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Quality Assurance for Essential Medicines

David Lee, M.D.

Strengthening Medicines Regulatory Systems Abroad: Adapting Messages from Recent IOM Consensus Studies for Disease Control Priorities, Third Edition

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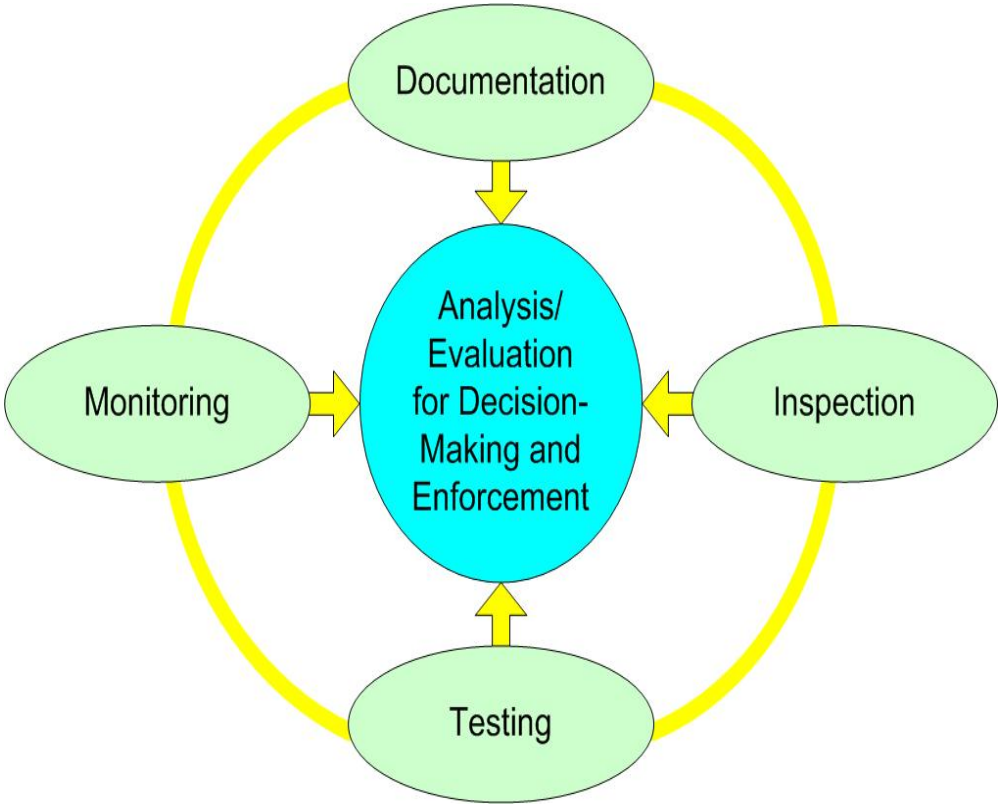
Session Outline

- **Framework for assuring medicines quality**
- **Challenges and solutions to medicines quality assurance in Developing Countries**
  - Beyond pre-qualification (Costa Rica)
  - Acting on findings of product testing program (Brazil)
  - A national inspection and tiered testing approach (Tanzania)
  - Adverse events and product defect reporting (Panama)
- **Global initiatives that support quality assurance**
  - Pre-qualification
  - Product quality testing
  - Product quality monitoring and information sharing
  - Enforcement
- **Concluding remarks**

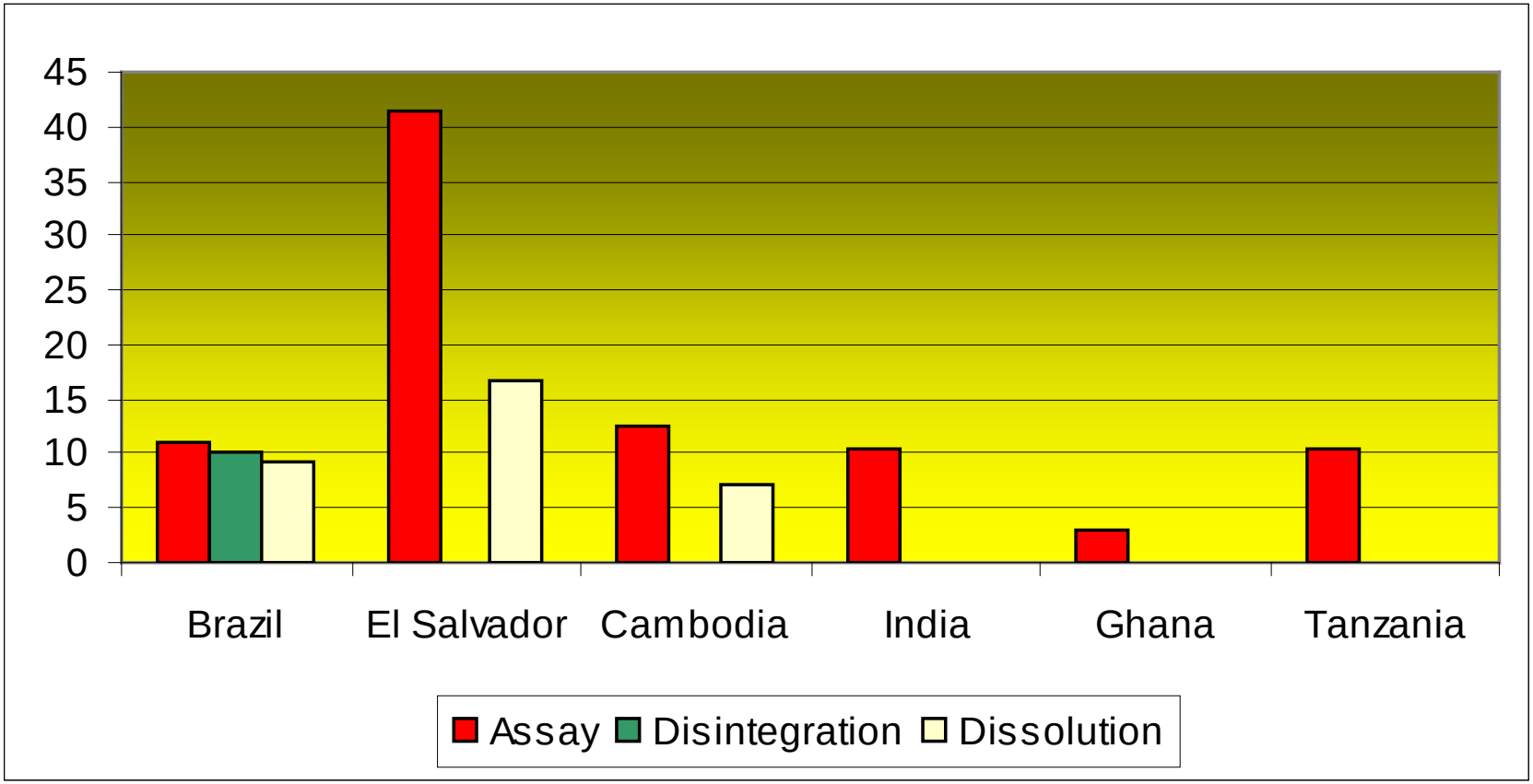
Assuring Pharmaceutical Product Quality: A Shared Responsibility



Stakeholders

- Manufacturers
- Pharmaceutical importers
- Medicines regulatory authority
- Quality control laboratory
- Procurement agencies
- Non-health sector agencies
- Port of entry officials
- Pharmaceutical distributors
- Providers
- Patients

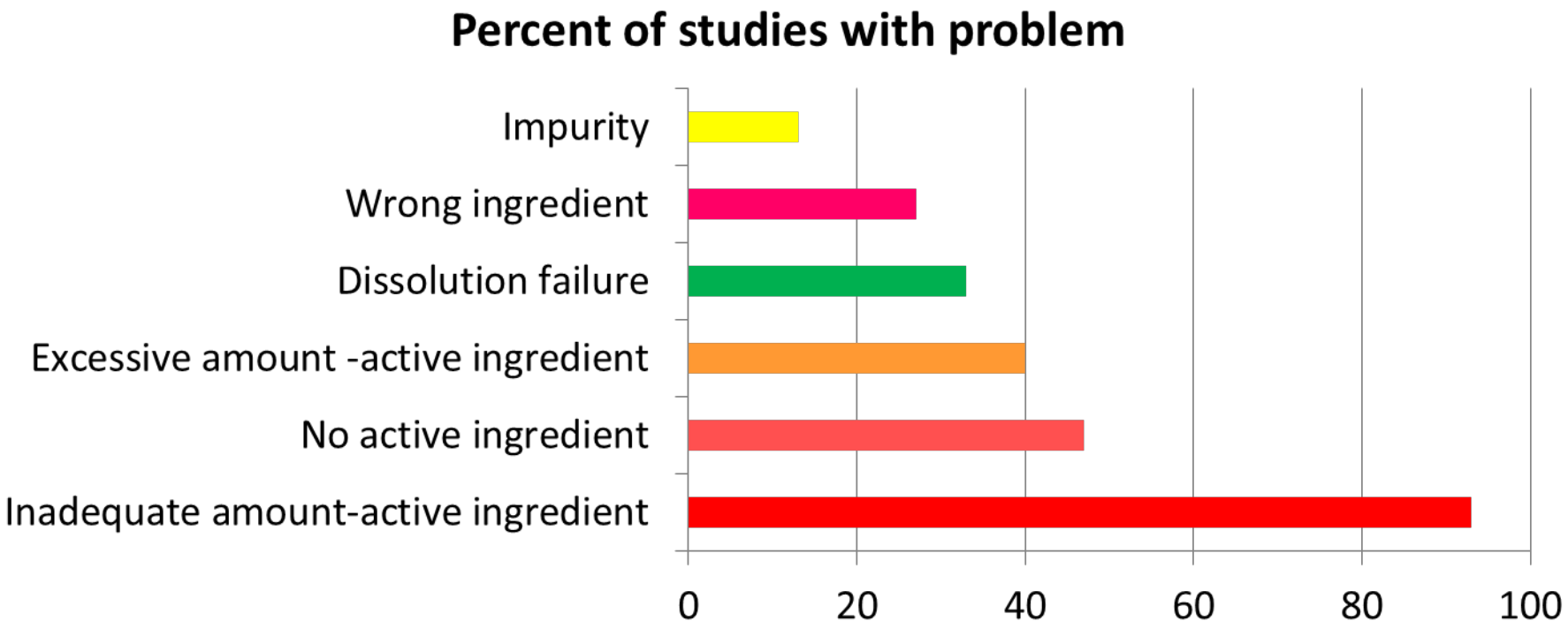
Essential Medicines: Percentage of substandard samples by type of test



Source: SEAM pharmaceutical access assessments, 2001

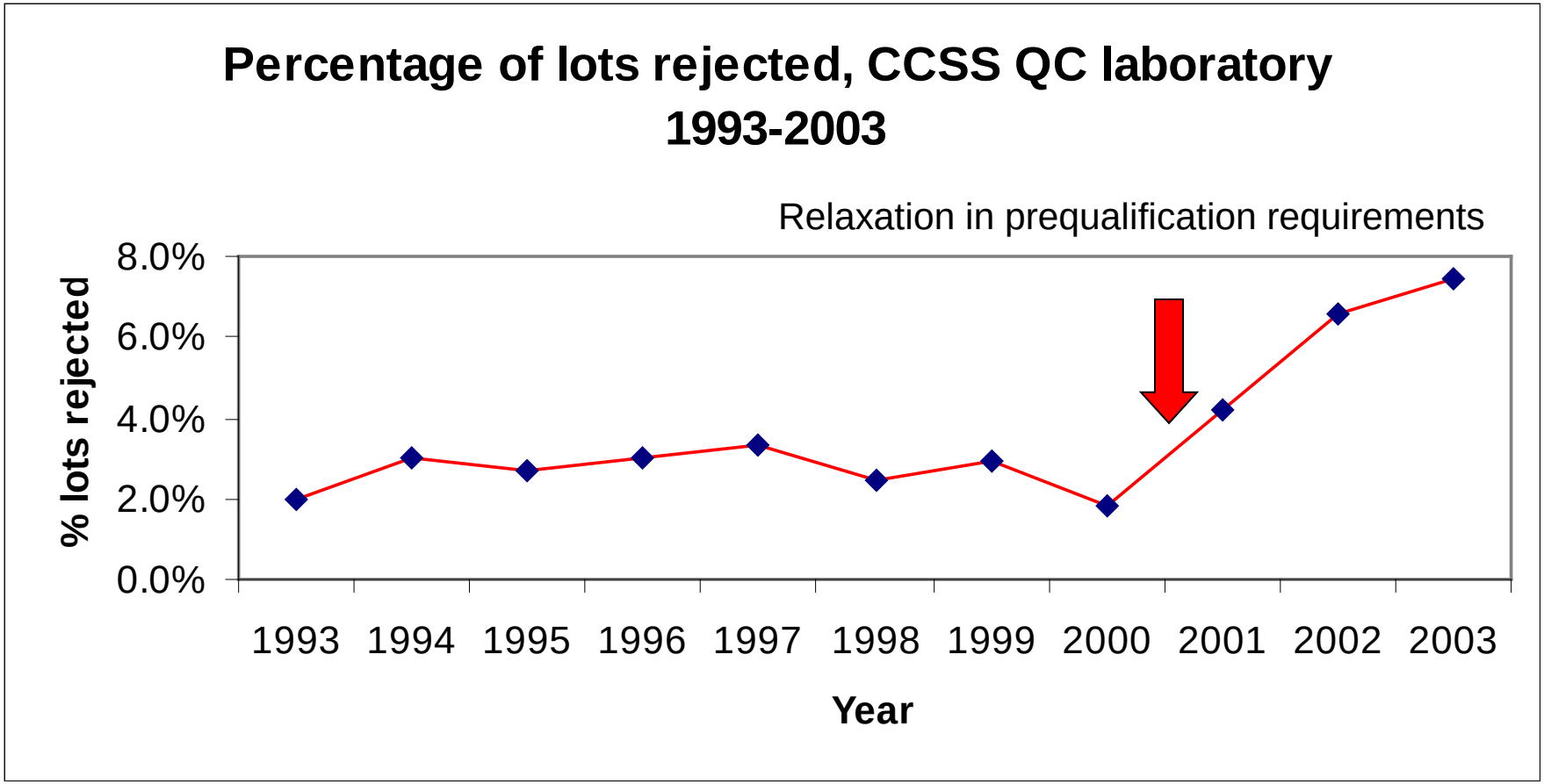
Prevalence of Types of Problems: Systematic Review of Literature

25 countries in Africa and Asia
15 studies
antimicrobials, paracetamol, ranitidine, salbutamol, diazepam, analgesics



Source: Almuzaini T, Choonara I, Sammons H. BMJ Open 2013;3:e002923.doi.1136/bmjopen-2013-002923

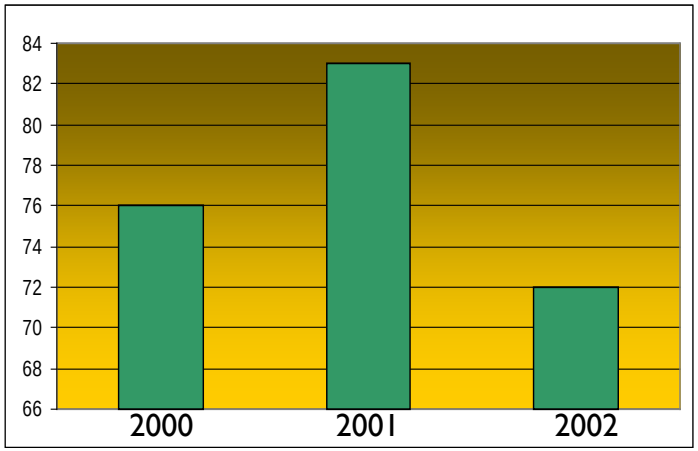
Prequalification Requirements and Essential Medicines Quality: Lessons from Costa Rica

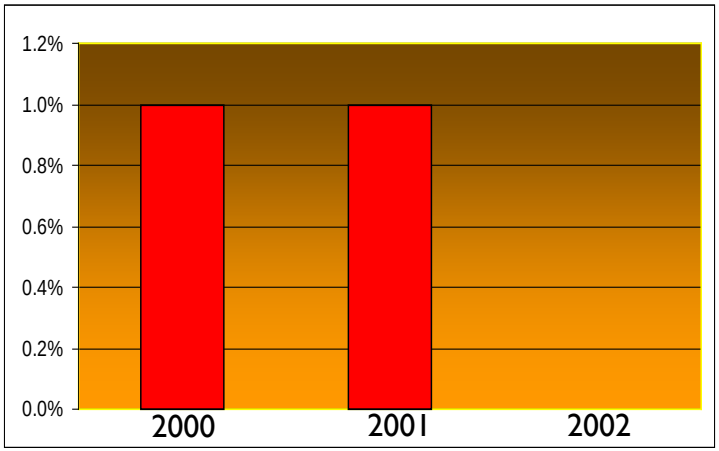


CCSS= Caja Costarricense de Seguro Social QC= Quality Control

Source: Bolaños A. Tesis de Maestría en Administración de Servicios de Salud. Universidad Estatal a Distancia. San José, Rica, 2004.

Challenges to Medicines Quality Testing: How Common is this Situation?

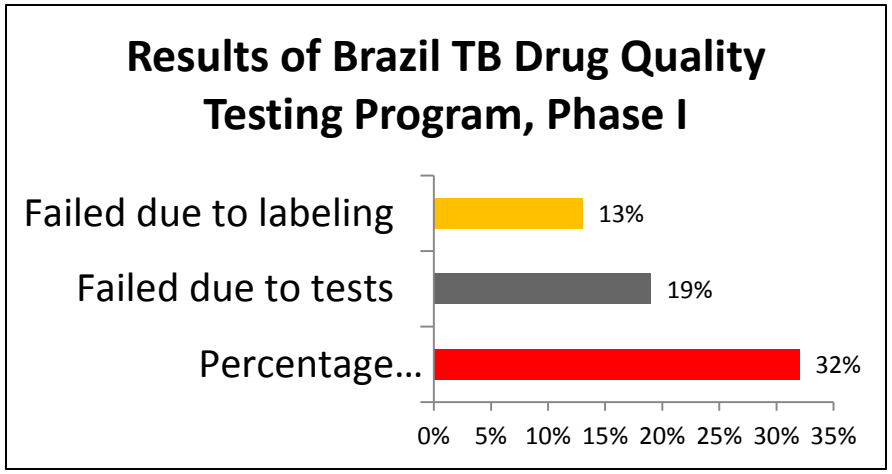




- 75% of samples cannot be analyzed according to pharmacopeial monographs
- Spectrophotometer and high-performance liquid chromatographer not operational at time of study (for 9 and 2 months, respectively)
- No regular equipment maintenance due to cost
- Shortage of reference standards and mobile phase for HPLC tests

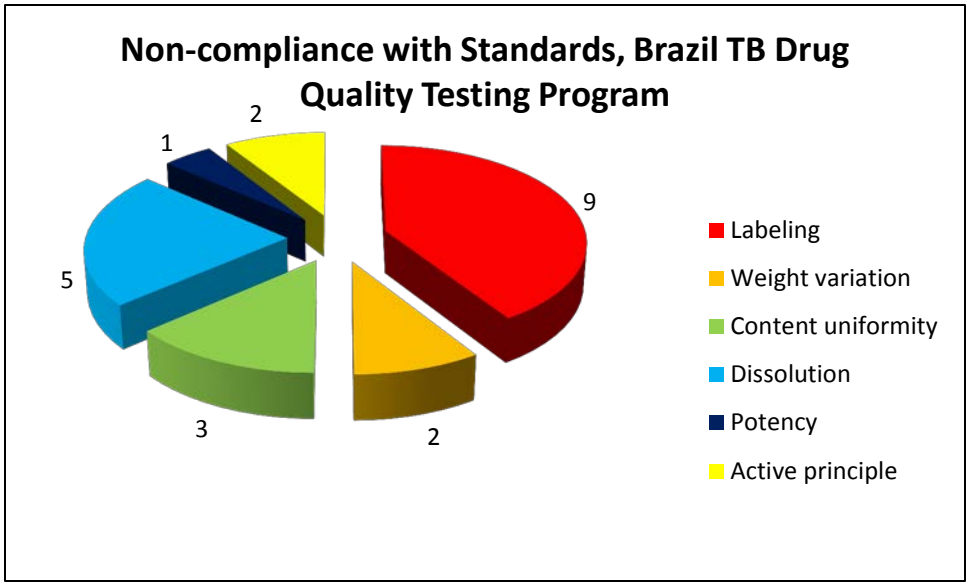
Source: Lee D,, Verhage R, Naarendorp M. Suriname Study on Public Sector Drug Procurerment. Management Sciences for Health, 2003.

TB Medicines Quality Testing Program: Key Findings in Brazil



71 samples collected
70 analyzed
14 different products
11 different manufacturers
10 active ingredients

Rifampicin
Isoniazid
Pyrazinamide
Isoniazid+rifampicin (2FDC)
Ethambutol
Clarithromycin
Clofazimin
Terezidon
Amikacin
Ethionamide



Source: Quality assurance policies and aliigning national regulations.: case of Brazil. 3rd Stop TB Partners Forum. Rio de Janeiro , March 2009

TB Medicines Quality Testing Program: Actions Taken in Brazil

- **Addressing quality defects:**
  - manufacturers notified by the National Regulatory Authority
    - Analytical Methods
    - APIs (active pharmaceutical ingredients)
    - Production process / formulation
  - analyzed by a multi-disciplinary group to determine any influence on the safety and efficacy of the product
  - batches which were not meeting adequate quality standards were recalled by NRA according to legislation
- **Working Group decisions:**
  - organize a workshop with manufacturers and quality experts to investigate discrepancies in results and methods for rifampicin quality testing + APIs characterization
  - switch from capsule to tablet for RH (2-FDC)

Source: Quality assurance policies and aligning national regulations.: Case of Brazil. 3rd Stop TB Partners Forum. Rio de Janeiro , March 2009

Medicines Quality Assurance in Brazil: System Strengthening Results

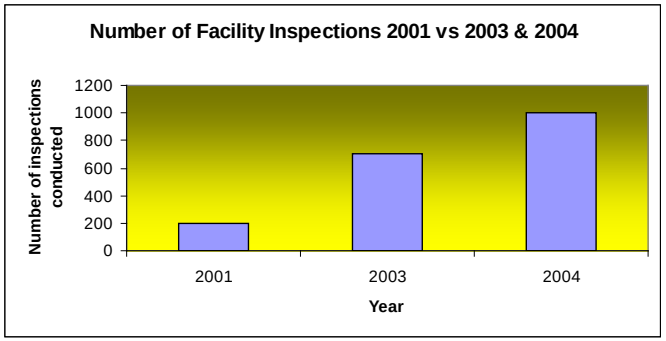
- **Environment created where agencies:**
  - interact with manufacturers for improving drug quality and harmonize analytical methods
  - define concerted legal actions limiting risk of creating shortage
  - more transparency for stakeholders (physicians, society in general)
    - access to reports from the public sector on product quality

- **New management and technical tools for laboratory capacity building developed*:**
  - identifying problems in quality systems and needed activities to achieve ISO 17025 certification
  - consistent use as a management model in 2 National Reference Laboratories and 5 State Reference Laboratories

* *LABMOST: um instrumento participativo para implementação de sistema da qualidade, novo modelo na gestão para laboratórios*. Rio de Janeiro: INCQS; Rio de Janeiro: Management Sciences for Health, 2008.

Improving Medicines Quality in the Private Sector: Program Design & Implementation in Tanzania

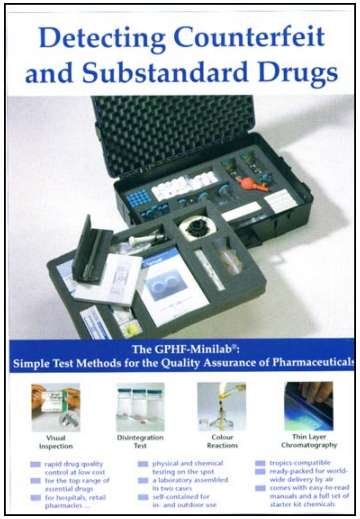
- **Assessment findings (lessons with essential medicines)**
  - Substandard amoxicillin, doxycycline, mebendazole, sulfadoxine/pyrimethamine
- **Tanzania Food and Drugs Authority surveillance program**
  - inspections (products and premises)
    - ports of entry
    - retail outlets

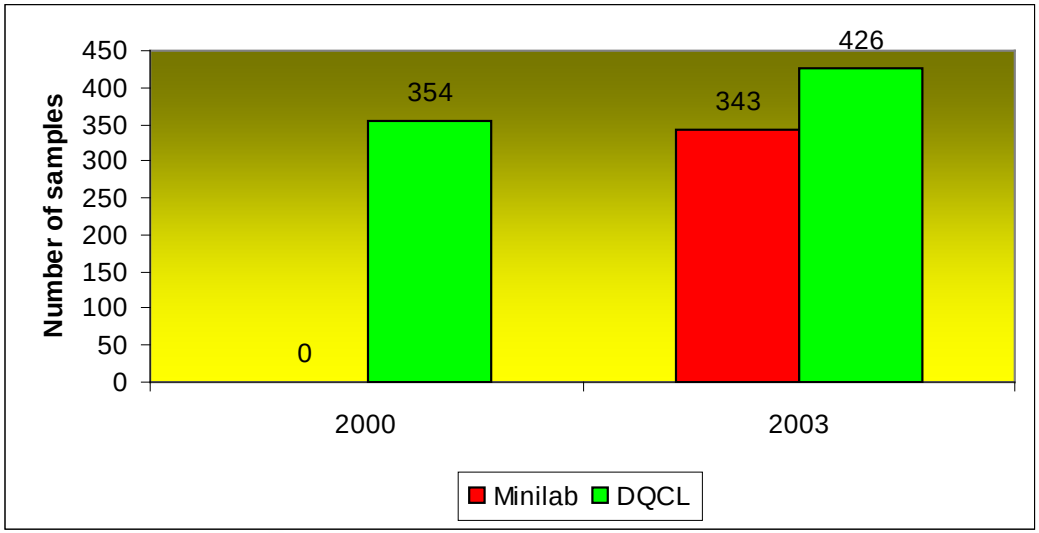


  - sampling and tiered testing

Use of Three Tier Testing Approach to Increase Testing Capacity in Tanzania

	Detects	Techniques
Primary	Significant substandard (80-120% or better) and counterfeit products	TLC with visual detection. Semi-quantitative (SD +/- 5%), colorimetric, disintegration
Secondary	Testing to determine legal compliance	Instrumented testing lab with an array of chromatography equipment--TLC, HPLC, & GLC.
Tertiary	Unusual impurities and identification	Highly specialized equipment and trained personnel



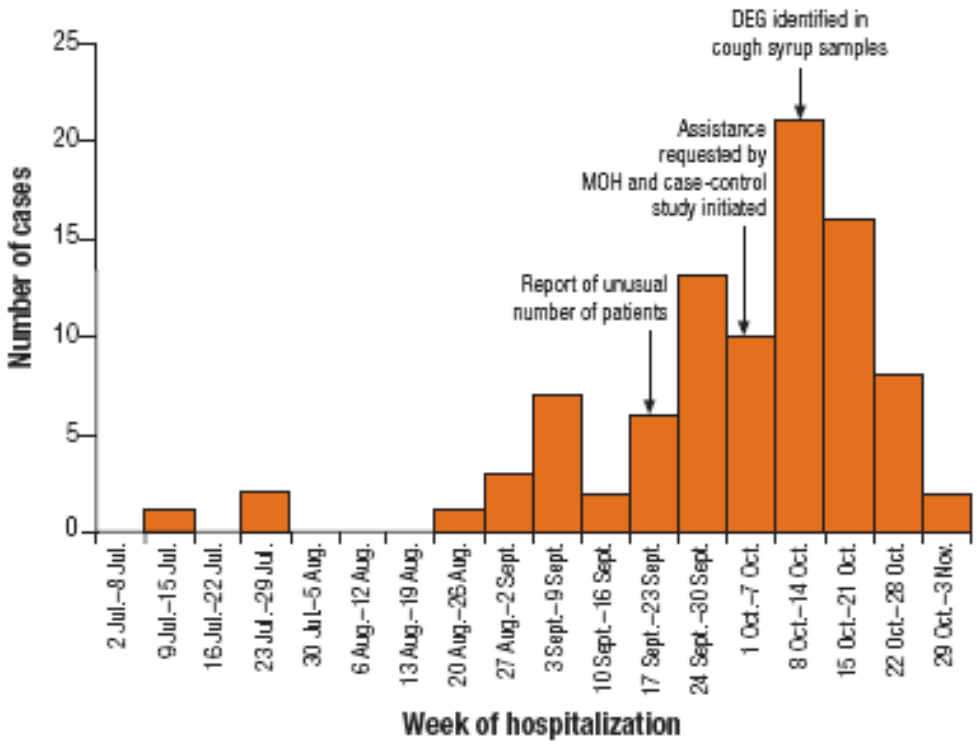


Tanzania Quality Assurance Achievements

- **Increased capability**
  - five ports of entry covered (25 consignments confiscated)
  - inspection (SOPs and training)
  - testing (Use of Minilab ® screening and Drug Quality Control Laboratory confirmation)
- **Detection of counterfeit and substandard products**
  - five counterfeit samples (three quinine, two erythromycin)
  - substandard dissolution (sulfadoxine/pyrimethamine) (1 imported batch refused entry, 5 locally manufactured batches recalled and destroyed)
- **Program implementation**
  - progressive expansion from antimalarials to six antibiotics and antiretrovirals
  - Sampling and testing of products in the market identified 16 antimalarial products that were recalled and destroyed (2005/2006), subsequently no substandards detected (2006/2007 and 2007/2008)

Diethylene Glycol Poisonings in Panama

Fig. 1. **Number of patients admitted with acute renal failure due to DEG poisoning in Panama, from 2 July 2006 to 3 November 2006**



DEG, diethylene glycol; MOH, Ministry of Health.

Source: Bull WHO 2008;86:749-756

700+ claims, 156 deaths

Panama Social Security production laboratory products
•cough syrup
• diphenhydramine syrup

•46 barrels of diethylene glycol-tainted material purchased
•260,000 bottles of cough syrup manufactured
•US$18,500 paid for DEG-tainted glycerin
•US$ 6,500,000 budget to indemnify victims

Sources:
New York Times February 14, 2008 [http://www,nytimes.com]
La Prensa 2 March 2007; 27 November 2010 [http://www.prensa.com.pa]

Diethylene Glycol Poisoings in Panama: A Lesson in System Failure

- **Good Governance**
  - double standard (GMP requirement not required for Social Security production facility)
  - lack of support for meeting GMP standards in Social Security
- **Good Manufacturing Practice**
  - Non-GMP conditions and procedures
- **Good Laboratory Practice**
  - NO quality control of ingredients
  - non-use of available national reference laboratory
- **Good Procurement Practice**
  - supplier selection issues
- **Good Prescribing Practice**
  - “reflex” prescribing

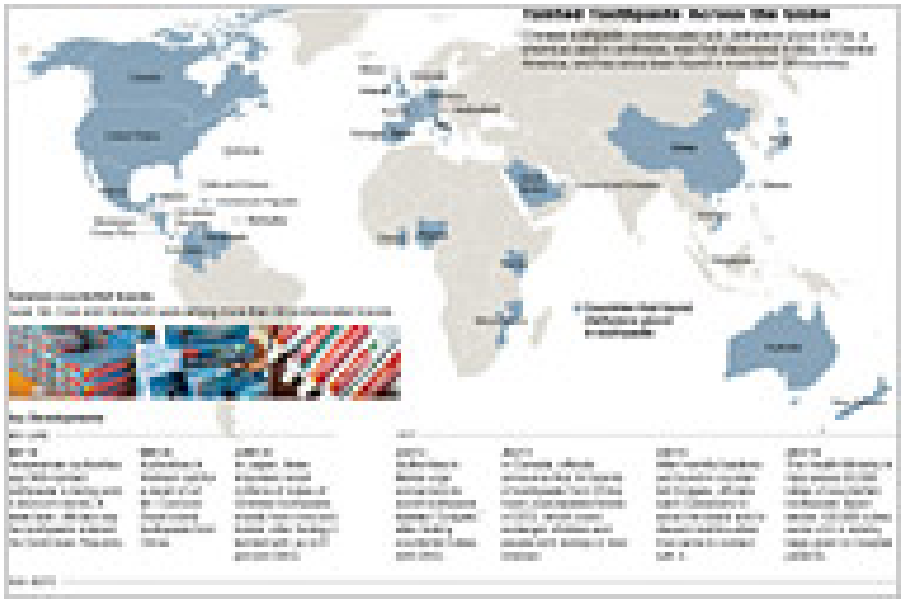
Diethylene Glycol in Toothpaste: Consumer Reporting

May 2007

- 5,000+ tubes entered Panama unnoticed
- Health alerts in 34 countries
  - Japan had 24m tubes
  - Canada had 24 brands
  - New Zealand had16 brands

June 2007

- USA Colgate counterfeits
- England Sensodyne ® counterfeits
- 30 countries ban Chinese-manufactured toothpaste



Source: *New York Times* October 1. 2007 [http://www.nytimes.com]

Differing Global (Program) and Country (System) Focus?

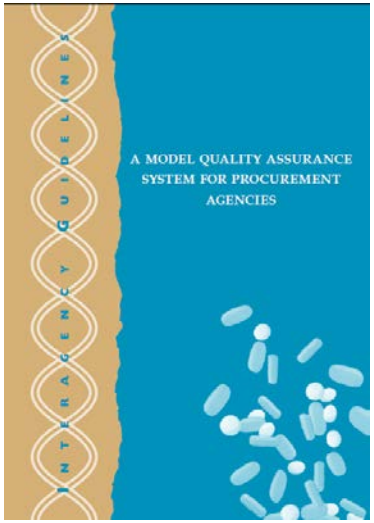
Donors

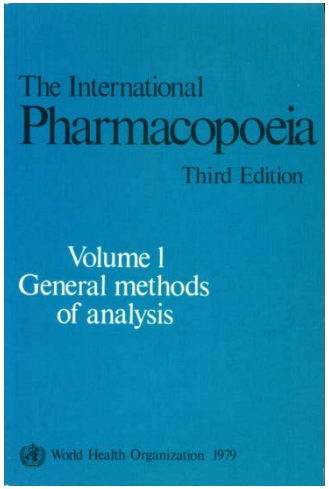
- **HIV/AIDS**
  - Antiretrovirals (ARVs)
  - Antimicrobials (Opportunistic infections)
- **Tuberculosis**
  - First-line medicines
  - Second-line medicines
- **Malaria**
  - Artemisinin-based combination therapies (ACTs)

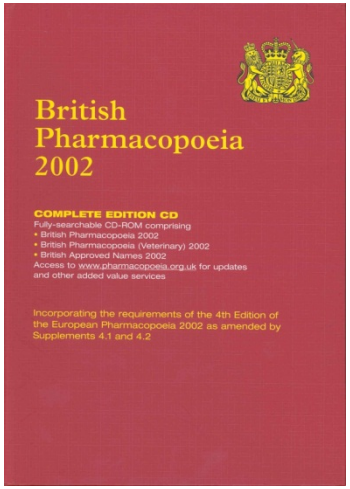
Developing Countries

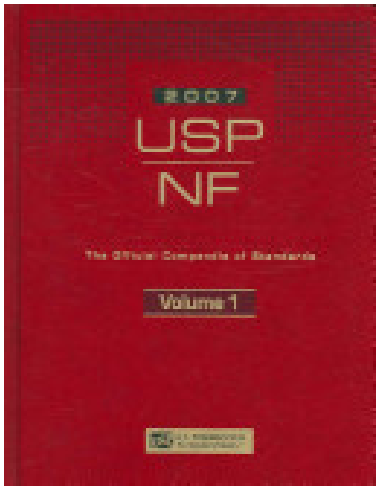
- **Multisource product (generics) manufacture and importation**
- **Product quality related tragedies**
  - Panama diethylene glycol poisonings (2006)
  - Nigeria diethylene glycol poisonings (2008/2009)
  - Pakistan pyrimethamine-contaminated isosorbide tablets (2012)

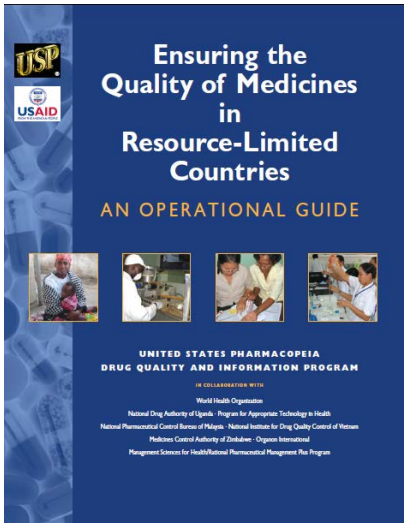
Quality Assurance for Medicines: Standards, Guidance and Technologies

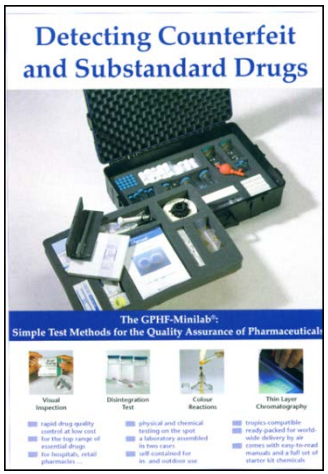


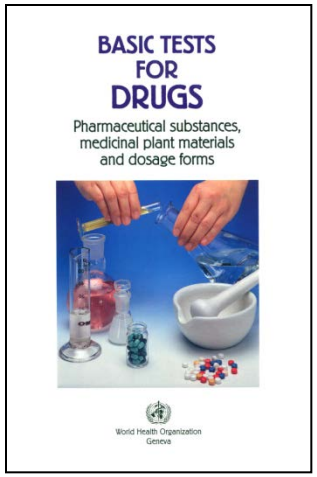












Global Initiatives that Support Quality Assurance for Medicines

Prequalification of products and suppliers

- **WHO Prequalification of Medicines Programme**
- **Stop TB Partnership Global Drug Facility**

Quality control testing

- **WHO Prequalification of Quality Control Testing Laboratories**

Monitoring medicines quality

- **Global Fund Price and Quality Reporting System**
- **USAID/USP Promoting Quality of Medicine (PQM) Program**

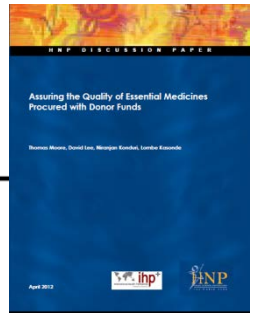
Enforcement

- **IMPACT (International Medical Products Anti-Counterfeiting Taskforce)**

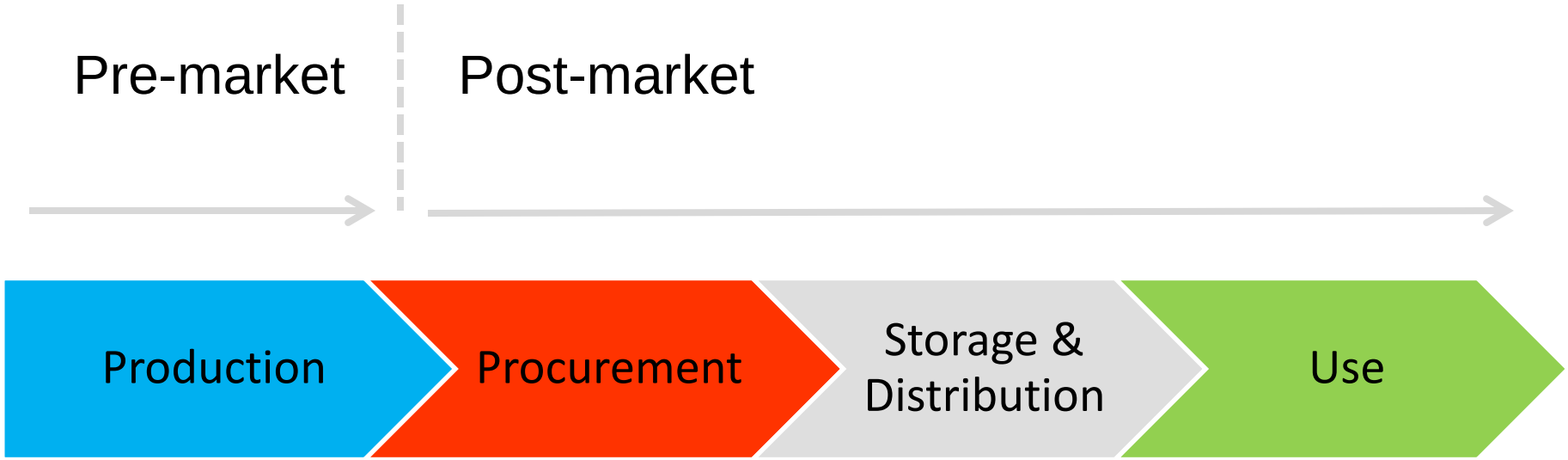
Towards a Pragmatic Approach

Table 6. Quality Assurance Approaches Coverage of Essential Medicines, Based on Risk Category

	Assessing Entity				
	WHO Prequalification Programme (PQP)	WHO-hosted Expert Review Panel (ERP)	Stringent regulatory authority (SRA) approval	National medicines regulatory authority (NMRA) approval	Procurement service agency MQAS-based qualification by an independent body
Risk level		*(Time-limited approval)*		*(Capacity building/ cooperation*	
High	HIV/AIDS, TB, malaria (ATM) medicines Non-ATM medicines on WHO-EOI list (opportunistic infections & others)	HIV/AIDS, TB, malaria (ATM) medicines Non-ATM medicines	HIV/AIDS, TB, malaria (ATM) medicines Non-ATM medicines	High-risk medicines to be defined *(through participation in WHO-PQP and regional initiatives)*	HIV/AIDS, TB, malaria (ATM) medicines Non-ATM medicines
Medium	Further discussion may be required to determine if this group should be covered	Further discussion may be required to determine if this group should be covered	Non-ATM medicines	Medium-risk non-ATM medicines to be defined *(through participation in regional initiatives)*	Non-ATM medicines
Low	Probably not cost-effective	Probably not cost-effective	Non-ATM medicines	Non-ATM medicines	Non-ATM medicines
Rationale	Prioritizes use of limited technical and financial resources to assess high-risk and high public health impact medicines	Temporary measure to access additional quality products	Already ongoing work for SRA country market	Builds country ownership in stringent QA of essential medicines (ATM and non-ATM) Allows NMRA to focus on strengthening postmarket surveillance and control while building capacity toward stringency	Supports quality assurance in procurement and increased rigor in evaluations



National Regulatory Authority Role



- Standards setting
- Guidance provision
- Dossier evaluation & approval
- GMP inspection
- Problem reporting
- Risk communication

- Mandatory product registration for procurement
- Risk communication

- Standards setting
- Licensing premises
- Inspections
- Product sampling and testing
- Problem reporting
- Risk communication

- Licensing premises
- Product promotion approval and monitoring
- Problem reporting
- Risk communication

Quality Assurance Begins at the Beginning …

- **Quality cannot be tested into a product, but must be built into it, therefore Good Manufacturing Practices cannot be overemphasized.**

- **Demand for GMP-produced essential medicines may be promoted through**
  - appropriate policies, regulations for marketing approval,
  - good procurement practices, product quality surveillance

- **Availability of technical assistance to manufacturers is likely to facilitate greater GMP acceptance and implementation.**

Concluding Remarks

- **Assuring the quality of essential medicines is a *shared responsibility* of all involved in their manufacture, regulatory approval, procurement, importation, storage and distribution, prescribing and use.**
- **There are international mechanisms and tools to support strengthening quality assurance of medicines. But, above all, it requires strong national political will to promote and enforce appropriate policies, regulations and standards, Good Manufacturing Practices, Good Distribution Practices, Good Laboratory Practices, Good Procurement Practices.**
- **It will also require engaging manufacturers and creating an environment for manufacturer investment in Good Manufacturing Practices.**
- **Medicines regulatory systems strengthening should be results-focused.**

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