceutical Co., Ltd. China

1-Name: AMPIMEX-500mg
2-Code:050/09/Q5/GFR6/RTK
3-Lot N:20081105
4-Mfg: Fu Li Pharmaceutical (China)
5-Mfg date: 11/08 , Exp:10/10
6-Result: failed API (00%)

Shen Wei Pharmaceutical Co., Ltd. China

AMPICILLIN Capsule SP 500mg
Manufactured by: Shen Wei Pharmaceutical Co., Ltd. China

AMOXICILLIN Capsule SP 500mg
Manufactured by: Shen Wei Pharmaceutical Co., Ltd. China

China Southern Da Zhong Pharmaceutical Co., Ltd. China

AMPICILLIN Capsule SP 500mg

SG. Pharmaceutical. China

1-Name: AMOXICILLIN Capsules B.P. 500mg
2-Code:102/09/Q7/GFR6/PVH
3-Lot N: 20081225
4- Register No : NO
5-Manufacturer: S.G. Pharmaceutical. China
6-Mfg date: N/A, Exp:11/2011
7-Result: API 67.52mg (13.50%)

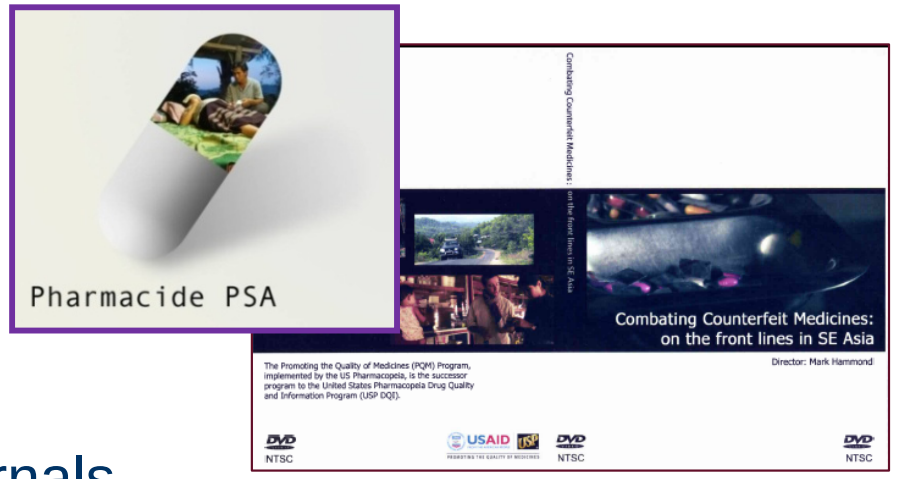
1-Name: Ampicillin Capsules BP 500mg
2-Code:078/09/Q7/GFR6/PVH
3-Lot N: 20081226
4-Register No : NO
5-Manufacturer: S.G. Pharmaceutical. China
6-Mfg date: N/A, Exp:11/2011
7-Result: API 00mg (00%)

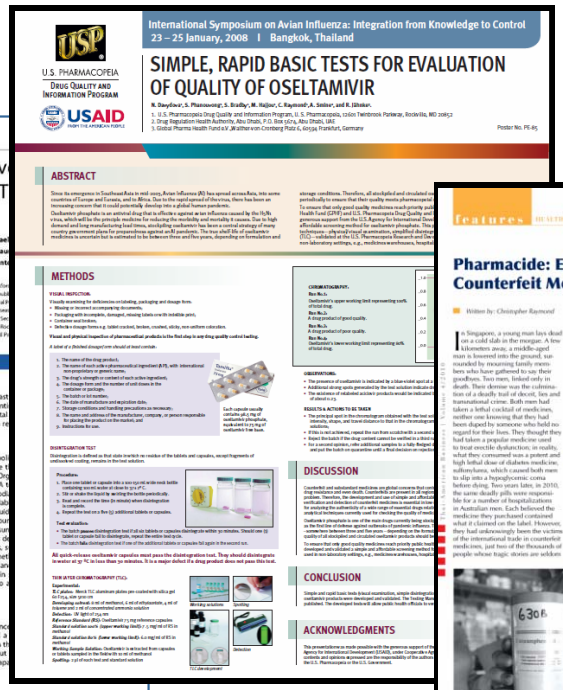
Raising Awareness – Media and Peer-reviewed Journals

PROMOTING THE QUALITY OF MEDICINES

Pharmacide Media Initiative:

- Pharmacide: PSA
- Combating Counterfeit and Substandard Medicines: on the Front-line in SE Asia
- Regional documentary film
- News/Magazine/Posters/Brochures/Journals





Impact Beyond National Level

- Increased collaboration
  - Piqued interest of partnerships (WHO, PSI, INTERPOL, Wellcome Trust, IMPACT, BMGF)
  - INTERPOL Operations Jupiter and Storm
  - Stronger relationships with NGOs active in fighting counterfeit medicines
- Raised awareness among healthcare workers, consumers
- MQM program in Mekong Subregion serves as model for 25+ other countries in Africa, Asia, and Latin America

Quality of AMLs Thailand-Cambodia Cross-border Study

PROMOTING THE QUALITY OF MEDICINES

Thailand sites:

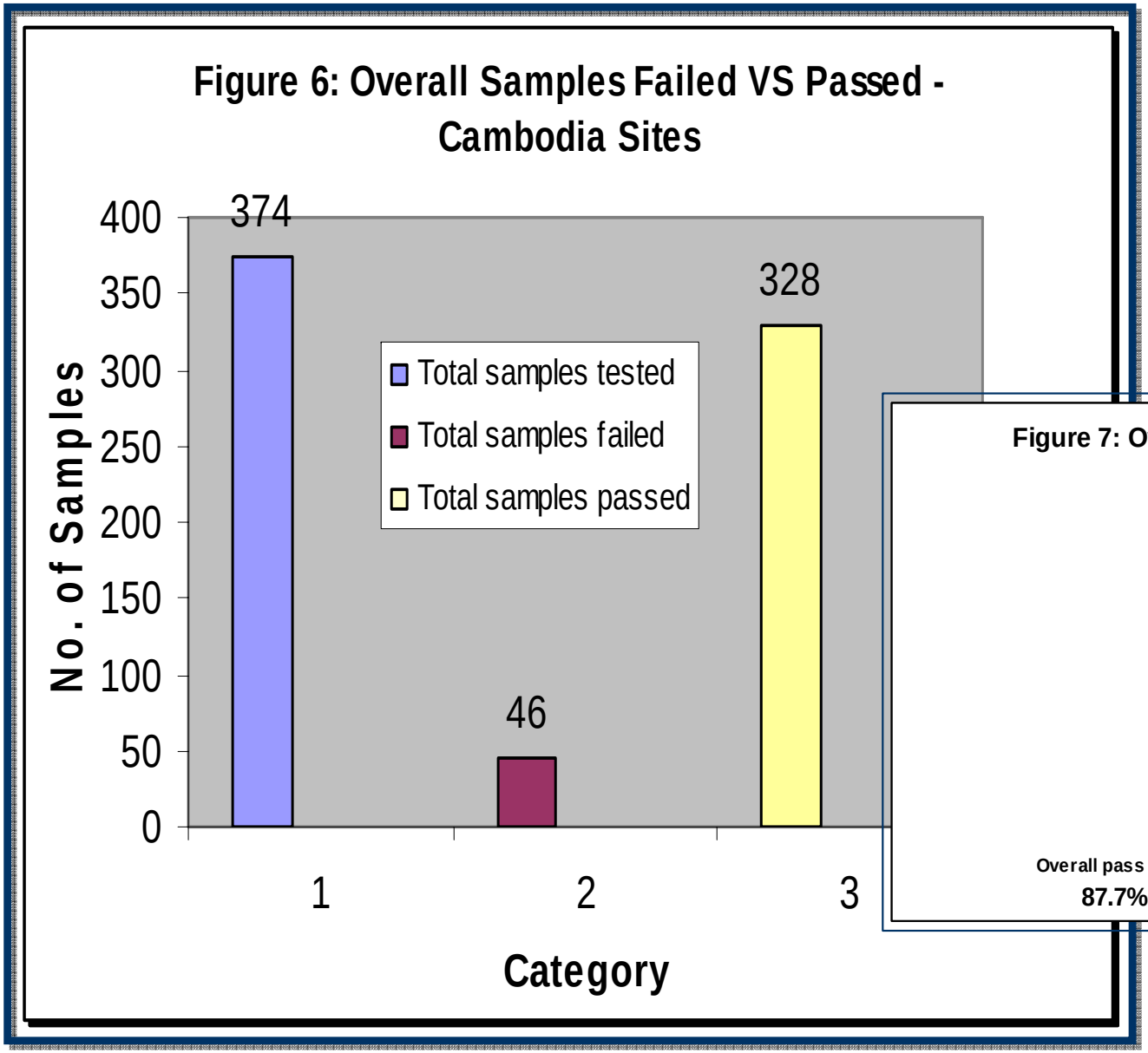
1. Si Sa Ket/Ubon Ratchathani
2. Surin
3. Buriram
4. Sa Kaeo
5. Chanthaburi
6. Trat

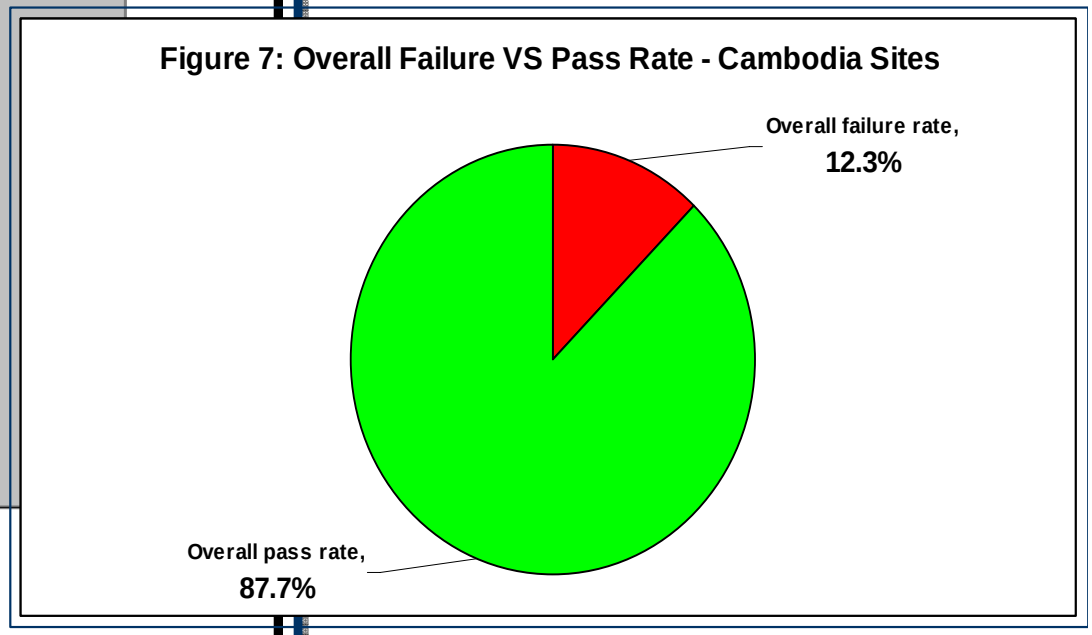
Cambodia sites:

1. Preah Vihea
2. Oddar Meanchey
3. Bantheay Meanchey
4. Battambang
5. Pailin
6. Pursat

Findings: AML Medicines Quality – Cambodia Sites

PROMOTING THE QUALITY OF MEDICINES





Findings: AML Medicines Quality – Cambodia Sites

PROMOTING THE QUALITY OF MEDICINES

Table 9: Cambodia Sites – Reasons for Failure by Product		
Name of Sample	**Reasons for Failure**	**No. of Samples**
ARS	Assay: API (86.96%) [ref. 90.0-110.0%]	**1**
	Assay: API (88.3%) [ref. 90.0-110.0%] + Related subs: >2% [ref. NMT 2%]	**1**
	Assay: API (0%) [ref. 90.0-110.0%] + Disinteg.> 1h [ref. LT 30mn]	**3**
	Dissol..: < 60% [ref. NLT 60% in 30mn] + Related subs > 2% [ref. NMT 2%]	**1**
	Related subs: > 2% [ref. NMT 2%]	**9**
ARS +MEQ	Assay: ARS API (77.7%) [ref. 90.0-110.0%] + Impurities in ARS > 2% [ref. NMT 2%] in Malarine	**2**
ARMN/PIP	Assay: ARMN:30.4mg/tab (48.6%) + PIP:189.1mg/Tab (50.4%) [ref. 90.0-110.0%] (Artequick)	**1**
	Assay: ARMN:29.8mg/tab (4.8%) + PIP:190.2mg/Tab (50.7%) [ref. 90.0-110.0%] (Artequick)	**1**
DHA	Assay: (87%) [ref. 90.0-110.0%] (Cotecxin)	**1**
	Subtotal	**20**

Findings: AML Medicines Quality – Cambodia Sites

Table 9: Cambodia Sites - Reasons for Failure by Product (cont'd)		
Name of Sample	**Reasons for failure**	**No. of Samples**
DHA/PIP	Dissol.: DHA: 1.9-31.7mg (4.7-79.2%) *PIP: 2.6-308.8mg (0.8-96.5%) (Duo-cotecxin)	**1**
	Dissol.: DHA: 0mg *PIP 0mg (0%) [NLT 75%]	**5**
	Dissol.: 0- 33 mg DHA + 0- 298.6 mg Pip phosphate in 45 mn (Duo-cotecxin)	**2**
	Dissol.: DHA: 0.8-29.3mg (2-73.2%) *PIP: 1.6-317.4mg (0.5- 99.1%) (Duo-cotecxin)	**1**
CHLQ PHOSP	Dissol.: < 75% [ref. NLT 75% in 45mn]	**1**
	Disinteg. > 1h [ref. NMT 60mn]	**6**
TETRA	Dissol.: 1.04%-13.8% [ref. NLT 80% in 60mn]	**3**
	Dissol.: 25.3% -35.2% [ref. NLT 80% in 60mn]	**1**
	Disinteg.: > 60mn [ref. NMT 60mn]	**1**
QUIN S	No API: - Quinine sulfate	**5**
	Subtotal	**26**

	Total	**46**

Findings: AML Medicines Quality – Thailand Sites

Figure 2: Overall Samples Failed VS Passed - Thailand Sites

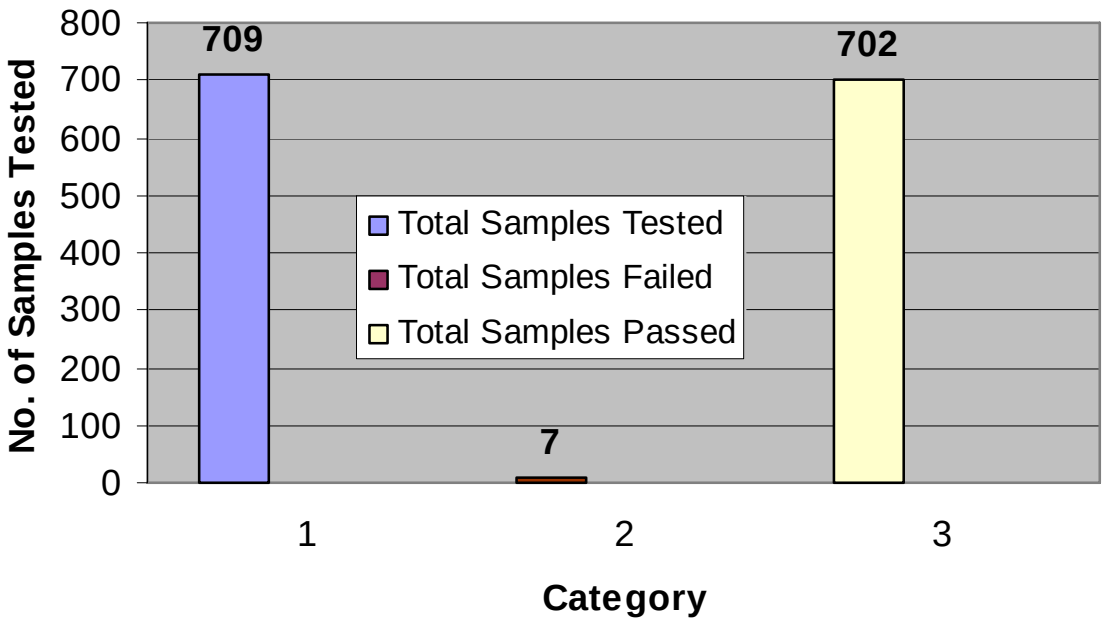
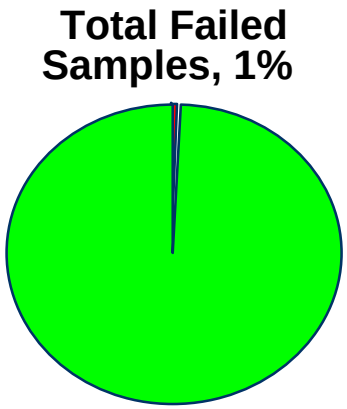


Figure 3: Overall Failure vs Pass Rate - Thailand Sites



Findings: AML Medicines Quality – Thailand Sites

Table 11. Thailand Sites – Reasons for Failure by Product		
Name of Sample	**Reasons for failure**	**No. of Samples**
Primaquine phosphate	ID: No API: Primaquine	**1**
Tetracycline HCL	Dissol.: 0 - 0.8% - Tetracycline HCl (Piomicin) [ref. NLT 80% in 60mn]	**1**
Chloroquine phosphate	Dissol.: 35.0%-39.8% - Chloroquine phosphate [ref. NLT 75% in 45mn]	**1**
	ID: Wrong API – contained Quinine Sulfate	**1**
	Assay: 108.9% [ref. 93.0-107.0%]	**1**
Artesunate	Related substances: > limit [ref. NMT 2%]	**1**
Quinine sulfate	ID: Wrong API – contained Chloroquine	**1**
	Total	**7**

Looking Ahead: Regional Strategy – Build Capacity

- Accredit (all) national QC laboratories to ISO/IEC-17025 and/or WHO Prequalification
- Support selected manufacturing facilities to attain WHO Prequalification status
- Strengthen MQM activities in strategic areas
- Develop a Regional Pharmacy Certification Program
- **B**uild **R**egional **E**xpertise in **Me**dicines **R**egulation and **E**nforcement (BREMERE) – add on to existing ANEQAM

Concluding Remarks

1. USP PQM has successfully established a model MQM for infectious diseases medicines in the Mekong Subregion and synergized the efforts of national and international partners. The model has already translated to other regions, e.g., Sub-Saharan Africa and Latin America.
2. MQM has been instrumental in fostering an environment of collaboration and exchange of information, ideas, and insights into the complexities of developing and strengthening functional medicine QA systems for the region.
3. Focus should be placed on integrating MQM activities into routine MRA functions for sustainability.

Acknowledgements

I wish to thank all of my QM colleagues for their contributions and input into this presentation, especially Dr.. Patrick Lukulay and Ms. Marilyn Foster.

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Thank You

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