

Fake antimalarials: Start with the Facts ♦ Geneva ♦ 28 May 2015

The Importance of Drug Quality: Setting the Scene



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Promoting the Quality of Medicines Program

1. Setting the scene...
2. Current situation of the quality of antimalarials (AMLs) in the Mekong Sub-region – USP PQM perspective
3. Key challenges in addressing the quality of AMLs
4. What would be the way forward in terms of strategy and approach to address the quality of AMLs?

Drug Quality — WHO Definition

The suitability of a drug product for its intended use is defined by:

- Its efficacy weighed against safety (health risks) according to a label claim or as promoted
- Its conformity to specifications regarding identity, strength, purity, and other characteristics, e.g. dissolution property, impurity, hardness, sterility, etc.
- Medicine = API + excipients + information + label + package
- Medicines quality assessment — compliance with established pharmacopeial specifications and regulatory requirements, or manufacturer's validated methods

What is drug quality and why is it important?

Examples of SFFC medicines:

1. Avastin (for cancer treatment). USA, 2012. Affected 19 medical practices in the USA. The drug lacked active ingredient
2. Viagra and Cialis (for erectile dysfunction). UK, 2012, smuggled into the UK. Contained undeclared active ingredients with possible serious health risks to the consumer
3. Truvada and Viread (for HIV/AIDS), UK, 2011, seized before reaching patients. Diverted authentic product in falsified packaging
4. Zidolam-N (for HIV/AIDS). Kenya, 2011, Nearly, 3, 000 patients affected by falsified batch of their antiretroviral therapy.

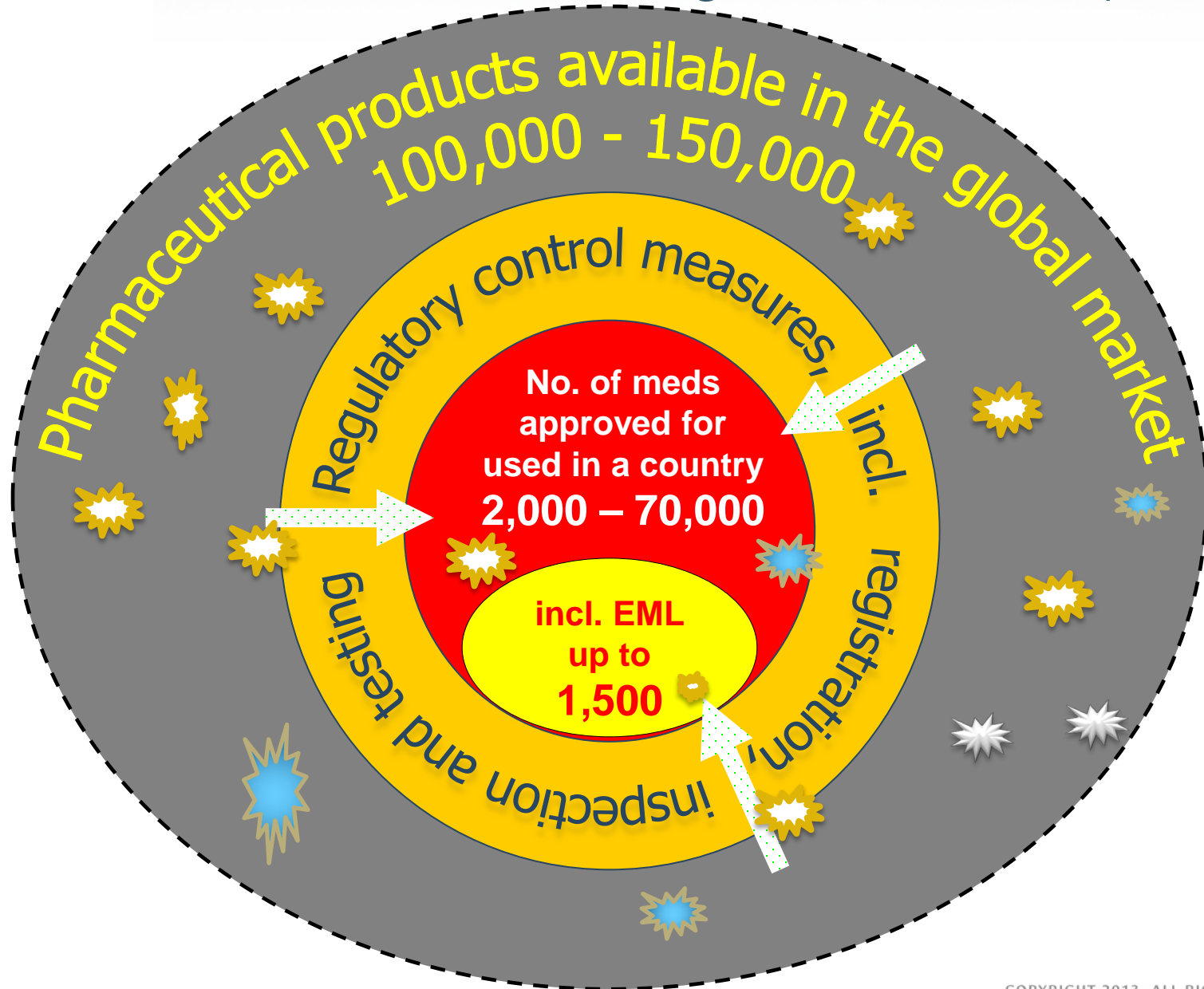
What is drug quality and why it is important?

Even if these principles are followed:

1. Qualified/trained health care provider consulted
2. Proper diagnosis made
3. STGs followed, i.e. “correct” drug prescribed in right dose and right route of administration
4. Objective information obtained
5. Treatment regimen complied

There will be no cure if the medicines being used are not of established quality

Challenges in filtering for quality-assured medicines, including antimalarials (AMLs)



Counterfeit, substandard and fake drugs – definition

A counterfeit drug: A pharmaceutical product that is **deliberately** and fraudulently **mislabeled** with respect to identity or source. Both branded and generic products can be counterfeited. Counterfeit drugs can include products with the correct ingredients, with the wrong ingredients, without active ingredients, with insufficient quantity of active ingredients. A counterfeit drug can be a deliberate imitation or a copy of a genuine product.

A substandard drug: A legal branded or generic drug that does not meet generally accepted national or international standards for quality, purity, strength or packaging

A fake drug product contains no API(s) as claimed on the label

Classification: Poor quality medicines

All medicines



FALSIFIED, COUNTERFEIT

Intentional criminal production of medicines at illegitimate manufacturers



SUBSTANDARD

Unintentional errors caused in production at genuine manufacturers



DEGRADED

Poor quality after leaving the factory due to poor storage or handling

*There is no shortage of medicines, **but there continues to be a shortage of quality-assured medicines***

Factors contributing to poor-quality medicines - compliance Gaps in GxPs

Central level



Provincial level



Peripheral level



Source: Some photos courtesy of Associate Prof. C. Sooksriwong

Common challenges: compliance gap in GLP/QMS

**National or
Central
level**



Inadequate
quality
management
system

Non-ISO/IEC-17025:2005 and/or non-WHO PQ

**Sub-
national or
Provincial
level**



Lack of or
inadequate
quality
management
system and
technical
performance

Contributing factors to med quality problems

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
 - ▶ 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

Contributing factors to med quality problems

1. Weak institutional capacity, e.g.,
 - a. Many non-GMP-compliant manufacturers exist
 - b. \approx 90–120 establishments to inspect/year by 1 inspector
 - Same inspector does both GMP and PMS
 - c. \approx 80–120 samples tested/year/lab analyst
 - Poorly equipped lab with limited qualified personnel
2. Ineffective and untimely regulatory enforcement due to:
 - a. Delay in obtaining test results/reports from the OMCL
 - b. Questionable results
 - c. In some cases, further verification/confirmation is needed – samples sent to reference lab outside the country – further delay
3. MRAs have no power to take action
 - a. No or minor punishment against violations

Challenges in most developing countries

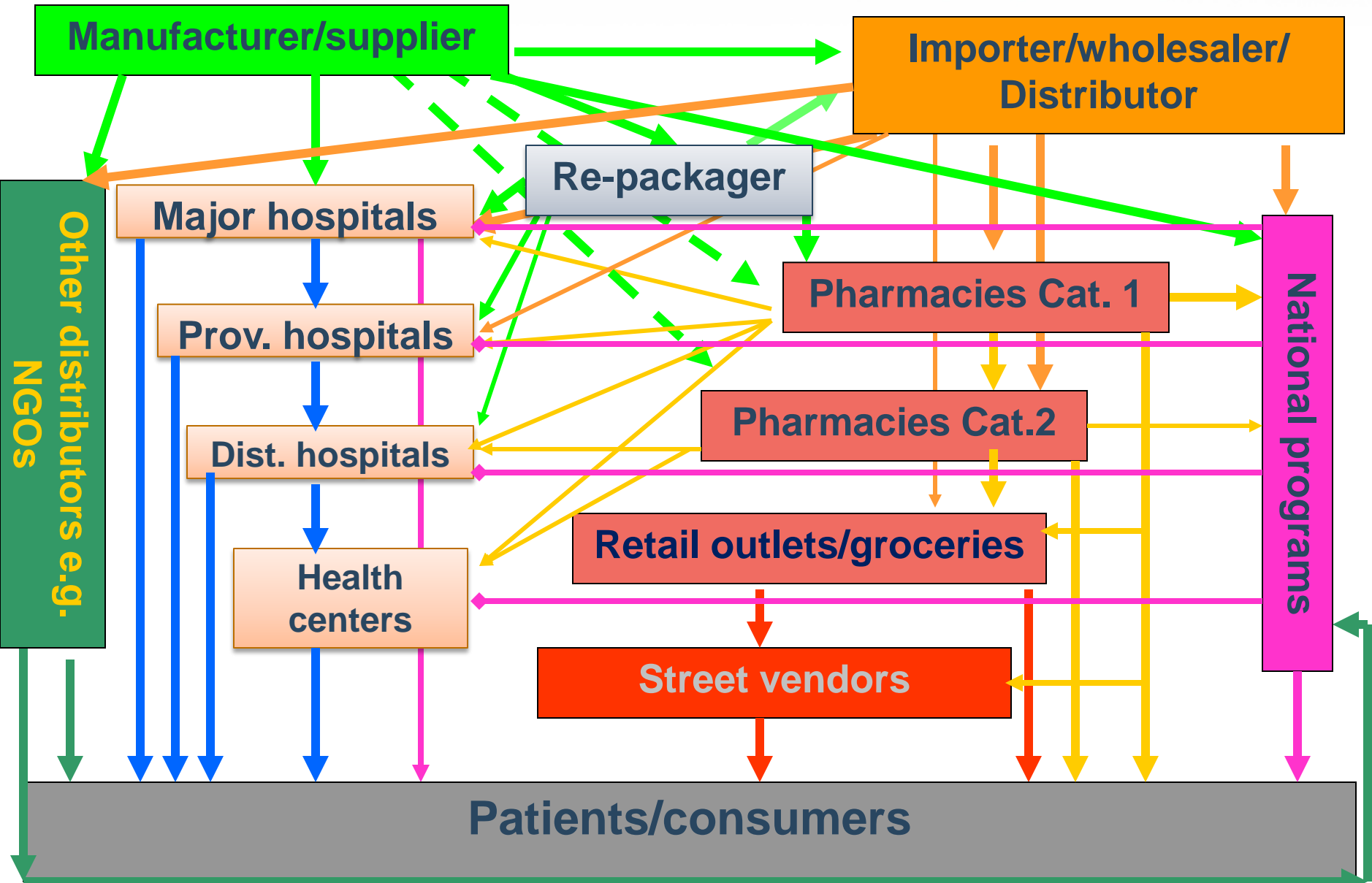
Business owner diagnoses, prescribes, and dispenses

Informal and illegal markets

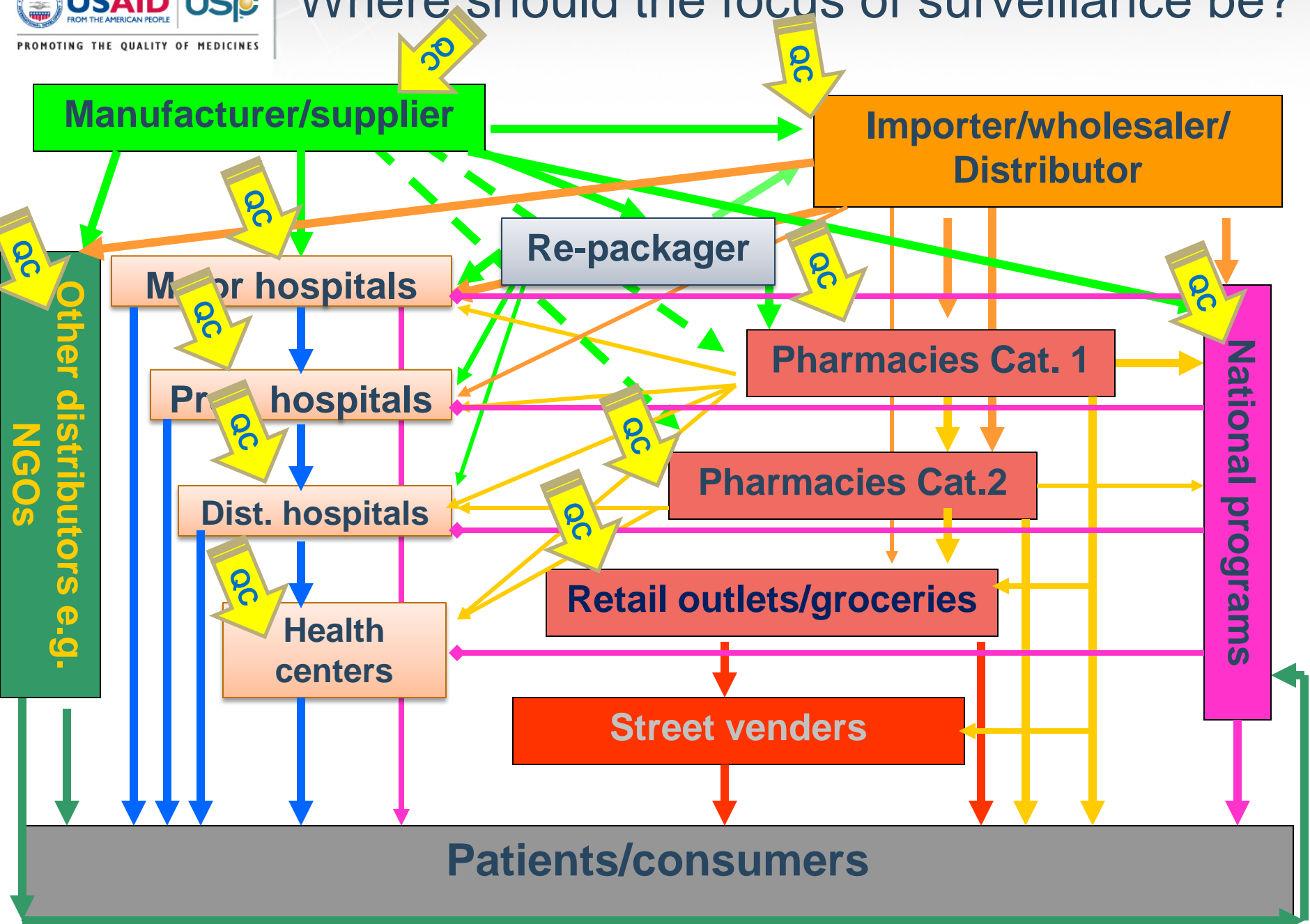
Uninformed consumer and patient



The supply chains of medicines are complex



Where should the focus of surveillance be?



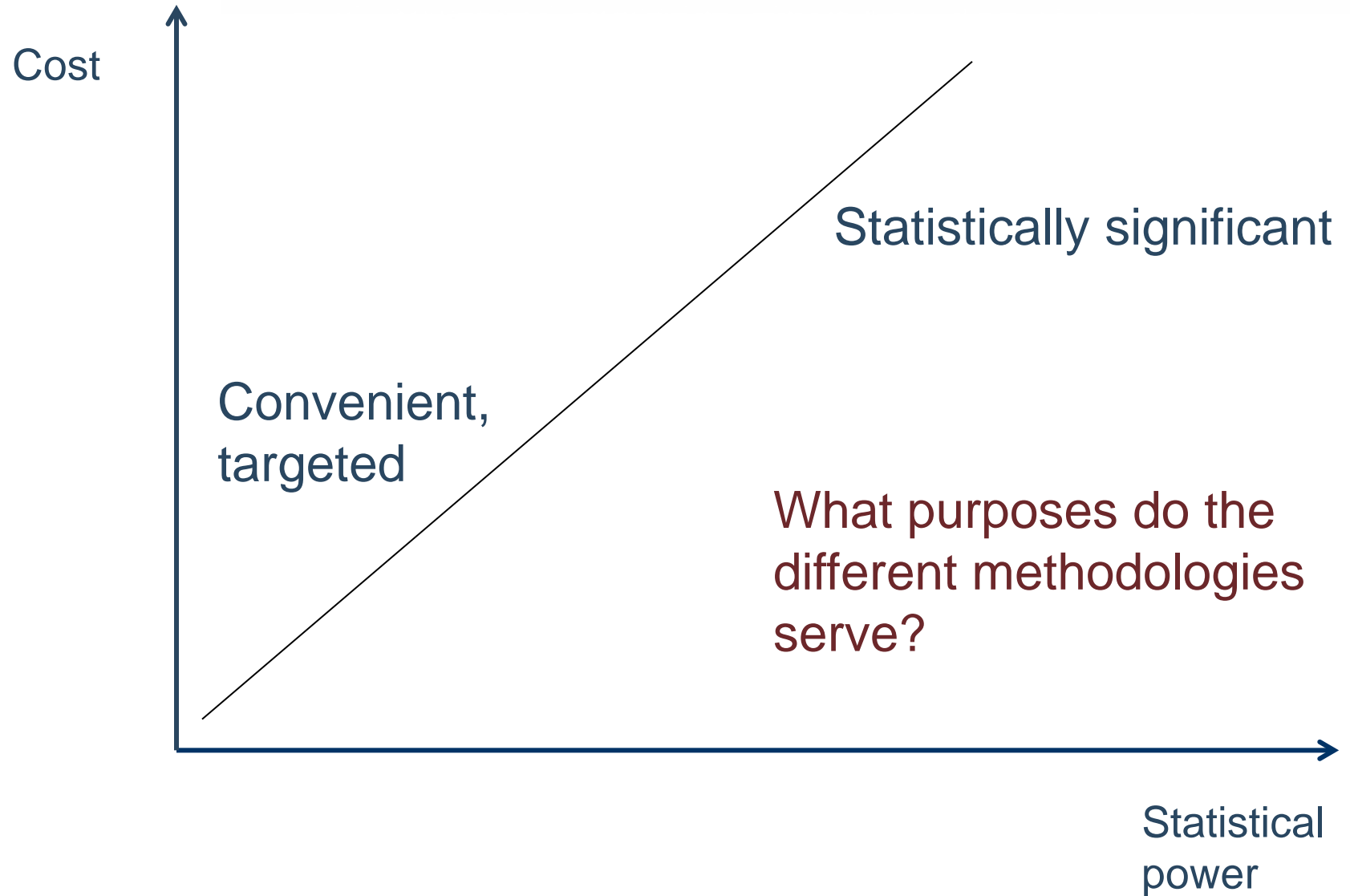
Debate on sampling methodologies

- ▶ Perhaps AMLs have been most extensively studied and reported on, in regards to quality
 - Poor-quality AMLs continue to threaten patients lives.
- ▶ *Data we'll hear more about today can be split into three large categories based on different sampling methodologies:*

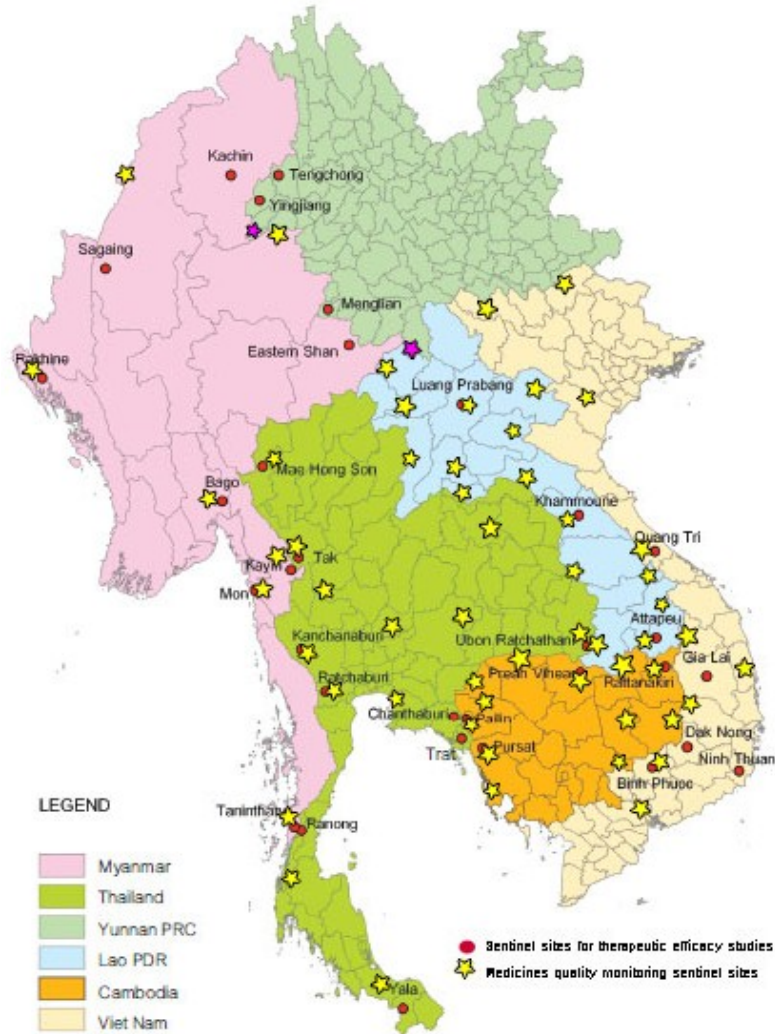


Level of accuracy to determine prevalence increases?

Est. cost associated with types of sampling

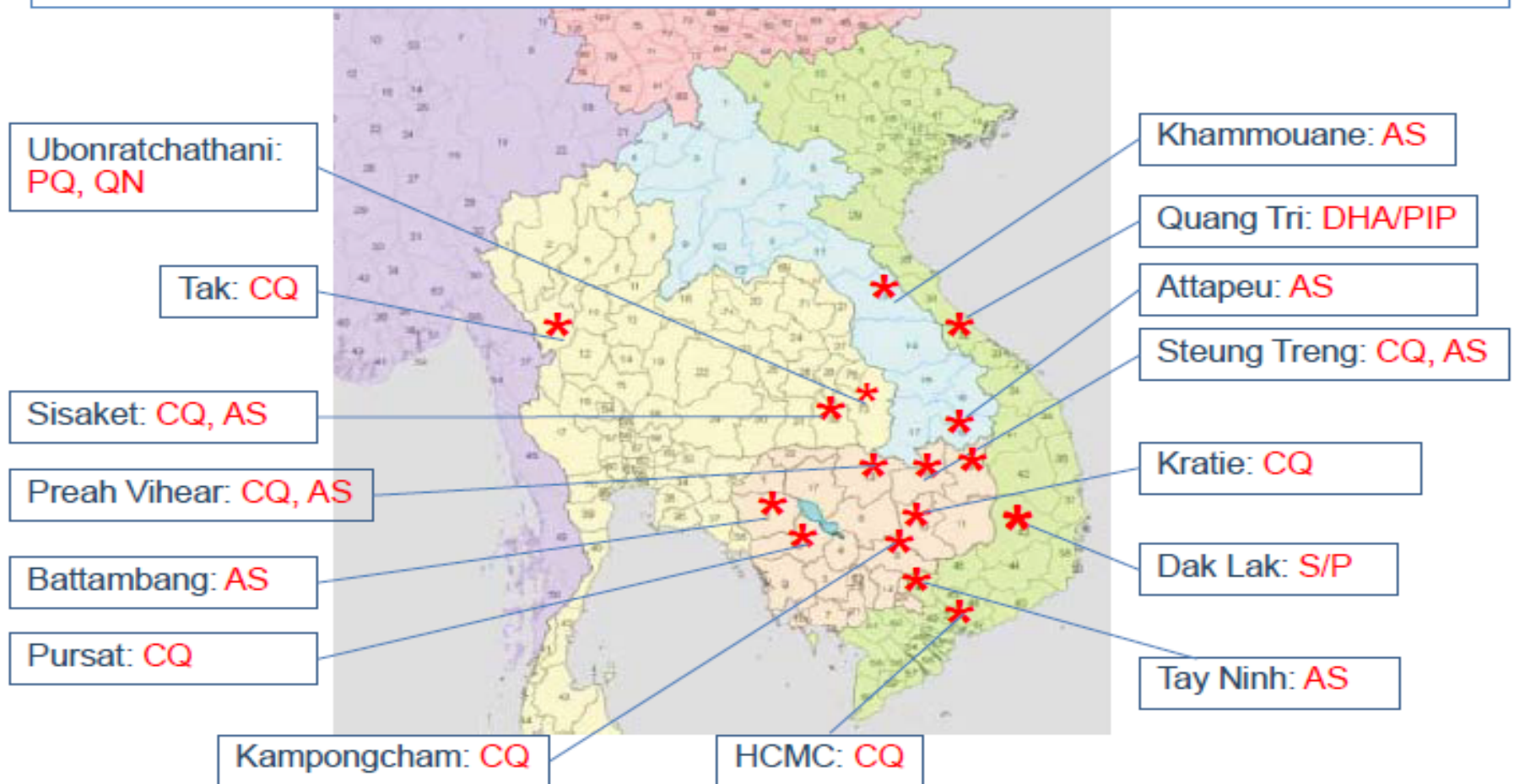


MQM in SE Asia supported by USP PQM



Locations where poor-quality antimalarials were found in 2009- 2011 (Note: MQM was not yet implemented in Burma)

Legend: AS: artesunate; A+M: artesunate + mefloquine; CQ: chloroquine; DHA/PIP: Dihydroartemisinin/piperaquine; DHCQ: dihydrochloroquine; PQ: primaquine; QN: quinine; S/P: sulfadoxine/pyrimethamine



Locations where poor-quality antimalarials were found in 2012- June 2014

Legend: AS: artesunate; A+M: artesunate + mefloquine; CQ: chloroquine;
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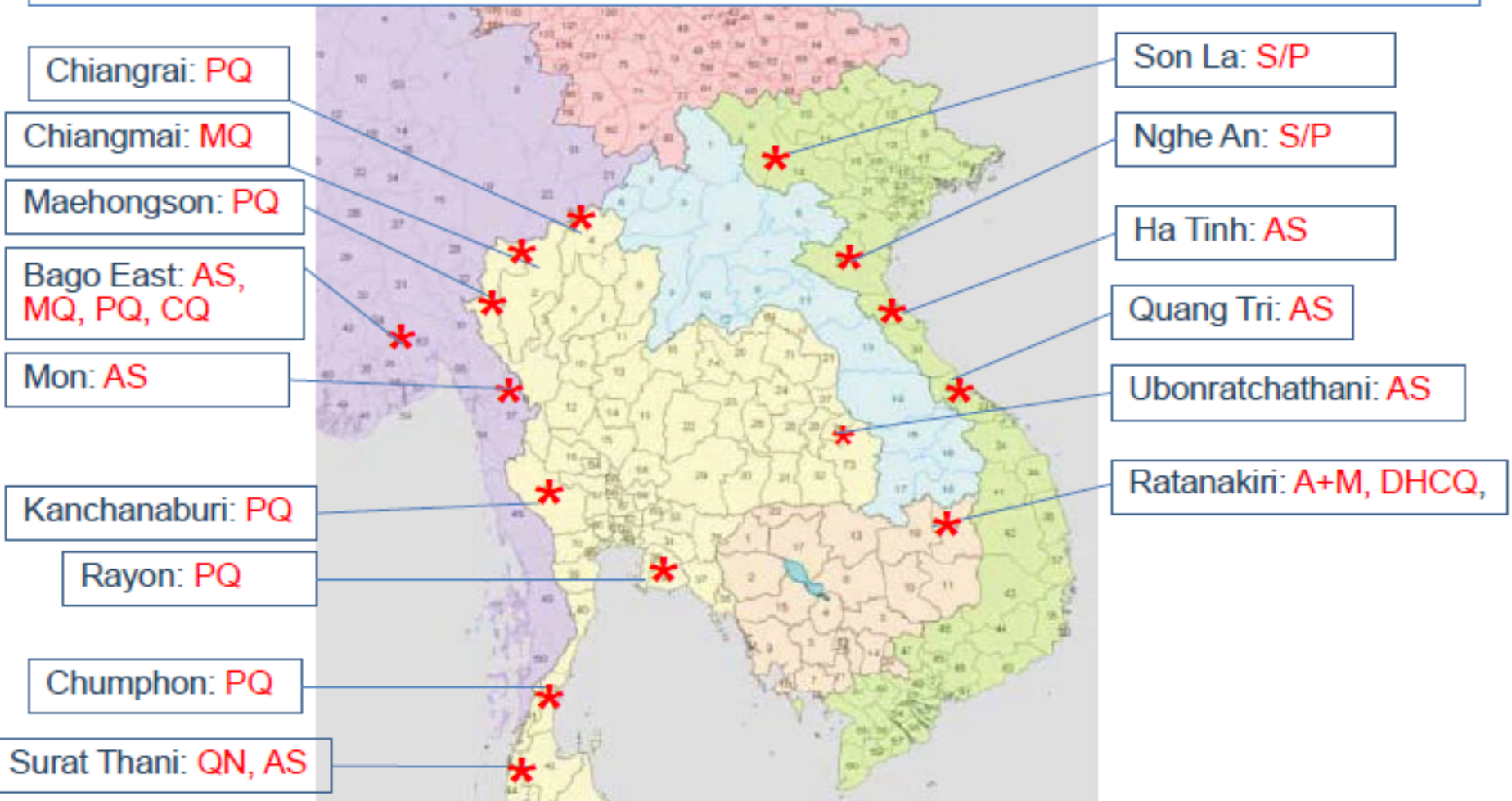
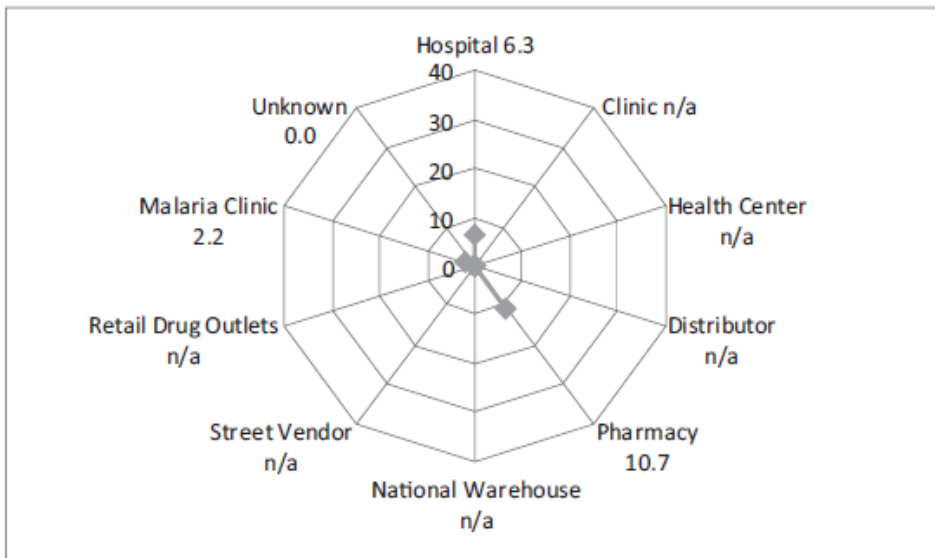
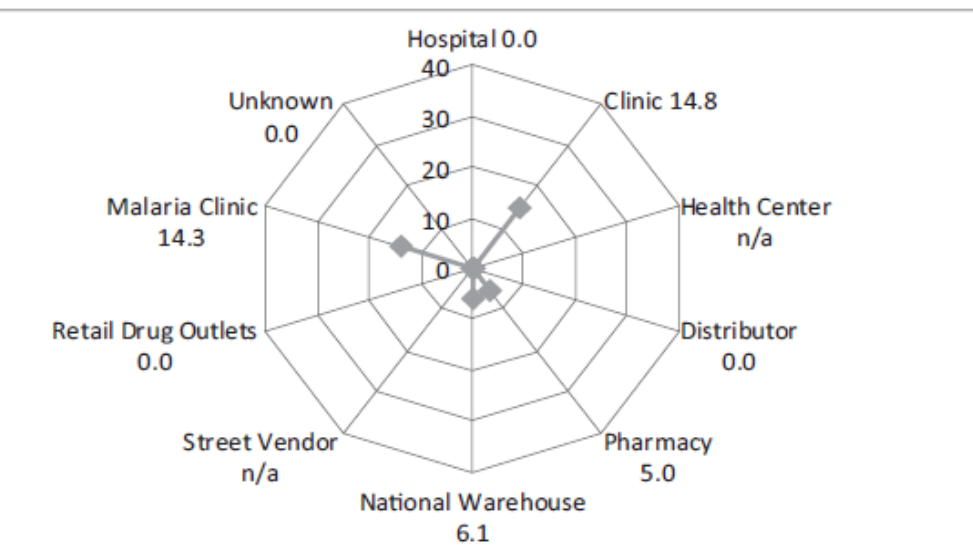


Figure 32: Consumers' risk of receiving poor quality medicines from various distribution channels in the border provinces of Thailand



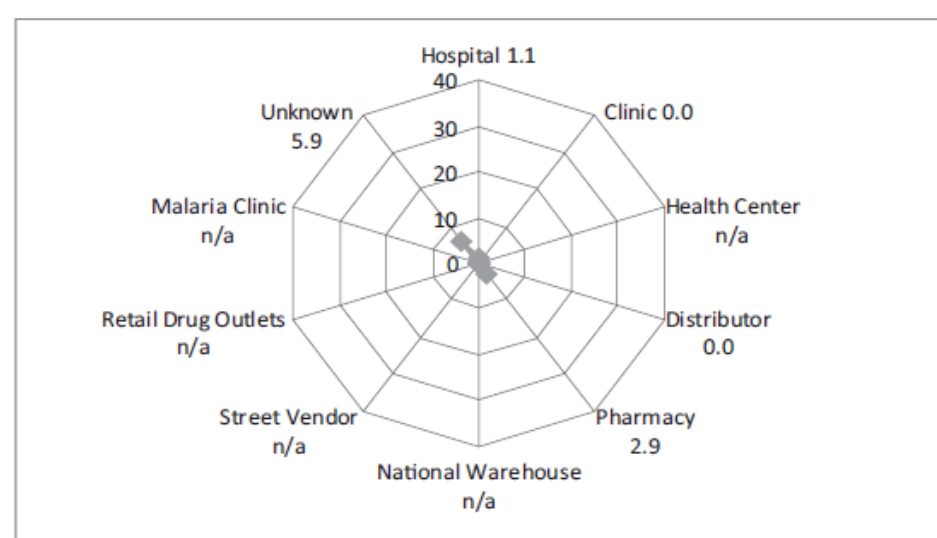
Note: the number indicates percentage

Figure 30: Consumers' risk of receiving poor quality medicines from various distribution channels in the border counties of Yunnan Province



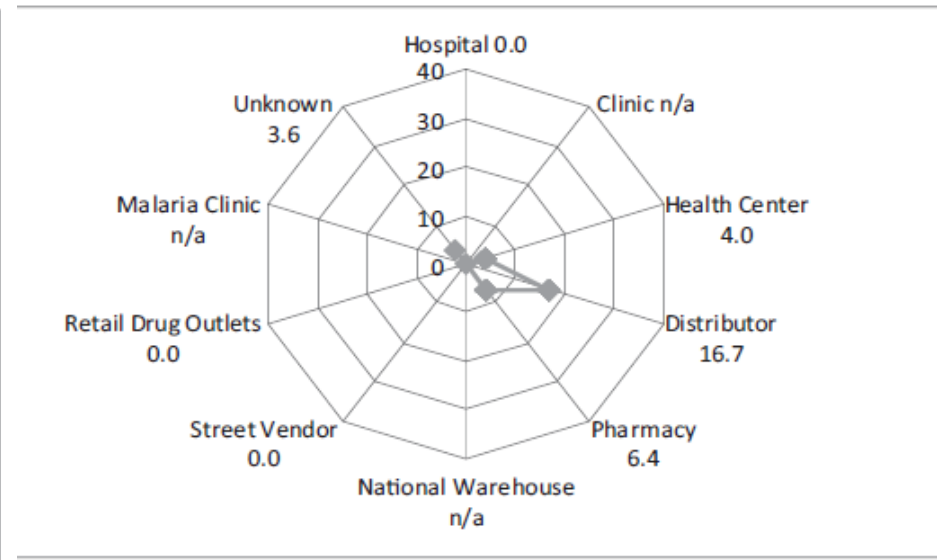
Note: the number indicates percentage

Figure 31: Consumers' risk of receiving poor quality medicines from various distribution channels in the border provinces of Lao PDR



Note: the number indicates percentage

Figure 33: Consumers' risk of receiving poor quality medicines from various distribution channels in the border provinces of Vietnam



Note: the number indicates percentage

Focus of MQM in resistant malaria zones in GMS



Corrective and enforcement action - examples

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 partners:

Countries MOH, Police, Customs, and external assistance, including WHO, French Ministry of Foreign Affairs, USP PQM, and the INTERPOL



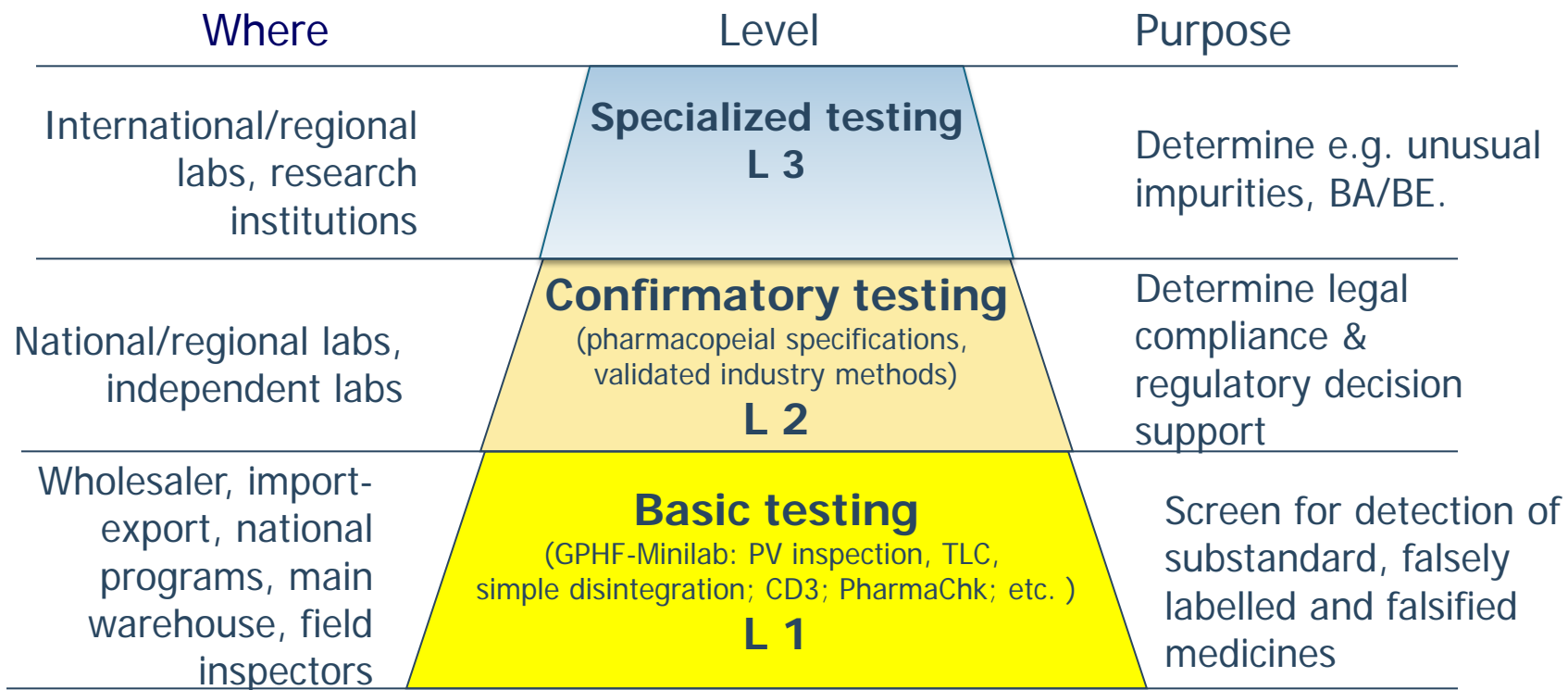
Of all the key areas of investment to combat poor quality medicines, 4 are of highest priority



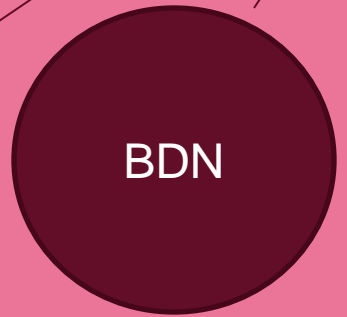
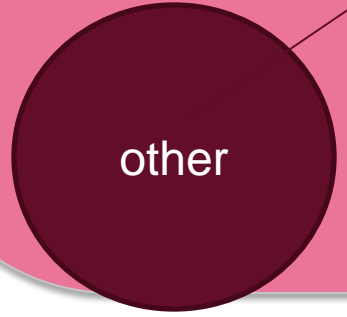
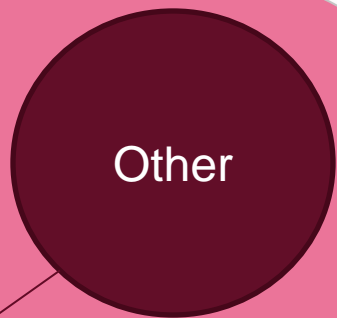
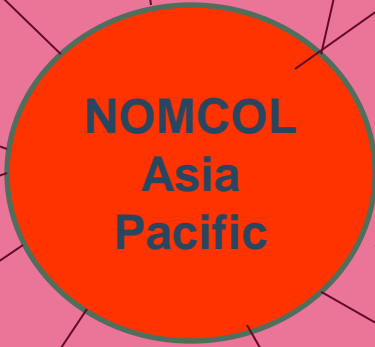
Current status of 8 reg. labs against international standard in SE Asia

		CAM	PHI	LAO	IND	THA	VNM		MMR
Partner Organization		NHQC	FDA Lab	FDQCC	NQCL-FD	BDN	NIDQC	IDQC HCMC	FDA Lab
Current Status on Achieving Accreditation and/or WHO PQ	ISO/IEC 17025	Prep and road map for ISO	☺ MB (TB)	☺ PB	☺ PB	☺ PB	☺ MB	☺ MB	Initial phase
	WHO PQ	–	Discussion initiated	–	Disc. initiated	☺	☺	Prep to submit IEO Sept 2015	–
Main role in USP and PQM program		NOMCOL RSAP MQM	NOMCOL RSAP MQM	NOMCOL RSAP MQM	NOMCOL ? MQM	NOMCOL RSAP MQM	NOMCOL RSAP MQM	NOMCOL RSAP MQM	NOMCOL RSAP MQM

Regulatory labs perform reliable and timely analysis results for confirmatory testing

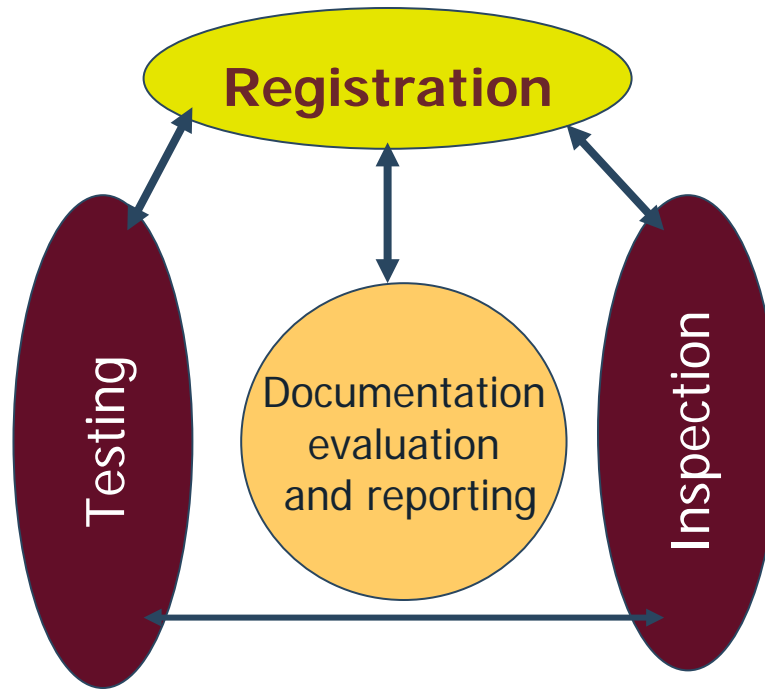


MRAs and BREMERE



The need for prioritization

All medicines for use
in the country-
except for special
schemes



- Product sources (production adequacy and MRA competency)
- Product types and characteristics
- The three-level testing approach framework

GMP:

- Locally produced: pre-approval
- Imported: rely on data from MRAs of export countries e.g. PIC/S and U.S. FDA

DISTRIBUTION CHAIN:

- targeted – for counterfeit & substandard meds
- Consignment acceptance or rejection

Conclusion: existing gaps below need to be addressed



Limited surveillance coverage: We are currently only covering MQM surveillance in 29% of the poor quality antimalarials found and focus only on artemisinin resistance hot-spots



Delayed data sharing: Delayed sharing of reports of failed medicines and associated investigations



Truncated reach to attack the problem at its roots: We are currently not conducting medicines quality monitoring activities in China (&India) key manufacturers and exporters of antimalarials to the region, often with dubious quality



National QC Labs poorly equipped:

- Reference standards (substances and documentary) and equipment
- Limited compliance with international standards



Limited number of human resources with adequate skills and motivation:

Increased number of trainings to improve expertise and skills in surveillance of medicines



Prioritizing responding to poor quality medicines: Limited regulatory systems capacity to prioritize quality assurance of medicines and integrated delivery of national programs

Conclusion



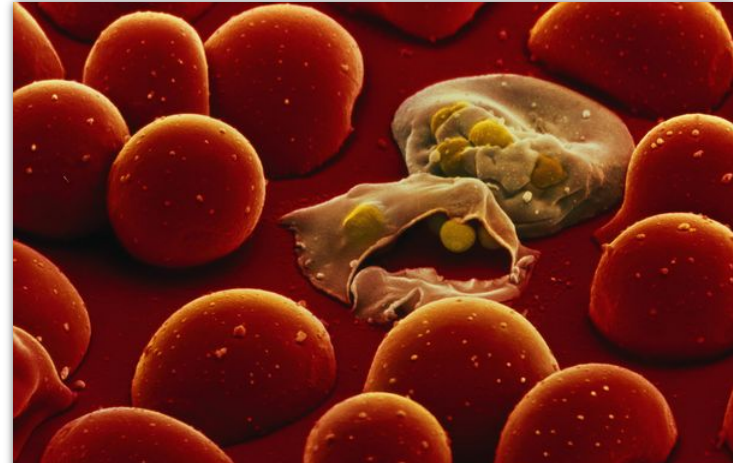
MORBIDITY AND MORTALITY



FINANCIAL CONSEQUENCES

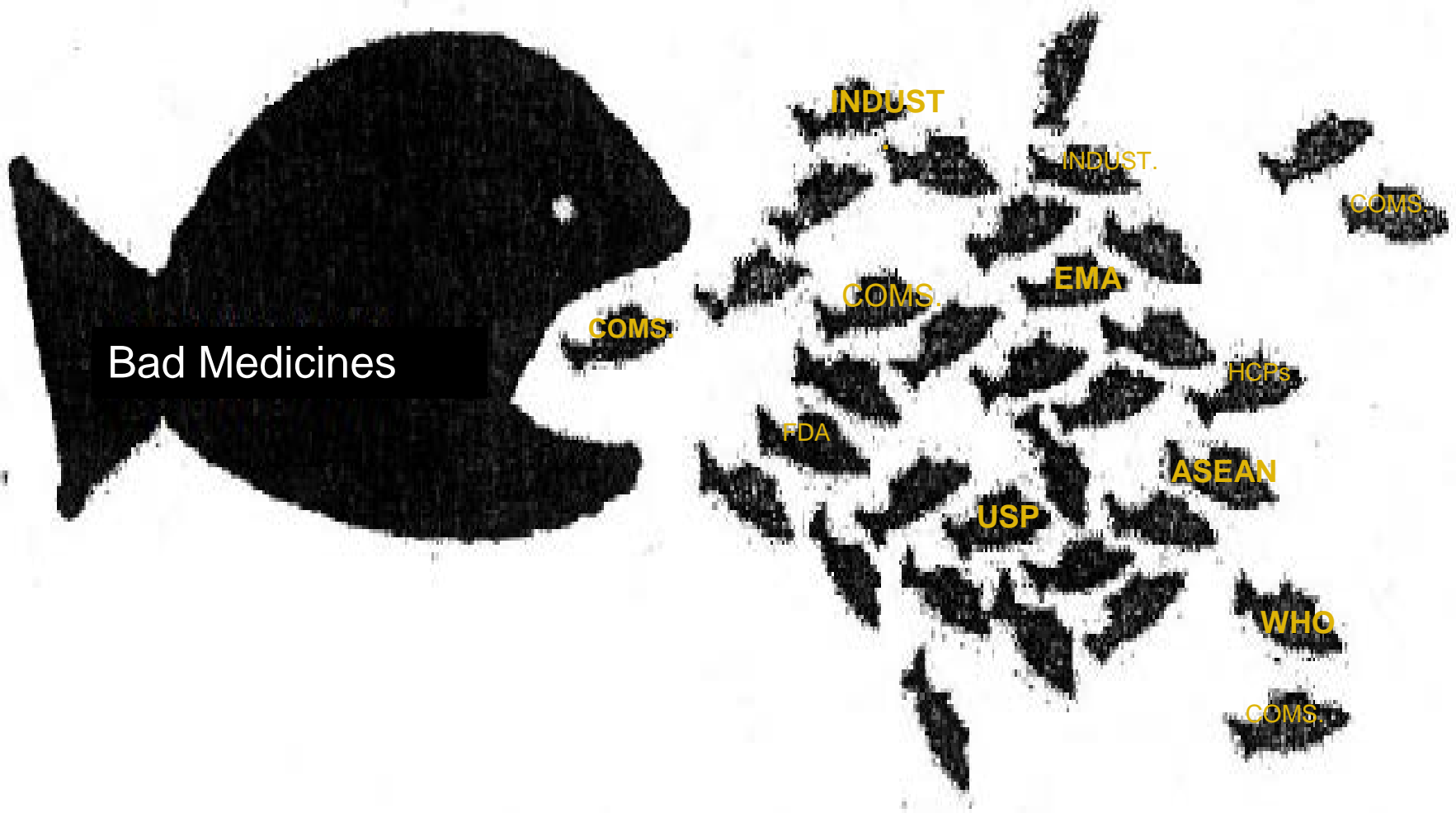


LOSS OF TRUST

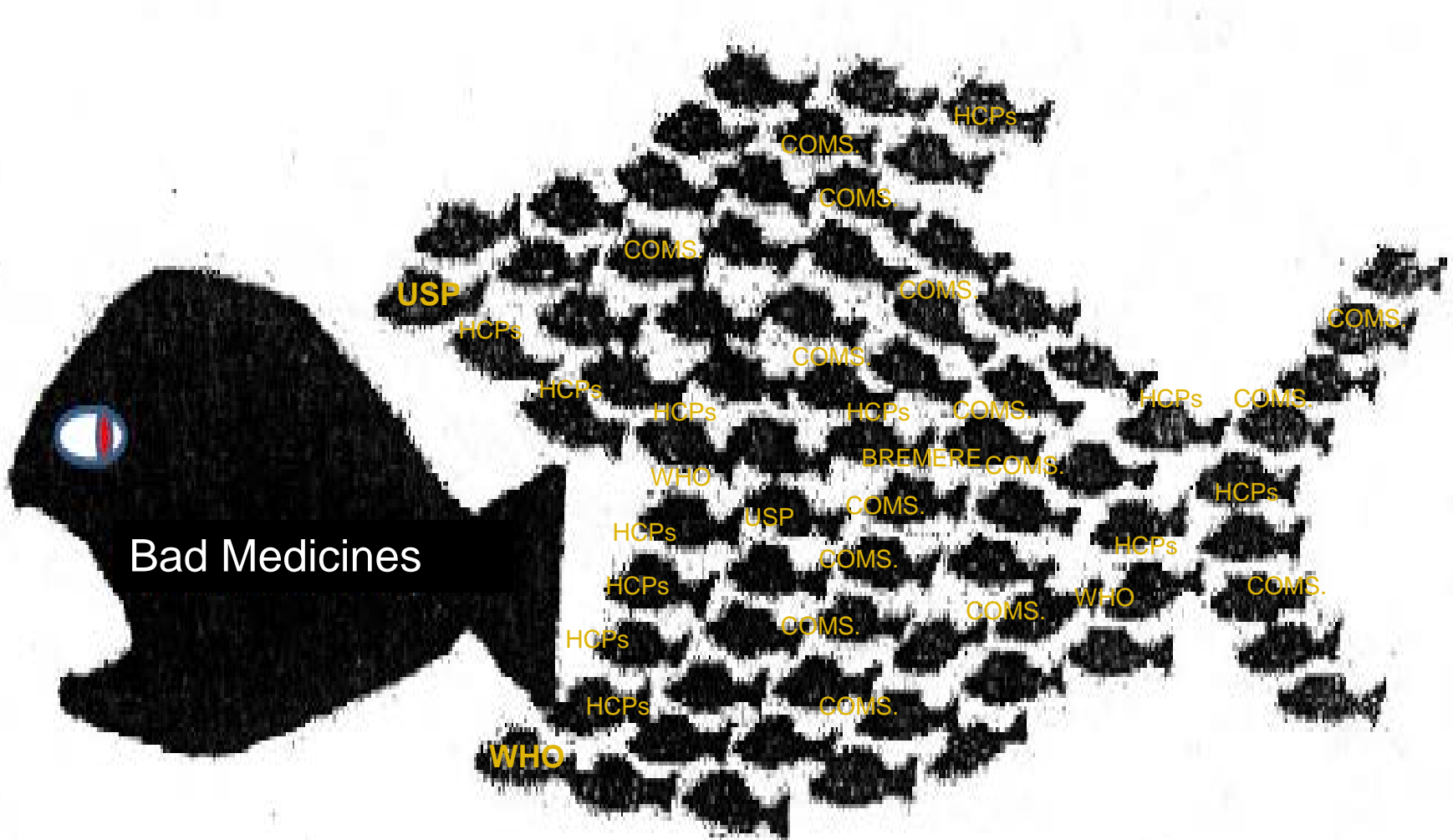


DRUG RESISTANCE

Uncoordinated and fragmented efforts...



Collaborative and coordinated efforts...





PROMOTING THE QUALITY OF MEDICINES

Thank You

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