Quality problems for API used in essential medicines : Role of WHO and its pre-qualification programme

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Pavia- 11 May 2012

A few key figures

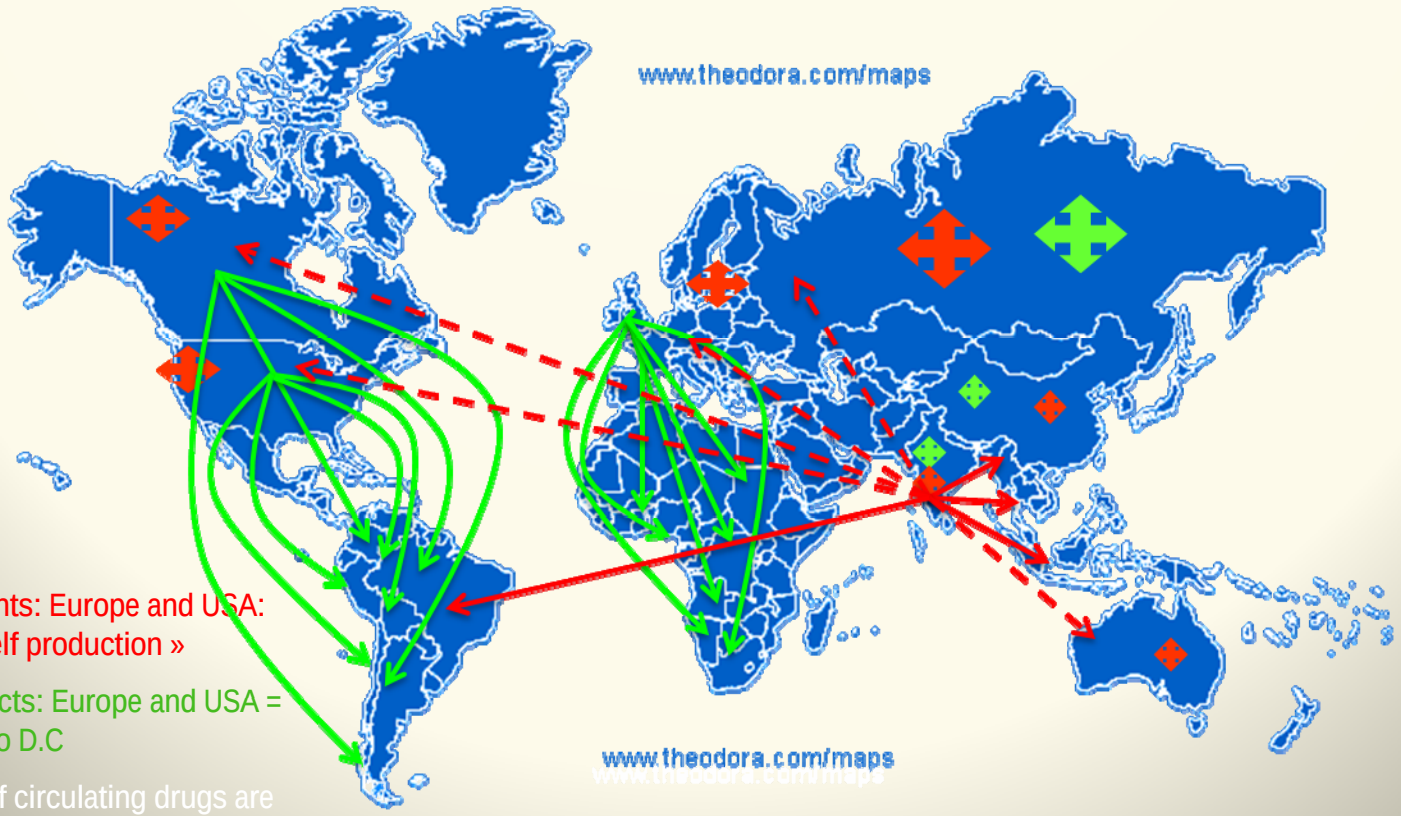
- 2010 WW Pharmaceutical market: a USD 837 Billion worth market (vs USD 200 Billion in 1990);
- Sub-Saharan Africa accounts for less than 0,5% of this amount;
- Up to 90% of the population in poor countries purchase medicines « out of pocket »;
- Medicines account for the 2nd expenditure of a poor household (just after food).

Summary

- The current global pharmaceutical context
- Extent of the problem for procurement in low income countries
- Role of WHO face to this problem
- Situation today and perspectives

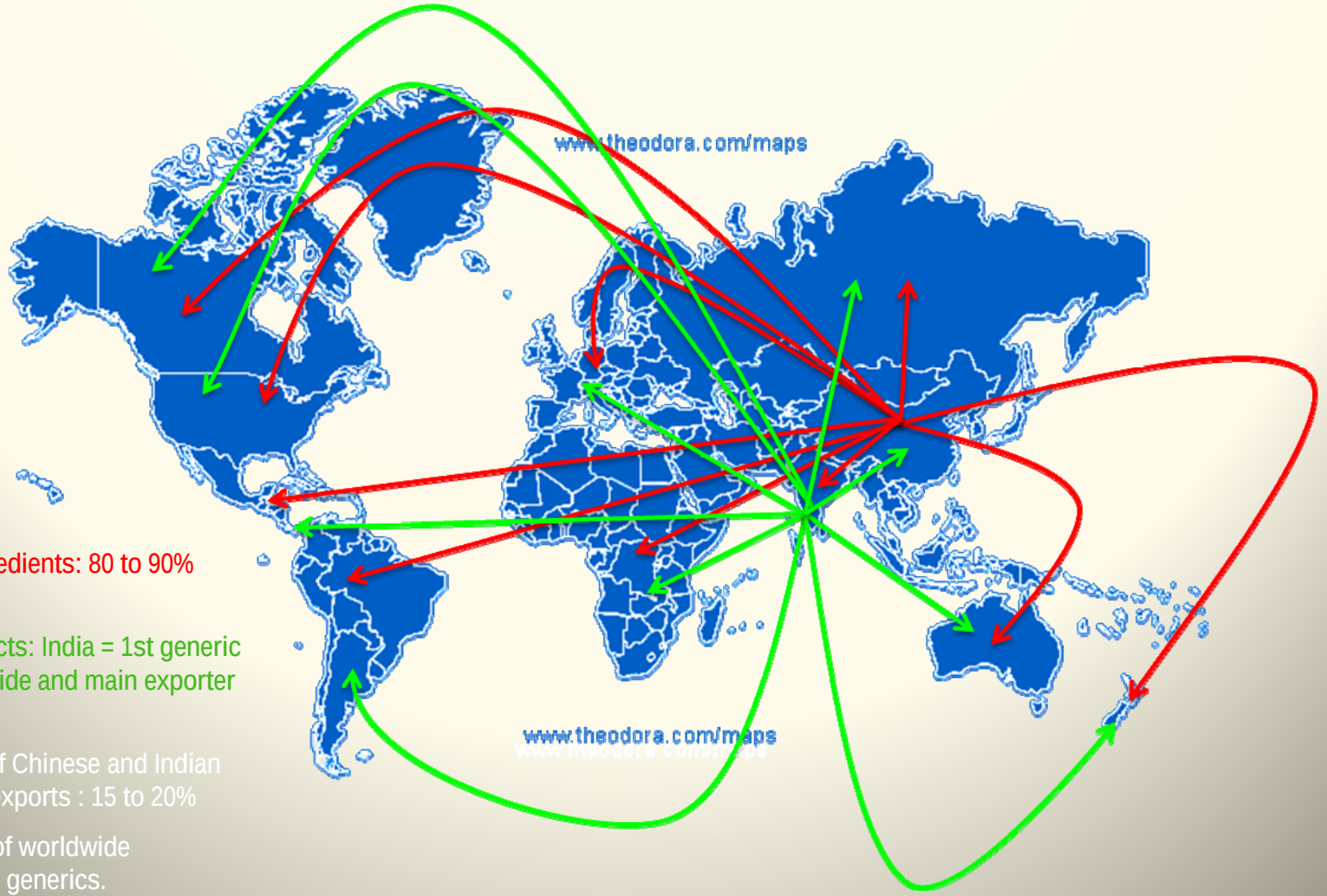
The current global pharmaceutical context

The manufacturing market before 1990



- Active Ingredients: Europe and USA: 90 to 95% of « self production »
- Finished Products: Europe and USA = main exporters to D.C
- Less than 5% of circulating drugs are generics

The manufacturing market today



- WW Active Ingredients: 80 to 90% come from Asia

- Finished Products: India = 1st generic producer worldwide and main exporter to D.C.

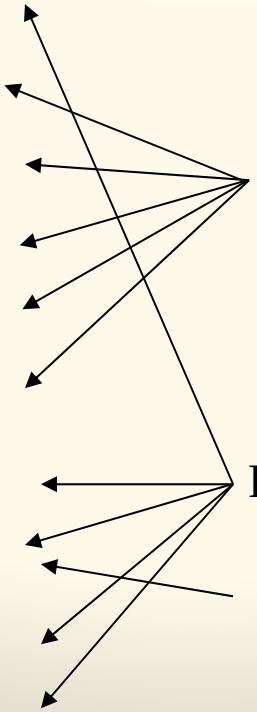
- Yearly growth of Chinese and Indian pharmaceutical exports : 15 to 20%

-more than 50% of worldwide prescriptions are generics.

Responsibility and regulation

Quality Assurance
Inspection of Manufacturing site
Active Ingredients ► Pharmacopoeias
Finished product ► Pharmacopoeias
Therapeutic Equivalence
Stability studies
Packaging/Labelling/Leaflet
Independent Quality Control
Distribution Channels ►GDP standards
Pharmacovigilance
Monitoring GMP = Re-inspection

10 critical levels



Competencies

Manufacturers

Regulatory authorities

Distributors

Responsibility and regulation

European Production

Quality Assurance	Originator Products
Manufacturing site ►GMP standards	YES
Active Ingredients ► Pharmacopoeias	YES
Finished product ► Pharmacopoeias	YES
Therapeutic Equivalence	N/A
Stability studies	YES
Packaging/Labelling/Leaflet	YES
Independent Quality Control	YES
Distribution Channels ►GDP standards	YES
Pharmacovigilance	YES
Re-inspection	YES

Responsibility and regulation

European Production

Quality Assurance	Originator Products	Generic Products
Manufacturing site ►GMP standards	YES	YES
Active Ingredients ► Pharmacopoeias	YES	YES
Finished product ► Pharmacopoeias	YES	YES
Therapeutic Equivalence	N/A	YES
Stability studies	YES	YES
Packaging/Labelling/Leaflet	YES	YES
Independent Quality Control	YES	YES
Distribution Channels ►GDP standards	YES	YES
Pharmacovigilance	YES	YES
Re-inspection	YES	YES

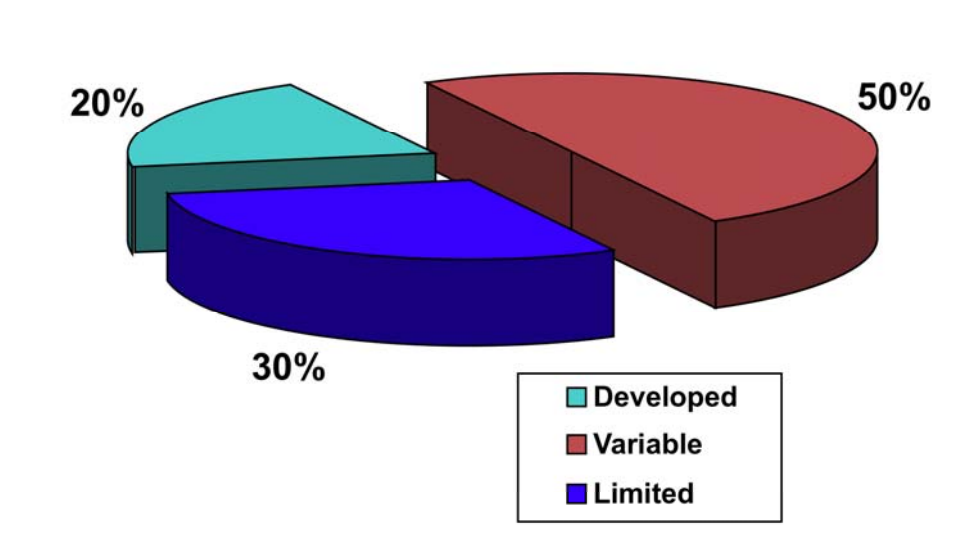
Responsibility and regulation

European Production

Quality Assurance	Originator Products	Generic Products	Export to WR countries
Manufacturing site ►GMP standards	YES	YES	YES
Active Ingredients ► Pharmacopoeias	YES	YES	NO
Finished product ► Pharmacopoeias	YES	YES	NO
Therapeutic Equivalence	N/A	YES	NO
Stability studies	YES	YES	NO
Packaging/Labelling/Leaflet	YES	YES	NO
Independent Quality Control	YES	YES	NO
Distribution Channels ►GDP standards	YES	YES	YES
Pharmacovigilance	YES	YES	NO
Re-inspection	YES	YES	YES

Responsibility and regulation

"The reality is that many regulatory authorities don't have the full capacity to perform all regulatory functions, due to chronic shortages of human, technical, financial and other resources" WHO



Risks and facts

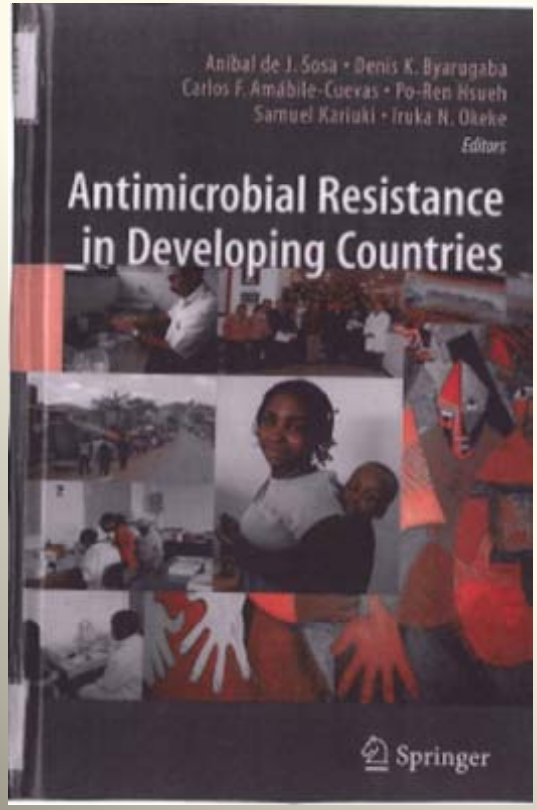
- Multiplicity of **standards** (WHO, ICH, EU ..) and difficulty to apply them;
- **QC/QA:** Blur concepts for a lot of actors (QC is considered sufficient);
- **Globalization** of the market: outsourcing, subcontracting and diversification of the supply chain for API and FPP -> **Tracability**?
- Increasing pressure on **price** -> Affordability >< Quality;
- **Lack of cooperation:** Solving this problem « **on its own** » is very difficult and very expensive.
- **Counterfeit** and **informal** markets hide the growing issue of substandard medicines
  - more than 25% of non-conformity in circulating medicines in non highly regulated countries are **sub-standards**
  - **API quality is one of the most frequent causes** with over/under API concentration, dissolution, contamination

Risks and facts

- **Concentration in API**: Over/Under-dosing
- **Poor quality** of API
- Poor bio-availability
- **Unexpected impurities**
- **Decreased efficacy of the active ingredient**
- **Development of drug resistance** (in particular for Antibiotics)
- Contamination with environmental pollutants, pyrogens, microbiological,
- Cross-contaminations with highly active molecules, toxic contaminants, including from the excipient, etc.
- Lack of stability
- Alteration of pH
- Accelerated deterioration due to poor packaging (e.g., IV fluids)

Risks and facts

- High prevalence of poor-quality medicines in insufficiently regulated countries (actual extent underestimated?): Antibiotics



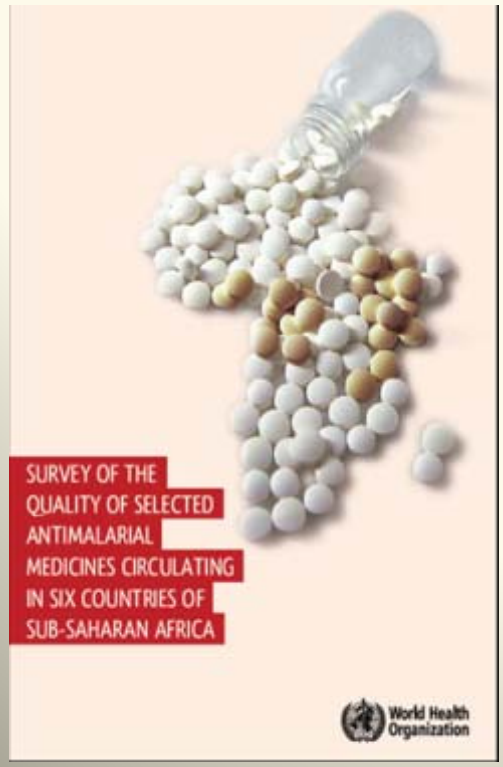
Chapter 24
Counterfeit and Substandard Anti-infectives in Developing Countries

Paul N. Newton, Facundo M. Fernández, Michael D. Green, Joyce Primo-Carpenter, and Nicholas J. White

Abstract There is considerable interest in optimizing the therapy for important infections in developing countries and in making the best treatments readily available and inexpensive. There is also great concern that resistance to anti-infective drugs is worsening, putting affordable treatments at risk. We argue that an important, but usually neglected aspect of these problems is drug quality. Drugs may be of poor quality if they are counterfeit, substandard or degraded. Few objective data on the prevalence of poor-quality drugs exist but surveys suggest that an alarming proportion of antimalarials and antibiotics in much of the developing world are of poor quality. For individual patients these will increase mortality and morbidity and lead to loss of faith in medicines and health systems. Counterfeit, substandard or degraded drugs with sub-therapeutic concentrations of the active ingredient or the wrong active ingredient are likely to engender the emergence and spread of resistance to these anti-infectives. Although modelling suggests that poor-quality drug should worsen drug resistance, there is sparse evidence from the field, as there has been little research. It will be very difficult to distinguish the effects of poor-drug quality and reduced patient adherence and incorrect health worker prescribing on the spread of resistance. Strengthening drug regulatory authorities, improving quality of drug production and facilitating the availability of relatively inexpensive, good-quality anti-infectives are likely to be key factors in improving drug quality.

Risks and facts

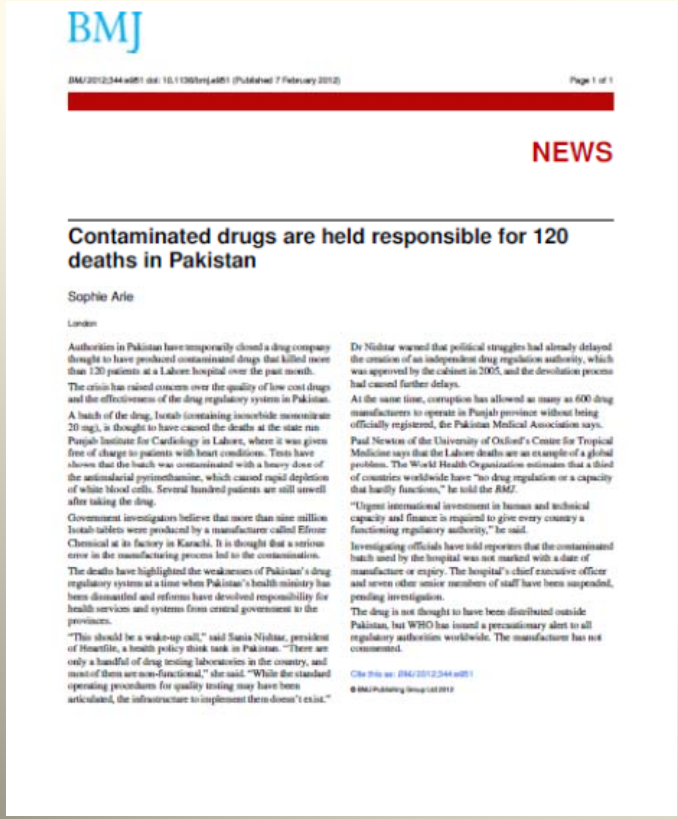
- High prevalence of poor-quality medicines in insufficiently regulated countries (actual extent underestimated?): Malaria



- Kenya, Tanzania: the quality of antimalarials seems to be reasonably under control;
- Ethiopia: No failing samples but 41% were not registered;
- Nigeria: The possibility to be treated with an antimalarial complying with quality standards is less than that of receiving substandard medicine (63,9% of the samples);
- Ghana and Cameroon: patient have an approximate 60% chance of obtaining medicine of good quality.

Risks and facts

- High prevalence of poor-quality medicines in insufficiently regulated countries (actual extent underestimated?): Chronic diseases



BMJ

NEWS

Contaminated drugs are held responsible for 120 deaths in Pakistan

Sophie Arie

London

Authorities in Pakistan have temporarily closed a drug company thought to have produced contaminated drugs that killed more than 120 patients at a Lahore hospital over the past month.

The crisis has raised concern over the quality of low cost drugs and the effectiveness of the drug regulatory system in Pakistan.

A batch of the drug, Isotab (containing isosorbide mononitrate 20 mg), is thought to have caused the deaths at the state run Punjab Institute for Cardiology in Lahore, where it was given free of charge to patients with heart conditions. Tests have shown that the batch was contaminated with a heavy dose of the antimalarial pyrimethamine, which caused rapid depletion of white blood cells. Several hundred patients are still unwell after taking the drug.

Government investigators believe that more than nine million Isotab tablets were produced by a manufacturer called Efroze Chemical at its factory in Karachi. It is thought that a serious error in the manufacturing process led to the contamination.

The deaths have highlighted the weaknesses of Pakistan's drug regulatory system at a time when Pakistan's health ministry has been dismantled and reforms have devolved responsibility for health services and systems from central government to the provinces.

"This should be a wake-up call," said Sania Nishtar, president of Heartfile, a health policy think tank in Pakistan. "There are only a handful of drug testing laboratories in the country, and most of them are non-functional," she said. "While the standard operating procedures for quality testing may have been articulated, the infrastructure to implement them doesn't exist."

Dr Nishtar warned that political struggles had already delayed the creation of an independent drug regulation authority, which was approved by the cabinet in 2005, and the devolution process had caused further delays.

At the same time, corruption has allowed as many as 600 drug manufacturers to operate in Punjab province without being officially registered, the Pakistan Medical Association says.

Paul Newton of the University of Oxford's Centre for Tropical Medicine says that the Lahore deaths are an example of a global problem. The World Health Organization estimates that a third of countries worldwide have "no drug regulation or a capacity that hardly functions," he told the *BMJ*.

"Urgent international investment in human and technical capacity and finance is required to give every country a functioning regulatory authority," he said.

Investigating officials have told reporters that the contaminated batch used by the hospital was not marked with a date of manufacture or expiry. The hospital's chief executive officer and seven other senior members of staff have been suspended, pending investigation.

The drug is not thought to have been distributed outside Pakistan, but WHO has issued a precautionary alert to all regulatory authorities worldwide. The manufacturer has not commented.

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Risks and facts

- High prevalence of poor-quality medicines in insufficiently regulated countries (actual extent underestimated?): IV fluids

Current global pharmaceutical context is at risk

- Balance for medicines : economical driver versus control of quality and safe use
  - Quality is costly but non-quality is of higher cost
- Medicines of multiple quality standards circulate on the market worldwide, in some cases **in full legacy**!
  - Public health risk (treatment failure or even death; drug resistance)
- Responsibilities are lost

The role of WHO face to this problem

Role of WHO face to this problem:

- WHO technical support to NDRA in emerging and developing countries
- Standardisation of requirements:
  - International Pharmacopeia
  - Elaboration of guidelines
  - Expert Committee on Biological Standardisation
  - Free publications (WHO Technical Report Series)
- Harmonisation of recommendations for treatments (Treatment guidelines)
- WHO PreQualification programme

WHO PreQualification programme

- Initiated in 2001, supported by UNAIDS, UNICEF, UNFPA and the World Bank
- To standardise the quality of medicines so that UN Agencies (eg UNAIDS and UNICEF) could procure from generic sources
- UNITAID is now by far the main funder with a USD 40 million project
  - continuing the PQprogramme in 2009-2012
  - Including technical support to NDRA and industry in emerging and developing countries

WHO PreQualification

- Procedure for evaluation of Quality, Safety and Efficacy of
  - Medicines for treating HIV/AIDS, TB, malaria
    - and since 2006, medicines for reproductive health, influenza and acute diarrhoea in children
  - API (since end 2010)
  - Vaccines
- Voluntary participation
- Open to innovator and multi-source/generic manufacturers
- Free of charge for applicants.

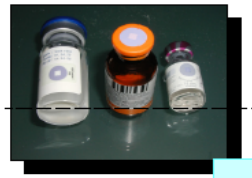
WHO-PQ Procedure Strengths

- Similar to those applied in most of SRAs
- Based on clear and strict requirements internationally recognized (WHO or ICH)
- Includes comprehensive and stringent:
  - evaluation,
  - inspection of manufacturing (FPP, API as necessary), clinical sites and QCLs,
  - monitoring (evaluation of changes/variations)
  - re-qualification, regular re-inspections)

WHO-PQ Procedure Strengths

- Participation of experts from national authorities from both North and South
  - Independence from any government
  - Specific needs of target populations considered
  - Capacity building for assessors
  - Sharing information, developing informal network
  - Help in harmonisation of requirements and mutual recognition

Situation at end 2010



Vaccines prequalified by WHO: Status 2010 (assured quality)

15 *industrialized country mfrs*

- ✓ Australia
- ✓ Belgium
- ✓ Canada
- ✓ Denmark
- ✓ France
- ✓ The Netherlands
- ✓ Germany
- ✓ Hungary
- ✓ Italy
- ✓ Japan
- ✓ Rep. of Korea
- ✓ Switzerland
- ✓ Sweden
- ✓ United Kingdom
- ✓ USA

8 *emerging economy country mfrs*

- ✓ Brazil
- ✓ Bulgaria
- ✓ Cuba
- ✓ India
- ✓ Indonesia
- ✓ Russia
- ✓ Senegal
- ✓ Thailand

29 manufacturers

115 pre-qualified vaccines

used in **124** countries

64% total population

Situation at end 2011

- 269 PQed medicines manufactured in 25 countries (India, China, EU, US..)
- 6 PQed API for antimalarials and 2 for anti-TB medicines
- Less than 4% for prequalified anti-malarial products, compared to 60 %, failed to comply with specifications (Ph.Int. or USP)
- 23 QCLs PQed, covering all WHO 6 regions,
  - A further 32 under PQ process

Some other initiatives and perspectives

Rationale

- To develop usable / non biased information;
- To improve the technical capacity of organisations involved in the procurement of essential medicines;
- To increase the number of qualified persons involved in medicines in the organizations (pharmacists);
- To share the information and the resources.

► To build a network of non for profits actors (*1*) who collect and share (*2*) reliable information (*3*) and the related costs (*4*) with a common approach of quality (same quality standards).

Some other international mutual initiatives

- The USFDA Tentative approval project: Assesses the quality of ARVs for use by PEPFAR funded projects
- The EMA art. 58: Provides a scientific opinion, in co-operation with the WHO, on products intended exclusively for markets outside of the European Union (EU).
- Certification procedure (CEP/COS) since 1994
- PIC/s for mutualisation of inspections
- Common API inspection programme with USFDA, EMA, EDQM, TGA since 2007 after heparin case
- Different regional initiatives to harmonize evaluation and quality control (in UEMOA, CEMAC, GCC, EAC with WHO-PQ...)

What could be done?

- Effective regulations must be implemented and enforced worldwide
- More API inspections needed
- Apply tough and enforced sanctions
- …and more…

➢ Requires resources!! Therefore….

Support and Mutualisation

- Develop widely communication between all stakeholders
  - More coordination between authorities worldwide
  - Transparency and exchange of information
  - Reporting on counterfeit or any suspected trading, sub-standard medicines…by any partner
  - Involving other partners (international policing agencies, NGOs,..)
  - Providing support to authorities for capacity building (WHO program)

Thank you !

QUAMED
Quality Medicine for All

www.quamed.org

A project hosted by the INSTITUTE OF TROPICAL MEDICINE
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Thank you

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