Quality Assurance for Essential Medicines

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National Academy of Sciences, Washington, DC
12-13 September 2013
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

Diagram:

- Documentation
- Analysis/Evaluation for Decision-Making and Enforcement
- Inspection
- Testing
- Monitoring
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

Percent of studies with problem

- Impurity
- Wrong ingredient
- Dissolution failure
- Excessive amount -active ingredient
- No active ingredient
- Inadequate amount-active ingredient

Prequalification Requirements and Essential Medicines Quality: Lessons from Costa Rica

Percentage of lots rejected, CCSS QC laboratory
1993-2003

Relaxation in prequalification requirements

CCSS= Caja Costarricense de Seguro Social   QC= Quality Control
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

TB Medicines Quality Testing Program: Key Findings in Brazil

Results of Brazil TB Drug Quality Testing Program, Phase I

- Failed due to labeling: 13%
- Failed due to tests: 19%
- Percentage...: 32%

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

Non-compliance with Standards, Brazil TB Drug Quality Testing Program

- Labeling: 1
- Weight variation: 2
- Content uniformity: 5
- Dissolution: 3
- Potency: 2
- Active principle: 9

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

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

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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

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

![Graph showing the number of samples tested from 2000 to 2003 for Minilab and DQCL.](image-url)
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

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:
Diethylene Glycol Poisonings 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 had 16 brands

June 2007
• USA Colgate counterfeits
• England Sensodyne ® counterfeits
• 30 countries ban Chinese-manufactured toothpaste

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)
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)
<table>
<thead>
<tr>
<th>Risk level</th>
<th>Assessing Entity</th>
<th>Procurement service agency MQAS-based qualification by an independent body</th>
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<tbody>
<tr>
<td>High</td>
<td>WHO Prequalification Programme (PQP)</td>
<td>WHO-hosted Expert Review Panel (ERP)</td>
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<tr>
<td></td>
<td>(Time-limited approval)</td>
<td></td>
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<tr>
<td>Medium</td>
<td>Further discussion may be required to determine if this group should be covered</td>
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</tr>
<tr>
<td>Low</td>
<td>Probably not cost-effective</td>
<td>Probably not cost-effective</td>
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<tr>
<td>Rationale</td>
<td>Prioritizes use of limited technical and financial resources to assess high-risk and high public health impact medicines</td>
<td>Temporary measure to access additional quality products</td>
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National Regulatory Authority Role

Pre-market
- Production
  - Standards setting
  - Guidance provision
  - Dossier evaluation & approval
  - GMP inspection
  - Problem reporting
  - Risk communication
- Procurement
  - Mandatory product registration for procurement
  - Risk communication

Post-market
- Storage & Distribution
  - Standards setting
  - Licensing premises
  - Inspections
  - Product sampling and testing
  - Problem reporting
  - Risk communication
- Use
  - 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.
Saving lives and improving the health of the world’s poorest and most vulnerable people by closing the gap between knowledge and action in public health.