Three-Level Approach for Ensuring the Quality of Medicines in Resource-Limited Countries

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1. ABSTRACT

The availability and use of medicines for the treatment of diseases are basic components of any healthcare system. Poor-quality medicines may result in impaired therapies and jeopardize patients' safety, posing a serious threat to consumers and wasting significant financial resources. Assessing a product's compliance with the appropriate quality standards requires performing quality control (QC) analysis by the Official Medicine Control Laboratory (OMCL). However, OMCLs in resource-limited countries may be understaffed, may not have appropriate financial support, and may lack the necessary infrastructure, equipment, and personnel to perform QC analysis according to product specifications. Geographical barriers to accessing OMCLs, which tend to be located in large cities, impose an additional constraint.

Because of the above limitations, a three-level approach for QC is proposed that could help resource-limited countries improve quality control within their regulatory framework. This approach encompasses the following: Level 1 analyses that include visual inspection of the package and label and physical inspection of the product; Level 2 analyses that utilize easy-to-use, simple, rapid, and cost-effective basic analytical methodology that can be implemented in the field to assess medicines quality; and Level 3 analyses that require the assessment of all critical quality attributes of a medicine via complete validated or compendial methodologies performed at the OMCL. The level to employ for a product at a given stage in the supply chain is based on risk-benefit analysis. By strategically implementing this approach throughout the supply chain, from procurement to patient use, health authorities may increase the frequency and number of medicines tested within their limited financial and human resources, resulting in more effective control of the national pharmaceutical market and the quality of medicines.

2. INTRODUCTION

The availability and use of medications for the treatment of diseases are basic components of any healthcare system. In order to treat illnesses effectively, medicines must

- Provide the desired therapeutic effect;
- Have an acceptable safety profile; and
- Be of the appropriate quality.

Compromising any of these three characteristics will lead to ineffective treatment.

Use of poor-quality medicines may

- Decrease therapeutic effect;
- Jeopardize patient safety;
- Pose a serious threat to consumers;
- Waste scarce financial resources for healthcare; and
- Cause loss of confidence in medicines and in national healthcare systems.

Moreover, their use may contribute to the development of resistance, impairing currently available treatments, many of which have no foreseeable replacement in the near future.

The economic and medical impact of these factors is more severely felt in countries with limited resources.

To ensure the quality of its medicines, country Medicine Regulatory Authorities (MRAs) should

- Control and regulate the entire pharmaceutical market;
- Establish an adequate Quality Assurance (QA) system from manufacture to procurement to distribution to use; and
- Rely on OMCL to perform quality control of the medicines to verify compliance with registration specifications.

3. RATIONALE

OMCLs in resource-limited countries often have severe human and financial constraints affecting their capabilities to assess the quality of medicines and support MRA needs. Key OMCL requirements that are affected by these constraints are

- Costly infrastructure, equipment, and consumable materials;
- High maintenance costs;
- Establishment of a stringent Quality Management System; and
- Specialized personnel and the need for continuous training.

Other aspects that may hinder and limit QC support provided by OMCLs are the central location of OMCLs that could result in limited geographical access, and low analysis throughput.

Due to the aforementioned requirements and limiting factors:

- Many resource-limited countries are severely constrained in their ability to establish appropriate QA and regulatory frameworks, and set up a functional OMCL.
- There is less oversight of the national pharmaceutical market, potentially resulting in a rise in the prevalence of poor-quality medicines.

Alternative approaches need to be developed to help health authorities in resource-limited countries ensure proper quality assurance and quality control of medicines in their pharmaceutical markets.

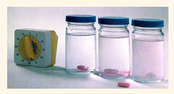
To address this need, the Promoting the Quality of Medicines (PQM) Program designed a three-level testing approach that is cost-effective and efficient for performing QC analysis throughout the supply chain. This is a risk-based approach that may be applied throughout the supply chain and implemented by a variety of stakeholders according to their particular context and needs.

4. COMPONENTS

The three-level approach encompasses the following:

- Level 1 (L1) analyses include visual inspection of the package and label and physical inspection of the product.
- Level 2 (L2) analyses utilize easy-to-use, simple, rapid, and cost-effective analytical chemistry methods to identify medicines with deficiencies in a limited number of critical quality attributes.
- Level 3 (L3) analyses require the assessment of all critical quality attributes of a medicine via complete validated or compendial tests.

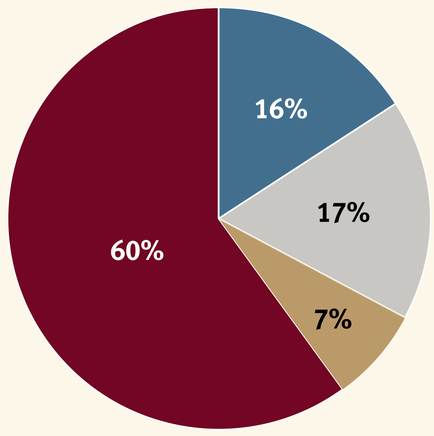
The following table summarizes the characteristics of each level.

LEVEL	TYPE OF ANALYSIS	TYPE OF TEST	PURPOSE	SITE PERSONNEL RESPONSIBLE FOR ANALYSIS
1	Visual & Physical Inspection 	Visual: ▸ Labeling and packaging properties Physical: ▸ Appearance, conditions and physical characteristics of medicine	Identify expired medicines and/or medicines with insufficient, erroneous, and/or fraudulent information; damage to packaging; damage and/or alterations to the condition of the medicine	Management staff at every stage of the supply chain cycle, from procurement to use
2	Basic Tests 	▸ Disintegration ▸ Colorimetric reactions[1] ▸ Thin Layer Chromatography (TLC)	Identify medicines with deficiencies in **four** critical quality attributes (identity, content, impurities, and disintegration for solid dosage forms)	Personnel trained in Basic Tests; OMCL personnel
3	Compendial/Validated Tests	According to registration specifications	Assessment of **all** the critical quality attributes of a medicine	OMCL personnel

1 The use of colorimetric methods is not recommended when a TLC method is available for the same medicine. Field colorimetric tests only provide information for one critical quality attribute (identity), TLC tests provide information on three critical quality attributes (identity, Content, and Impurities).

5. BASIC TESTS MAY DETECT A LARGE PERCENTAGE OF POOR-QUALITY MEDICINES

Percentage breakdown of data on 325 of total of 771 substandard drugs reported from around the world to WHO database between 1982–1999. This includes antibiotic, antimalarial, and antituberculosis medicines.



76% of counterfeit drugs could be found by a simple identity test

WHO/EDM/QSM/99.3

http://www.wpro.who.int/media_centre/fact_sheets/fs_200311_Counterfeit+drugs.htm, accessed on December 2009

6. LEVERAGING USE OF L2 ANALYSIS

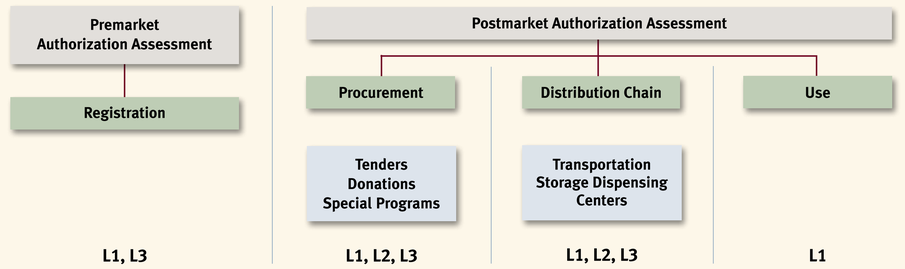
Benefits

- **Capability to Identify Poor-quality Medicines:** Potential to detect most frequent reasons medicines fail quality standards.
- **Reliability of Results:** L2 analyses are highly reproducible, trustworthy, and valid.
- **Large Analysis Throughput:** L2 analyses are significantly shorter than validated methods (L3).
- **Minimal Infrastructure Requirements:** Equipment and tools are minimal, economical, and readily accessible.
- **Minimal Need for Specialized Human Resources:** Personnel training is rapid and economical.
- **Low Acquisition and Maintenance Costs:** Costs of procuring and maintaining equipment, tools, and supplies are low.
- **Capability to Test a Wide Range of Therapeutic Treatments:** Pre-made, self-contained portable units are available that contain methods and Reference Standards for over 50 medicines for a wide range of therapies (e.g., antimalarial, antiretroviral, anti-tuberculosis, etc.). L2 tests and Reference Standards for other medicines can be developed according to country needs.

Limitations

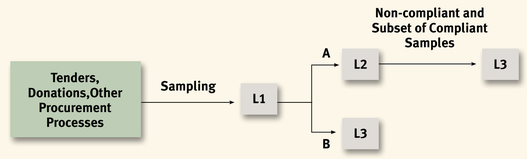
- **Capability to Assess Only a Limited Number of Critical Quality Attributes:** Cannot assess all critical quality attributes (i.e., dissolution, uniformity of dosage units, water content, impurities requiring a high level of sensitivity).
- **Limited Support for Implementing Corrective Actions:** For implementation of corrective actions, country regulations may require testing with validated methods (L3) according to registration specifications.
- **Limited Experience of Personnel Performing L2 Analyses:** To ensure validity of the results obtained by personnel lacking extensive experience, proper steps need to be implemented to enable other competent institutions (i.e., OMCL) to repeat and verify results.
- **Inconclusive Results:** The testing conditions or methodology may provide inconclusive results that could require repeating the tests in a lab setting or using other methods.

7. THREE-LEVEL APPROACH IN THE QA FRAMEWORK



8. APPLICATIONS OF THREE-LEVEL APPROACH

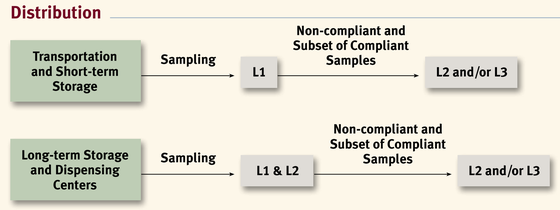
Procurement



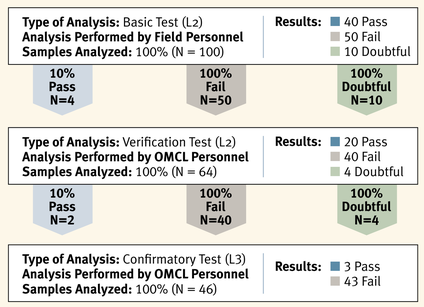
A) Medicines procured from reliable manufacturers

B) 1. Medicines procured for the first time
2. Medicines that may pose a risk based on history of the manufacturer or intrinsic product attributes

Distribution



Medicine Quality Monitoring (MQM) Activities in the Marketplace



Procurement Practical Example

- **Source of medicine:** Medicines with a history of compliant QC data.
- **Current QC practice:** National regulation requires L3 analysis for all incoming lots prior to distribution.
- **Three-level approach:** Combination of L2 and L3 analysis prior to distribution (Path "A" and Path "B").
- **Justification:** In cases where a country's regulations require submitting all procured medicines to L3 testing, and limited resources or time constraints may not make this feasible, the institutions responsible for procurement could substitute L3 with L2 analyses for a subset of medicines according to a risk-based approach. The risk-based approach could be established taking into consideration variables such as a product's stability, shipment storage conditions, visual state of shipment, or previous history of compliant QC data from a particular manufacturer. Products failing L2 analysis would be quarantined and then sent to an OMCL to perform L3 testing.
- **Benefits:** Provides a flexible approach by taking into consideration time and resource limitations and provides added assurance that medicines entering the distribution chain are of adequate quality.

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