Ensuring Quality of Donated Medicines and Supplies during a Global Health Emergency

Christine Chacko

pwc | Public Sector

During times of global health emergency, the potential to introduce substandard and falsified medicines is increased

A target of the Sustainable Development Goals is access to safe, effective and quality medicines and vaccines.

Many countries are seeing increasing numbers of substandard and falsified medical products that pose an unacceptable risk to public health.

This issue is compounded by the introduction of inappropriate drug donations including:

- Expired drugs / drugs close to expiry
- Unsorted drugs
- Lack of sufficient labeling

NRAs ensure medicine quality through regulatory requirements which can be diverse and complex

- There are many country-specific requirements especially with respect to Chemistry, Manufacturing and Controls (CMC)
  - Active Pharmaceutical Ingredient
  - Formulations and Excipients
  - Stability
  - Analytical Testing
  - Quality
  - Packaging and Labeling

- LMIC National Regulatory Authorities are maturing with evolving guidance and scarce resources

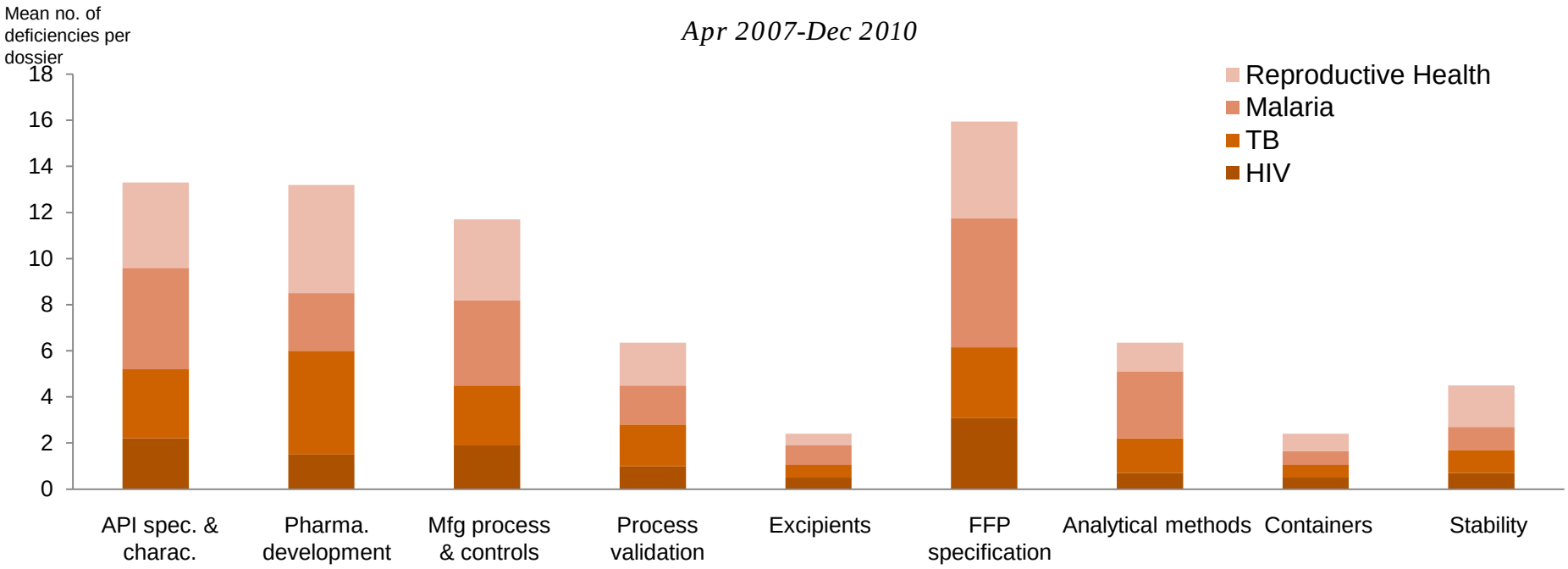
- Requirements are not well understood by developers

*Addressing all of the unique challenges often **increases the cost and time** needed to develop global health drugs*

Global health drug product introductions are often delayed by regulatory deficiencies

Deficiencies in generic product dossiers submitted for WHO prequalification

Apr 2007-Dec 2010



Source: Worku W, Gordon J, Stahl M, Rago L. Deficiencies in generic product dossiers as submitted to the WHO Prequalification of Medicines Programme. Journal or Generic Medicines 9(2) 63-74. May 2012.

Some of these deficiencies can be addressed through ***improved planning enabled by upfront visibility*** *into LMIC CMC requirements*

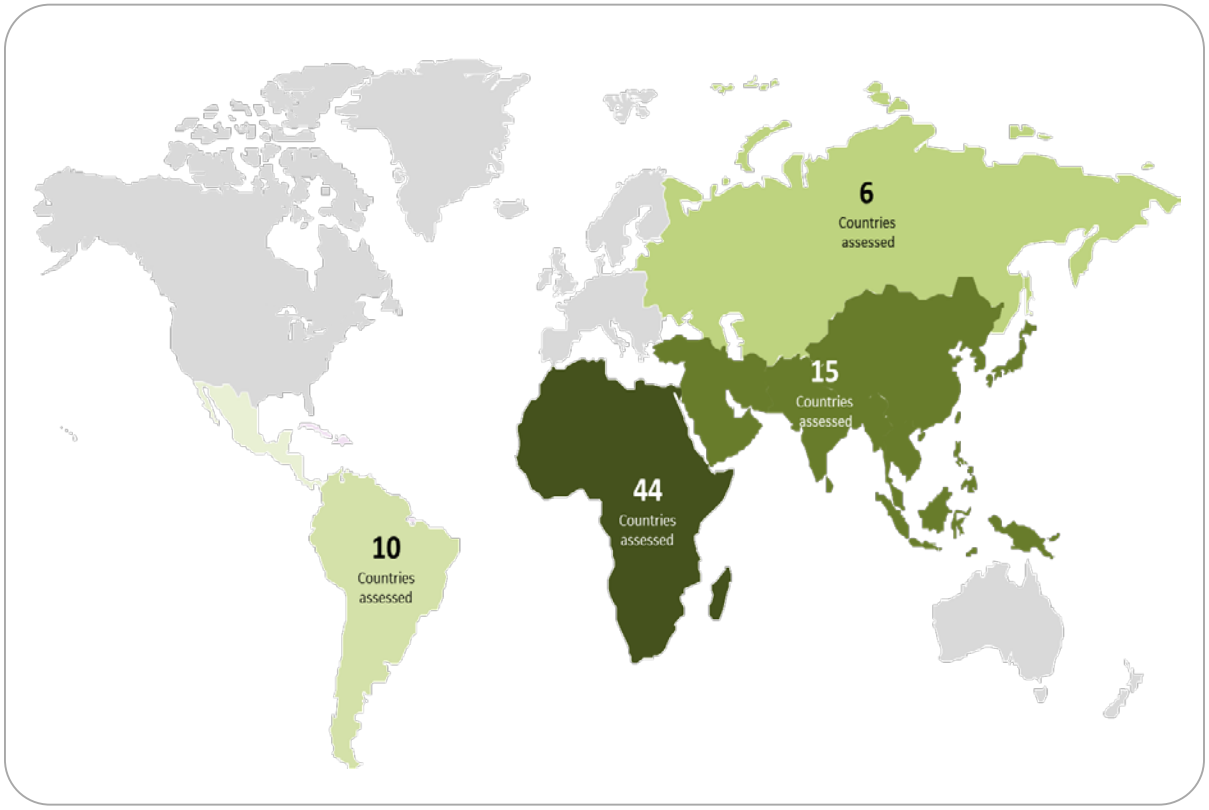
We developed a database to help accelerate the introduction of life-saving drugs

The database provides information along 3 domains structured based on the ICH Common Technical Document Module 3 contents.

		Example requirements	
1	**Prerequisites & administrative requirements**	• No objection certificate issued by Central License Authority (India) • Form 29 as issued by State Licensing Authority (India)	• Specific requirements to source materials for clinical mfg. • Storage requirements for clinical supplies • Import & export requirements
2	**CMC requirements for clinical & commercial manufacturing**	• Batch size/quantity for clinical supplies, registration, validation • Stability study requirements / environmental conditions (e.g., ACC, CRT, Zone IV etc.) • API and excipient requirement	• Manufacturing facility requirements for clinical/registration batches • Process validation requirements • Facility cGMP approval and inspection requirements
3	**CMC documentation requirements for product registration**	• Specific regional information • Executed batch records • Documents (chromatograms, CoAs, etc.)	• Safety requirements • Comparability protocol • Validation package

The database captures regulatory requirements for 75 LMICs and 10 Procurement Agencies

75 Low- and Middle-Income Countries



10 Procurement Agencies

The Global Fund
unicef
IDA FOUNDATION
Pan American Health Organization
PFSCM
UNFPA

Countries were selected that represented model/baseline countries (Brazil, China, India, South Africa), Gavi countries eligible for support in 2015, countries participating in the WHO Collaborative Registration Procedure (CRP), and additional middle income countries of interest to BMGF PDPs with a high burden of TB, HIV, Malaria and/or Neglected Tropical Diseases.

The project revealed specific LMIC requirements that are challenging

A global health product is generally introduced in over 30 countries, therefore each requirement can add cumulative cost and delays in product introduction

Focus Today

- ***In-country QC testing***
- ***Prior NRA marketing authorization***
- ***Diverse labeling requirements***
- ***GMP inspections***
- ***In-country manufacturing***
- ***Varied stability study requirements***
- ***API assessments***
- ***Excipient restrictions***
- ***Reference product selection***

Many LMICs prevent the use of substandard and falsified medicines through Quality Control Testing

In-country QC testing of commercial samples is required for initial registration and each import to ensure medicine quality for many low- and middle-income countries. The sampling and testing supports assurance of the quality of medicines, however the requirement has some unintended consequences:

- Delays delivery of medicines to patients as medicines sit in depots waiting to be tested and for results to be released
- Creates duplicative testing of samples in regions

	Initial Registration QC Testing	**Import QC Testing**
Requirement	Submission of materials in case QC testing is performed prior to registration: • **Commercial samples** per presentation • **Materials and documentation** for analytical testing e.g., chromatography columns	• Sample products from **each import** batch for QC testing
Example Countries	Certified Labs • Bangladesh • Benin • Chad • China • DRC • Guinea • Kenya • Liberia • Malaysia • Mexico • Nepal • Sudan • Tanzania • Togo • Uganda Government & certified labs • Nigeria • South Africa Government labs • Russia	Certified Labs • Brazil • China • Mexico • Liberia Government & certified labs • Nigeria • South Africa Government labs • Russia

The EMA and WAHO regionalization efforts show what can be implemented more broadly across LMICs to reduce duplication of effort of QC testing

What has worked?

EMA efforts

- QC test sharing with market surveillance

Supranational efforts

- Aggregate data and build lab capacity

WAHO

- Used a coordinating body like WHO and capacity building support from SRAs

What has not worked?

Skip testing

- Limited data at initial submission limits applicability to post-approval

Waivers

- Failed to implement to-date (NRAs cannot assure quality)

Implications to solution

Learnings

- Leverage regional QC testing, enhanced market surveillance and data sharing
- Utilize a network of qualified labs
- Develop coordination/oversight body
- Include external support

Supranational initiatives by various stakeholders are supporting LMICs to improve the quality of products

	Organization	Region	Objective
Lab strengthening & capacity building	Promoting the Quality of Medicines (PQM)	LMICs	▪ Strengthen lab capacity to address proliferation of falsified and substandard medicines. ▪ Collaborate with WHO to train 11 African countries on sampling and lab support, and support 4 labs in the region to obtain ISO accreditation ▪ Reinforce Quality Management Systems for 30 labs in 13 countries ▪ Support Medicines Quality Monitoring through sampling in 136 active sites in 16 countries
	West African Health Org (WAHO)	West Africa	▪ Upgrading 5 regional labs to meet ISO standards with the intention to serve as regional centers of excellence. Also developing guidelines/training manuals for laboratory quality management systems, and conducting lab staff training. ▪ Countries: Benin, Burkina Faso, Cabo Verde, Côte D'Ivoire, Gambia, Ghana, Guinea, Guinea Bissau, Liberia, Mali, Niger, Nigeria, Senegal, Sierra Leone, Togo
Market surveillance & quality monitoring	WHO Substandard, Spurious, Falsely labelled, Falsified and Counterfeit (SSFFC) Med Products Initiatives	Global	▪ A global surveillance and monitoring system for countries to systematically prevent, detect and respond to incidents involving SSFFC medical products. ▪ Also provides technical support to member states to develop policies, strengthen lab capacity, improve reporting/surveillance, and adopt standard guidelines such as Guidelines for Drug Donation
	Medicines Quality Database (MQD) by PQM	LMICs	▪ Provide a database of poor quality medicines for programs in USAID priority countries. ▪ In 2014, 17 countries conducted medicine quality monitoring and surveillance, increasing the number of records in the MQD to 13,000
	The Pharm. Security Inst Incident Reporting System	Global	▪ A secure database where 33 major pharmaceutical companies report cases of fraudulent manufacture and mislabeling of drugs, as well as cases of fraudulent packaging.

Sources: USP, WAHO, WHO SSFFC, MQD, Pharma Security Institute, EDQM

Additional supranational initiatives led by WHO, Gates Foundation and others are supporting LMICs to improve the quality of products

	Organization	Region	Objective
QC Testing	WHO PQ Quality Testing	Global	▪ WHO certifies PQ labs (NRA or commercial. labs) to promote and facilitate access to safe, reliable and appropriate in vitro diagnostic technologies and laboratory services ▪ PQ labs are used by the PQ surveillance team and procurement agencies for post market testing ▪ WHO recommends post market testing in country and supports capacity building of national regulatory authorities and national reference laboratories
	PAHO	LatAm CARICOM	▪ Setup External Quality Control Program (EQCP) in collaboration with USP with the participation of the Official Drug Quality Control Laboratories of PAHO Member States ▪ EQCP optimizes testing capacity and reporting, evaluates the quality of drugs used in priority programs, and develops the concept of Reference QC Laboratories throughout the region
Supply Chain Integrity	BMGF	LMICs	▪ Supporting regulatory components of supply chain integrity through WHO Substandard, spurious, falsely labelled, falsified and counterfeit (SSFFC) medical products program
	Rx360	Global	▪ Information and processes to improve the integrity of the health care supply chain and the quality of materials within the supply chain ▪ Includes list of qualified suppliers
Waiver	IFPMA import testing waiver (not adopted)	Global	▪ Recommended use of an Import Testing Waiver to either eliminate import testing requirements or establish exemptions from import testing under well-defined conditions, where appropriate manufacturing and distribution controls have been demonstrated ▪ Example provided that the products are uninterruptedly controlled according to GMP and GDP

Sources: WHO PQ, PAHO External Quality Control Program of Official Drug Quality Control Laboratories (EQCP), IFPMA, Rx360, BMGF

A regional, risk-based approach for in-country QC testing should be evaluated especially during times of global health emergencies

In-country Quality Control Testing: Impact associated with product introduction, and release of commercial samples to perform in-country QC testing for initial registration and each import.

Drivers

Assuring drug quality

Building NRA capabilities and operational sustainability

Impact

- Inconsistent application of analytical methods on samples
- Additional cost to manufacture and supply sample batches with 12 months shelf-life
- Provision of working/reference standards, and impurities are costly and require temperature-controlled shipping

Potential Solutions

- Regional network of QC labs
- Risk-based approach
- Standard guidelines

Data source: Anecdotal information gathered from manufacturer interviews

Proposed solutions align with seven overarching themes although there may be others to explore

Interviews with the global health community confirmed the “pain points” and provided input for solution development.