Risk-based post-marketing surveillance of medicines:

Implementation resources for low- and middle-income countries

October 2021

Introduction

Medicines play an essential role in maintaining and restoring the health and well-being of the public. Quality-assured medicines support their efficacy, while poor-quality medicines[1] may not only fail to treat a disease, but can cause harm, lead to death in extreme circumstances, and may also contribute to drug resistance. National Medicines Regulatory Agencies (NMRAs) are responsible for the registration and authorization of safe, efficacious, and quality-assured products. To make sure that medical product quality is maintained until it reaches the patient, NMRAs establish post-marketing surveillance (PMS) programs.

Poor-quality medicines impact low- and middle-income countries (LMICs) in particular. Several studies estimate that around 10% of medicines in LMICs may be of poor quality, and actual figures may be higher, depending on the country and therapy in question.[2] The economic costs of poor-quality medicines on individuals and health systems range from tens of millions to hundreds of billions of dollars.[3]

The capacity of NMRAs to implement PMS programs varies greatly among countries. The WHO's *Global Benchmarking Tool (GBT)*[4] *for Evaluation of National Regulatory System of Medical Products* allows NMRAs to self-evaluate and assess their capabilities. However, many countries have competing priorities and constraints on financial and human resources. Risk-based approaches to sampling and testing medicines offer a potential solution.

The U.S. Pharmacopeia (USP) has provided technical assistance to help ensure medicines quality and support regulatory strengthening in more than 40 countries in Africa, Asia, Central and South America and Eastern Europe since the early 2000s. During this time, USP's approach has evolved and progressed from spot-checking surveys (known as Medicines Quality Monitoring (MQM)) that aimed to support the early detection of substandard and falsified medicines into institutionalized, routine and risk-based PMS programs for sampling and testing (**Figure 1**).

Along the process, USP has developed guidelines, tools, country reports, and scientific articles.[5]

This document provides a brief description of key resources developed by USP to support the adoption of risk-based PMS. Several of these resources were developed by the Promoting the Quality of Medicines (PQM) and PQM+ programs, funded by the US Agency of International Development (USAID) and implemented by USP. All resources included here are publicly available and accessible for free.

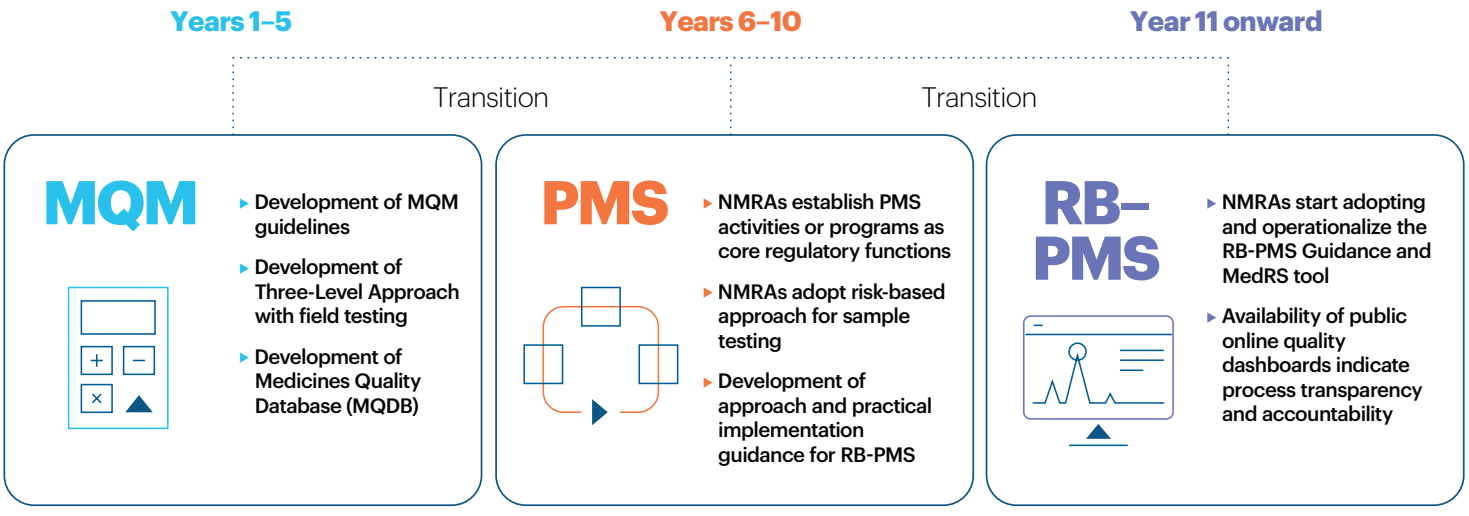

Figure 1: Evolution of USP assistance and support to ensure medicines quality post-registration.

Guidelines, tools, and resources to support development of sampling and quality testing protocols for risk-based PMS of medicines.

Guidelines to Establishing a Medicine Quality Monitoring Program

These guidelines were developed to help authorities create uniform protocols for sampling, testing, and reporting procedures in medicines' quality surveillance programs. Initially implemented through monitoring activities supporting National Disease Programs, the guidelines adopt a risk-based approach for quality control, utilizing simple testing methodologies that can be applied in the field (e.g., colorimetric methods and thin-layer chromatography) which evolved into the Three-Level Approach described below.

The Three-Level Approach: a framework for ensuring medicines quality in limited-resource countries

This approach provides a framework for medicines testing through three successive, complementary, and increasingly rigorous levels of analysis: (1) visual and physical inspection; (2) screening with field-based methodologies; and (3) laboratory testing utilizing compendial or manufacturer methodologies (**Figure 2**).

The gradual approach can accelerate the output of results by reducing the number of samples that require compendial testing, a process that incurs substantial time, costs and human resources requirements. By using simpler methods to assess quality at the first two levels, the Three-Level Approach can save substantial resources and can yield data for decision making faster than traditional compendial testing performed at the laboratory. The Visual Inspection Guide to help identify falsified COVID-19 Vaccines provides an example of the type of information one can assess in the field during Level 1.

The publicly available Medicine Quality Database (MQDB)[6] which currently contains over 17000 records, includes data generated through implementation of the Three-Level Approach in 16 countries from Africa, Asia, and Central and South America between 2003-2017. Several studies detailing implementation of the approach in those regions have been published.[7]

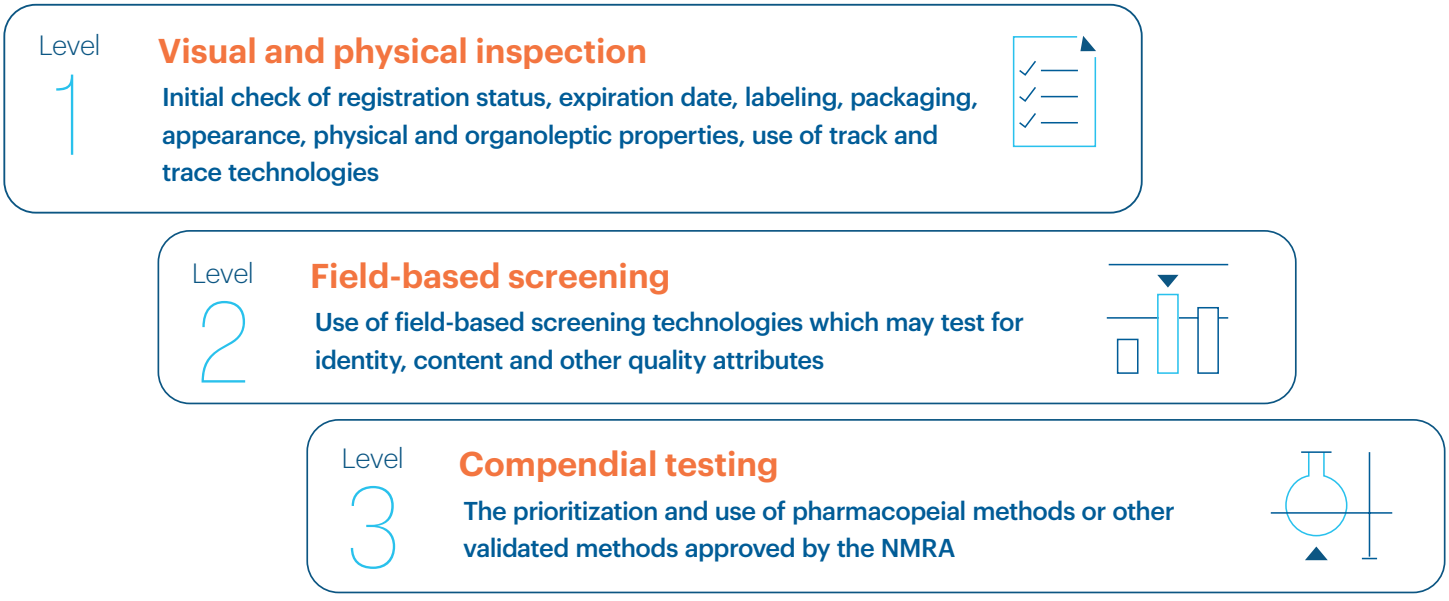

Figure 2: The Three-Level Approach: A cost effective high-throughput methodology for quality testing

Guidance for Implementing Risk-Based Post-Marketing Quality Surveillance in Low- and Middle-Income Countries

Through consultation with international experts, USP developed guidance for the implementation of comprehensive risk-based PMS programs in LMICs.

LMICs can use this framework (**Figure 3**) to establish sustainable programs by utilizing risk considerations.

The approach focuses sampling on the most susceptible medicines and in geographical areas and facilities where poor-quality medicines are more likely to be found.

The framework also provides guidelines for risk-based testing using the Three-Level Approach, including a flow-chart for decision making at each level of testing.

Knowledge Sharing Videos: Protecting Patients from Bad Drugs: A Risk-Based Approach to Medicines Quality Surveillance

These videos expand on the guidelines described above and explain how designing and implementing programs that sample and monitor medicines quality through a risk-based approach allows countries to tailor activities according to local needs, optimize limited resources, and focus efforts on areas that present the greatest risks to public health.

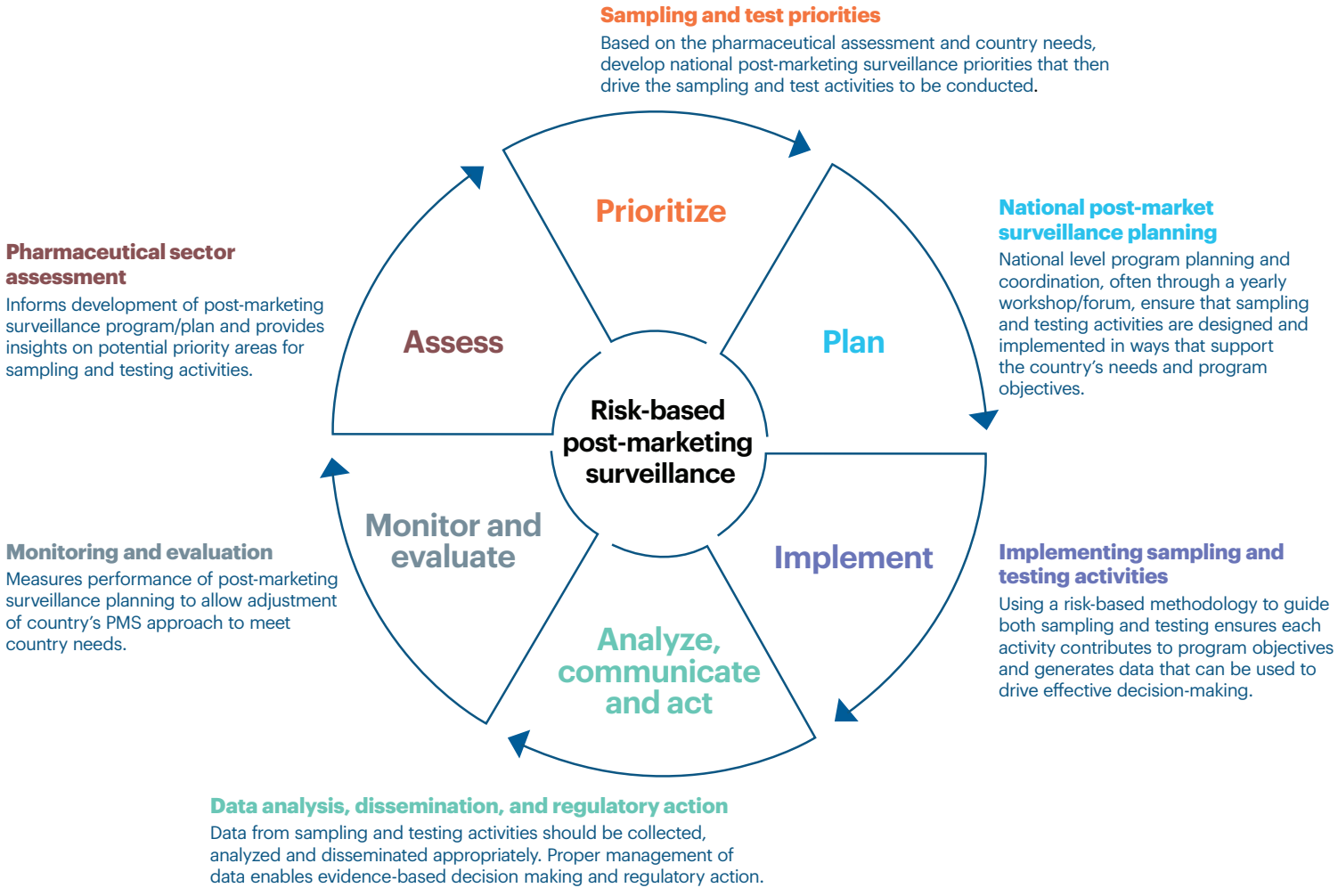

Figure 3: Framework for developing and implementing PMS programs.

Medicines Risk-based Surveillance (MedRS) Tool

MedRS is a tool that facilitates the planning, design, and development of sampling protocols for a risk-based PMS. The tool helps evaluate risks associated with medicines, geographic locations, and supply and distribution chains. By calculating composite risk scores, the tool can help determine what medicines to sample, how many samples to collect, and where to collect those samples. MedRS is available online and also allows users to upload their protocols, results and share substandard and falsified medicines information with WHO rapid alert system. An example of a practical application of the tool can be found in the Guidance Document for Developing and Implementing a Risk-based PMS for Maternal, Neonatal, and Child Health.[8]

Technology Review Program

The Technology Review program rigorously evaluates available and emerging screening technologies that can be used in Level 2 of the Three-Level Approach. The program publishes these evaluations to inform the global health community of their relative strengths and limitations. The site includes methodology reviews and overview articles.

USP–NF General Chapter on the 'Evaluation of Screening Technologies for Assessing Medicine Quality

This chapter addresses the need to evaluate the potential and actual capabilities and limitations of portable screening tools and their performance in field settings. It provides the structure and recommendations for performing an appropriate and pragmatic review of a given technology.

A Risk-Based Resource Allocation Framework for Pharmaceutical Quality Assurance for Medicines Regulatory Authorities in Low- and Middle-Income Countries

This document proposes a framework to assist NMRAs in LMICs in managing priorities and sustainably supporting pharmaceutical quality assurance to achieve maximum health impact and efficiencies.

Additional quality-assurance related resources can be found at USP.org, and particularly at USP's PQM and PQM+ program websites.

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