USAID MEDICINES, TECHNOLOGIES, AND PHARMACEUTICAL SERVICES (MTaPS) PROGRAM

Improved Access. Improved Services. Better Health Outcomes.

ADVANCING REGULATORY SYSTEMS FOR IMPROVED ACCESS TO SAFE, EFFECTIVE, AFFORDABLE, AND QUALITY-ASSURED MEDICAL PRODUCTS

Technical Program Update | December 2022

> *"Good regulatory systems, providing oversight of health products throughout their life-cycle from the laboratory to the health facility, are the linchpin of quality prevention, diagnosis and treatment. They are [an] essential part of WHO's drive towards universal health coverage [UHC] and a key contribution to reaching the "triple billion" target (1 billion more people benefiting from universal health coverage, 1 billion more people better protected from health emergencies and 1 billion more people enjoying better health and well-being)."*
>
> - Dr. Mariângela Simão, Assistant Director-General, Access to Medicines, Vaccines and Pharmaceuticals, World Health Organization, 2019

Why Regulatory Systems Strengthening Matters to Public Health

Achieving universal health coverage per Sustainable Development Goal 3.8 and the US Agency for International Development's (USAID) goal of enabling high-performing health care systems relies on access to safe, effective, affordable, and quality-assured medical products (including medicines, vaccines, devices, and other health technologies). Poor-quality products can contribute to antimicrobial resistance, worsen health outcomes, and result in disability or death. A well-functioning national regulatory system that is supported by sound legislation enables timely access to essential medical products and puts controls in place to ensure their ongoing quality and safety once in the market and in use. Effective national regulatory systems require competencies across eight regulatory functions (product registration or marketing authorization, vigilance, market surveillance and control, licensing establishments, regulatory inspection, laboratory testing, clinical trial oversight, and lot release) and in the overarching national regulatory system, as defined by the World Health Organization's (WHO) Global Benchmarking Tool (GBT).[1]

[1] WHO Global Benchmarking Tool (GBT) for evaluation of national regulatory systems of medical products, revision VI. Geneva: World Health Organization; 2021. Licence: CC BY-NC-SA 3.0 IGO.

In most countries, a national medicines regulatory authority (NMRA) is responsible for ensuring the safety, efficacy, and quality of medical products as they traverse the supply chain from the research and development phase to the end user by fulfilling various functions, including licensing, regulatory inspections, clinical trial oversight, and product registration/marketing authorization (figure 1).

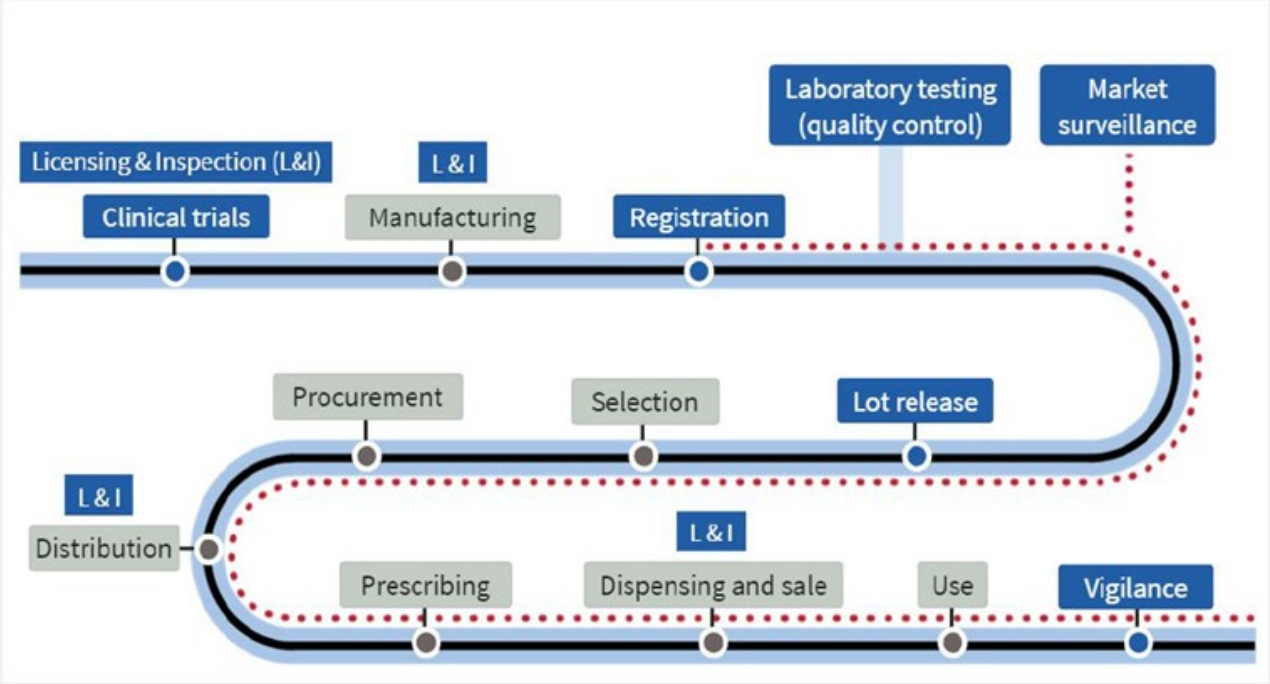

Figure 1: Key regulatory functions through the medical products supply chain

Diagram based on concepts from: *The Many Faces of Corruption: Tracking Vulnerabilities at the Sector Level and WHO Good Governance for Medicines Programme: an innovative approach to prevent corruption in the pharmaceutical sector.*

However, many low- and middle-income countries (LMICs) do not have NMRAs that can effectively perform all of these functions. Limitations include inadequate numbers of personnel with the right competencies, a lack of sustainable financial resources, and information management systems that rely on manual upkeep and/or do not provide reliable data for regulatory decisions. Laws and regulations are often outdated or insufficient and require a sustained political commitment and environment for them to be changed or updated. An assessment of 26 NMRAs in sub-Saharan African countries conducted by WHO in 2010 found that although the countries had established legal structures for the most essential aspects of medicine control, capacity was inadequate, and regulatory measures did not form a coherent system.[2] Another WHO assessment conducted in 2019 found that 144 (or 74%) of its Member States did not have a stable and well-functioning regulatory system, and 99 (51%) were at the lowest level of maturity.[3]

MTaPS' Regulatory Systems Strengthening Approach

The five-year (2018–2023) USAID Medicines, Technologies, and Pharmaceutical Services (MTaPS) Program supports LMICs to improve their regulatory capacity by strengthening governance, building institutional and individual capacity, advocating for adequate staffing and financing, promoting regulatory reliance, and increasing the availability and use of

[2] WHO. 2010. Assessment of medicines regulatory systems in sub-Saharan African countries An overview of findings from 26 assessment reports. Geneva: WHO.

[3] Khadem Broojerdi A, Baran Sillo H, Ostad Ali Dehaghi R, Ward M, Refaat M, Parry J. The World Health Organization Global Benchmarking Tool an Instrument to Strengthen Medical Products Regulation and Promote Universal Health Coverage. Front Med (Lausanne). 2020 Aug 19;7:457. doi: 10.3389/fmed.2020.00457. PMID: 32974367; PMCID: PMC7466745.

information for regulatory decision making. MTaPS works with countries to first assess their regulatory capacity and then use the findings to inform interventions and action plans (figure 2).

Figure 2: MTaPS' approach to strengthening regulatory systems

Using the WHO GBT to objectively evaluate a country's capacity to regulate medical products, MTaPS works with countries to identify gaps and weaknesses in the regulatory system. The GBT is the first global tool to provide countries with a systematic process for evaluating and strengthening their regulatory systems.

The GBT benchmarking exercise uses 268 indicators grouped by regulatory function to classify each NMRA's maturity on a 4-level scale of 1 (no formal approach), 2 (reactive approach), 3 (stable formal system approach), and 4 (continual improvement emphasized). Maturity level 3 represents a well-functioning regulatory system and is identified as a target in World Health Assembly Resolution 67.20.[4] Level 4 is considered best in class and operating at an advanced level of performance.

GBT scores provide an NMRA with a measure of control over the regulatory processes of medical products' availability in the market. An institutional development plan (IDP) is generated to address areas that need improvement with corresponding resources and possible partners to support interventions. Importantly, the IDP enables technical, advocacy, and funding partners and agencies to collaborate in strengthening regulatory systems, limits duplication, and promotes the efficient use of limited resources.

MTaPS works with national governing bodies, NMRAs, and ministries of health to apply the GBT and use the results to enable NMRAs to identify strengths and areas for improvement, formulate an IDP to build on the strengths and address the identified gap, prioritize IDP interventions, and monitor progress and achievements against the IDP.

[4] World Health Assembly Resolution 67.20 in 2014 recognized the importance of strong regulatory systems to a well-functioning health care system and the attainment of health-related SDGs and UHC.

MTaPS' Interventions for Strengthening Regulatory Systems

MTaPS' interventions for regulatory systems strengthening focus on:

- Ensuring a strong regulatory framework for the pharmaceutical sector by helping governments draft or update evidence-based policies, laws, regulations, guidelines, norms, and standards and strengthening the governance structures to better oversee and enforce them
- Strengthening regulatory capacity and pharmaceutical-sector governance to protect the public from substandard and falsified products
- Introducing and institutionalizing proven methods for human resource capacity building to gain and apply the skills that increase NMRAs' ability to carry out their regulatory mandate
- Working with governments to build the institutional capacity needed for the regulatory system to run effectively, such as the establishment of a quality management system (QMS) and electronic information management system
- Supporting the convergence and harmonization of medical products regulation in Africa and Asia

MTaPS prioritizes the convergence of technical standards and regulatory requirements for medical products regulation among regional networks and NMRAs to implement a QMS with the goal of obtaining ISO 9001:2015 certification for their regulatory systems. In this light, MTaPS collaborates with other development partners, such as the Promoting the Quality of Medicines Plus program, WHO, and UNICEF, to better coordinate efforts.

In collaboration with WHO and other partners, MTaPS has supported Bangladesh, Mozambique, Nepal, Rwanda, and other countries to use the GBT to identify gaps and weaknesses, assess the maturity level, and develop and implement IDPs to address regulatory system challenges with the aim of attaining a maturity level of 3.

Improving Legal and Regulatory Frameworks

Effective legislation is critical to having a functional national regulatory framework and is complemented by specific regulations that together serve to control the availability, distribution, prescribing, and dispensing of medical products; the provision of product information; and the licensing, accreditation, and oversight of medical product establishments and professional staff. Legislation and regulations should also provide for the establishment and operation of an NMRA to assess the safety, quality, and efficacy of medical products; oversee clinical trials; and undertake post-marketing surveillance and vigilance to monitor their quality and safety. Legislation that is developed in a transparent and participatory way reinforces principles of good governance and accountability and increases the likelihood that its implementation will be acceptable, feasible, and enforceable.

In **Bangladesh, Kenya, Mozambique**, **Nepal,** and **Rwanda**, MTaPS is ensuring that an adequate legal and regulatory framework is in place that provides for the establishment and/or effective operation of an NMRA. In **Nepal**, MTaPS is working with the government to update its drug law, which has been in place since 1978. MTaPS and the International Law Institute-African Center for Legal Excellence conducted a gap analysis of Nepal's legal and regulatory framework and prepared a zero draft of a revised drug law that was finalized in consultative meetings with the policy, legislation, and reorganization technical working group; Ministry of Health and Population (MOHP); and Ministry of Law, Justice, and Parliamentary Affairs. The draft law is ready for the MOHP to seek approval from the Council of Ministers to be put as a bill in the federal parliament. Once approved, the new drug law will serve as the foundation for overall improvement in the functions of the Department of Drug Administration (DDA) and the regulatory system as a whole. In **Rwanda**, MTaPS provided support to the Rwanda Food and Drugs Authority (FDA) to develop a five-year business plan for growth and financial sustainability and a five-year strategic plan (2021–2024). MTaPS provides assistance to the Rwanda FDA in drafting and validating regulations, guidelines, and standard operating procedures (SOPs), including those regulating medical

gases (oxygen); registering vaccines and biological products; and assessing registration applications for generic medicines, including WHO-prequalified products. The Rwanda FDA's Board of Directors approved a four-year strategic plan developed with support from MTaPS that sets out the Rwanda FDA's vision, priorities, and strategic objectives. In **Mozambique**, MTaPS supported the National Directorate of Pharmacy in its transformation into the autonomous authority *Autoridade Nacional Reguladora de Medicamento, Instituto Público* (ANARME, IP) through the establishment of an effective regulatory framework, capacity building, and support to the strategic plan. MTaPS also provided assistance in the drafting of regulations and guidelines for medical products registration, regulatory inspections, licensing of medical products' establishments, pharmacovigilance (PV), pharmacy practice, and price control to address important gaps that the GBT assessment identified in 2018.

In **Bangladesh**, MTaPS supported the Directorate General of Drug Administration (DGDA) and other partners to identify and formulate the legal provisions for strengthening the regulatory system based on the GBT assessment, including the incorporation of provisions for PV, emergency use authorization, and donation of medical products. The amended drug act 2019 was reviewed by the cabinet of the Ministry of Health and Family Welfare and is awaiting approval from parliament. MTaPS also provided technical assistance to the DGDA to develop an annual action plan (2020–2021) and a new five-year strategic plan (2022–2026).

In **Kenya**, MTaPS supported the Pharmacy and Poisons Board (PPB)—Kenya's national regulatory authority—to review the national scheduling guidelines to incorporate the WHO Access, Watch, and Reserve (AWaRe)[5] categories, which are key for promoting appropriate use of antimicrobials. MTaPS also provides technical assistance to the Kenya COVID-19 Regulatory and Safety Monitoring sub-committee to establish mechanisms for handling COVID-19 adverse events that may occur after vaccination.

MTaPS helped draft an inspection strategy and establish an electronic inspection and licensing system for private-sector medicine outlets in Bangladesh. Photo credit: MTaPS Bangladesh

A SURVEY OF NMRAS TO INFORM THE REORGANIZATION OF THE NEPAL DDA

MTaPS advocated with the Government of Nepal to update the current drug law with a new act that encompasses health technology and products and cosmetics but excludes food safety control. The drug law update will also include a new proposed structure and staffing norms for the DDA. The proposed reorganization will help the DDA perform its key regulatory functions more efficiently and ensure sustainable access to and appropriate use of safe, effective, quality-assured, and affordable essential medical products. MTaPS drafted a concept note for the Nepal MOHP on the legislative revision and the required reorganization and decentralization of the DDA.

To help the Government of Nepal reorganize the DDA, MTaPS conducted a comparative survey of 10 NMRAs in 2020. The survey findings assessed the following features of NMRAs:

- Regulatory functions, including scope
- Autonomy
- Funding

[5] The AWaRe Classification of antibiotics was developed in 2017 by the WHO Expert Committee on Selection and Use of Essential Medicines as a tool to support antibiotic stewardship efforts at the local, national, and global levels, Antibiotics are classified into three groups—Access, Watch, and Reserve—taking into account the impact of different antibiotics and antibiotic classes on antimicrobial resistance to emphasize the importance of their appropriate use. The 2021 update of the AWaRe classification includes an additional 78 antibiotics not previously classified, bringing the total to 258.

- Structure in terms of oversight of regulatory duties at the central, regional, and local levels and interaction with ministries, councils, and committees
- Staffing levels and resources required to ensure key functions for an effective national regulatory system

The surveyed NMRAs ranged from simple structures with a regulatory scope limited to allopathic, medical devices, vaccines, and traditional medicines (e.g., Bangladesh); to a regulatory scope that included medicines and medical devices (e.g., Nepal, South Africa, Sri Lanka, India); to a broad regulatory scope that additionally included food safety control (e.g., Philippines, Thailand, South Korea, Indonesia).

The study showed that the type and size of the NMRAs' organizational structures depended on the scope of products they regulated and their degree of autonomy. The degree of autonomy was defined by their ability to make independent financial, technical, and operational decisions. Countries ensured autonomy of their NMRAs by having the head of an NMRA appointed by one agency but reporting to another agency or by creating an independent board to lead the NMRA. The study suggested that the NMRAs of the Philippines, Sri Lanka, and South Africa be used as references for Nepal's DDA restructuring process since they share similar characteristics.

MTaPS supported the DDA to hold a DDA reorganization conference, draft a revised structure, and prepare updated staffing norms that await approval once the updated drug law is enacted by the Parliament of Nepal.

Establishing QMS for Improving Regulatory System Efficiency

A major component of MTaPS' institutional capacity building strategy involves helping NMRAs establish a QMS. A QMS provides uniform, standardized, and transparent implementation and documentation of the NMRA's work processes and is a step toward ISO 9001:2015 certification. MTaPS provided technical assistance to the regulatory authorities in **Mozambique, Rwanda,** and **Nepal** to conduct situational analyses to determine the level of QMS implementation. In addition, technical assistance was provided to develop quality manuals and SOPs for regulatory functions, which are part of QMS requirements. MTaPS also provided senior management and staff with an orientation on QMS procedures, conducted training in risk management, and provided support to regulatory authorities to build capacity to conduct internal audits. Findings from the internal audits will enable the regulatory authorities to prepare for external audits, preemptively fill identified gaps, and facilitate ISO 9001:2015 certification and fulfillment of the GBT requirements for QMS implementation.

In **Nepal**, GBT results identified where SOPs and documentation are needed, and with MTaPS' support, the QMS technical working group developed the SOPs and a quality assurance manual that will be institutionalized and serve as a standing reference for DDA regulators. MTaPS provided an orientation to DDA and National Medicines Laboratory staff and management on QMS, risk management, and conducting internal audits, and select staff completed in-depth QMS assessor training to allow certification as auditors for ISO 9001:2015.

In **Bangladesh**, MTaPS collaborated with the DGDA to establish a QMS department with clearly defined roles and responsibilities; prepared a functional organogram of the DGDA; updated the QMS quality manual and regulatory procedures; conducted a QMS internal audit; and drafted a roadmap for the QMS implementation plan in line with the WHO guidelines, ISO 9001:2015, and the latest national regulatory authority manual.

Streamlining Product Registration/ Marketing Authorization

A primary NMRA function is registration, or granting marketing authorization, of medicines and other health products before they are allowed to be manufactured, imported, distributed, sold, or supplied in the country. Strong registration systems are foundational to pharmaceutical systems for guaranteeing timely access to safe, effective, affordable, and quality-assured medical products. An onerous, opaque, or expensive registration process discourages product license holders (e.g., manufacturers) from registering their products in a country, which in turn decreases competition among suppliers, limits access to new products, and increases the risk of stock-outs. In contrast, a superficialregistration process can allow poor quality and unsafe products on the market without the proper controls or oversight to protect patients from harm. As part of its work, MTaPS helps countries streamline their registration process to expedite bringing medical products to market.

A common problem in LMICs is a lack of personnel with the specialized skills needed for registration. For example, the DDA in **Nepal** has four assessors to review about 60 marketing authorization applications every month. In Nepal, MTaPS collaborated with the DDA to develop job descriptions for seven key positions in its reorganized structure. MTaPS helped the Rwanda FDA recruit new personnel, including medicine assessors, to increase the organization's capacity in this area. In **Rwanda** and **Tanzania**, MTaPS is also supporting assessors to clear backlogs by convening product dossier evaluation retreats to expedite quality evaluations, with the aim to complete 70 dossier applications in one session. To develop specialized skills aligned with international best practices, MTaPS conducted training sessions to build the capacity of medicines assessors in **Bangladesh, Mozambique, Nepal,** and **Rwanda** on evaluating product dossiers in compliance with Common Technical Document[6] guidelines and use of Good Review Practices.

UPDATING PRODUCT REGISTERS AND GUIDELINES TO STREAMLINE REGISTRATION

In the **Democratic Republic of Congo** (DRC) and **Mali**, MTaPS is supporting the regulatory authorities to update and disseminate the directory of registered medical products. In DRC, the updated directory is available online, and printed copies were disseminated to inspectors and customs officers in the provinces to track and confiscate unregistered products. MTaPS provides ongoing support by convening quarterly medicine registration sessions to facilitate the evaluation of product dossiers to ensure the timely registration of maternal, newborn, and child health (MNCH), family planning/reproductive health, and other essential health products. These sessions also established a cadre of trainers to build the skills and knowledge of other assessors. In **Nepal**, MTaPS conducted a situational analysis and developed an implementation plan to strengthen the regulation of medical devices, which will support improving the quality and effectiveness of registered medical devices on the market. Finally, in **Kenya**, MTaPS supported the review of the Guidelines for Emergency Use and Compassionate Use Authorization of Health Products and Technologies to include introduction of new and experimental health products and technologies to address public health emergencies, such as COVID-19.

Improving Efficiency through Electronic Registration Systems

Another problem is inadequate registration systems—sometimes paper based—that drastically reduce efficiency. MTaPS is working with the regulatory authorities in **Mozambique** and **Nepal** to deploy Pharmadex, a web-based tool that streamlines and tracks medical products registration. MTaPS will train master trainers in each country who will be responsible for ensuring that new employees are oriented on how to use the tool. In **Rwanda**, MTaPS is providing technical assistance to the Rwanda FDA to deploy its electronic Integrated Regulatory Information Management System for regulation and inspection of pharmaceutical products, including training users on the electronic system.

MTaPS supported the Rwanda FDA in building the capacity of medicine assessors by training them to evaluate product dossiers in compliance with Common Technical Document guidelines and use of Good Review Practices. Photo credit: Abimana Rwandenzi Eugene

[6] A standardized format to submit quality, safety, and efficacy information for medical product registration.

Gaining Efficiencies through Regulatory Reliance

Many countries also lack clear national legal provisions for recognition of regulatory decisions and/or reliance, and some do not have a mechanism for the application of good reliance practices, according to WHO's principles in regulatory decision making[7] (see box).

Reliance: The act whereby the regulatory authority in one jurisdiction may take into account and give significant weight to (i.e., totally or partially rely on) evaluations performed by another regulatory authority or trusted institution in reaching its own decision. The relying authority remains responsible and accountable for decisions made, even when it relies on the decisions and information of others.[8]

Recognition: The routine acceptance by the national regulatory authority in one jurisdiction of the regulatory decision of another national regulatory authority or other trusted institution. Recognition indicates that evidence of conformity with the regulatory requirements of country A is sufficient to meet the regulatory requirements of country B. Recognition may be unilateral or multilateral and may be the subject of a mutual recognition agreement.[9]

Regulatory harmonization: Adoption of the same technical requirements, standards, and guidelines for quality, safety, and efficacy by all regulatory authorities. While each NMRA has decision making authority, the same process is followed, with common documentation and alignment of legal frameworks.[10]

In **Jordan**, MTaPS worked with the Jordan Food and Drug Administration (JFDA) to streamline the registration process to recognize WHO prequalified vaccines. The JFDA modified registration principles to include the acceptance of and priority for registration of WHO-prequalified vaccines. In **Mali,** MTaPS provides support to the Pharmacy and Medicines Directorate to strengthen reliance on prequalification and other stringent regulatory bodies. In **Rwanda**, MTaPS provided training to Rwanda FDA staff in basic Good Manufacturing Practice (GMP) inspections, which is a prerequisite to product registration. In addition, assessors developed their skills on good reliance practices and increased their capacity to rely on regulatory decisions by other regulatory authorities, which is an important strategy to streamline registration of medical products. The trained assessors are able to implement the WHO-issued good reliance practices guidelines to improve registration practices.

MTaPS is supporting the **Philippine** Food and Drug Administration to improve the product registration system by introducing a reliance pathway. Toward this end, MTaPS organized a national dialogue with the Philippine Food and Drug Administration, Department of Health, Anti Red-Tape Authority (national authority to reduce bureaucratic inefficiencies in government procedures), Pharmaceutical Association, patient groups, and development partners to discuss how the medical product registration system can be made more efficient by recognizing decisions made by reference regulatory authorities and optimizing the product registration process through technology. In **Bangladesh** and **Nepal**, MTaPS facilitated a five-day virtual joint technical workshop for both national regulatory authorities on evaluating vaccines and biologics dossiers in December 2021 to build regulatory capacity and strengthen pharmaceutical systems. The workshop included information on the general regulatory framework, an overview of key principles related to evaluation on different modules, and a review of real dossiers to mimic the review that participants will have to conduct when performing their function as evaluators.

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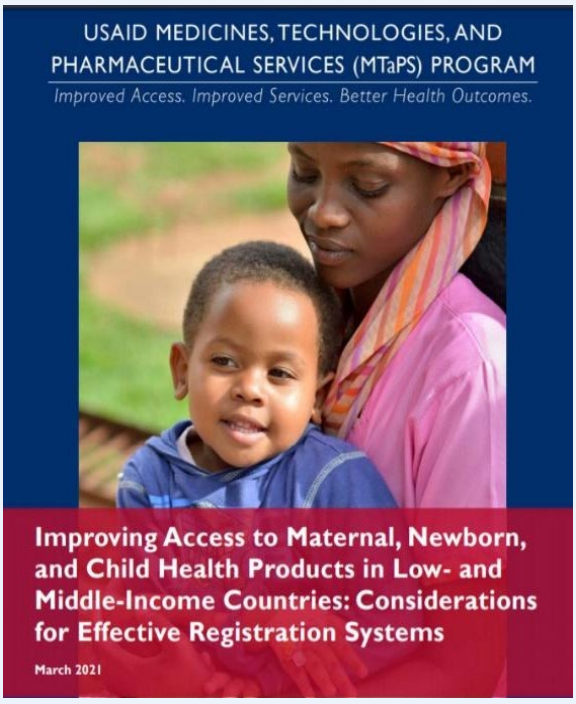
[7] Draft working document: Good reliance practices in regulatory decision-making: high-level principles and recommendations. WHO, 2021.
[8] WHO Global Benchmarking Tool (GBT) for Evaluation of National Regulatory System of Medical Products: Glossary and Definitions Revision V1, version 1, November 2018.
[9] Ibid.
[10] Pharma's Almanac: https://www.pharmasalmanac.com/articles/from-regulatory-convergence-to-global-regulatory-harmonization.

EFFECTIVE REGISTRATION OF MNCH MEDICINES AND PRODUCTS IN LMICS



Difficulties with the registration process can limit the availability of lifesaving, quality-assured MNCH medical products. As a result, innovative products may be slow to enter markets, and quality-assured generic products may not be registered or have their registration renewed, potentially leaving a void that can be filled by sub-standard or falsified products, especially in countries with weak enforcement. MTaPS conducted a study in 2020 to identify challenges in registering MNCH medical products in several USAID-supported countries: **Bangladesh, DRC, Mali, Mozambique, Nepal, Rwanda, Senegal, Tanzania,** and **Uganda**. The study looked at the registration status of 18 essential MNCH tracer medicines and included a review of national policies, laws, and guidelines and interviews with regulators from each country and with medical product manufacturers. Barriers included slow or expensive processes that deterred applications and a registration approach that is not risk based (e.g., lengthy registration procedures for products approved by WHO or well-resourced NMRAs). In response, medicines registration can be improved by shaping the market to promote local manufacturing; streamlining the policy and legal framework; revising the fee system; and reviewing registration requirements, processes, and decisions. A technical report synthesizes the findings from the nine countries and compares them with international standards. In the report, MTaPS describes tools that regulatory authorities can use and 20 actions that they can take to streamline the registration of MNCH products and improve access.

Supporting Licensing Establishments and Regulatory Inspections

Key functions of a national regulatory authority include licensing and inspection of manufacturers, importers, exporters, wholesalers, distributors, pharmacies, and retail outlets. Licensing ensures that medical products conform to acceptable standards of quality, safety, and efficacy, but few countries have guidelines meeting WHO standards, including GMP, Good Storage and Distribution Practice (GSDP), and Good Pharmacy Practice (GPP). Licensing must be complemented by inspections, but countries lack the capacity to conduct them regularly and in accordance with international standards.[11] Toward this end, MTaPS supported the regulatory authorities in **Nepal** to develop and update inspection tools for checking pharmacy owners' compliance with GPP standards and wholesalers' compliance with GSDP standards. MTaPS provides technical assistance to Nepal's DDA to develop guidelines and electronic tools for inspection that cover both the private and public sectors. A team of MTaPS staff and DDA inspectors piloted the tools in two provinces, and it is expected that introducing WHO GPP inspection standards will improve service quality and enhance the number of pharmacies allowed to operate. MTaPS also worked with DDA inspectors to pilot the GSDP inspection tools in three provinces.

To advance automation at **Bangladesh**'s DGDA, MTaPS helped pilot an electronic pharmacy inspection and licensing system at two sites in Dhaka city. The DGDA is leading the national roll-out of the electronic system to review and approve licensing applications across all eight divisions of the country. In **Rwanda,** MTaPS assisted the Rwanda FDA inspectors in developing their knowledge and skills in basic GMP inspections to enable quality inspections of manufacturers, which is required to grant marketing authorization for medical products. In **DRC**, MTaPS supported pharmacist inspectors to conduct field visits to pharmaceutical wholesalers and nongovernmental organizations to inspect whether imported products are registered and authorized for sale. As a result, the regulatory authority identified unregistered or expired

[11] WHO. 2010. Assessment of medicines regulatory systems in sub-Saharan African countries. An overview of findings from 26 assessment reports. Geneva: WHO.

products in the market and alerted wholesalers and importers to renew their registration.

Establishing PV Systems to Improve Patient Safety and Confidence

Monitoring medicines and vaccines under real-life conditions once they enter the market and are in use is critical for determining their true safety and efficacy profile, including the detection of effects not necessarily seen in clinical trials. The activities related to the detection, assessment, understanding, and prevention of adverse effects or other medicine-related problems, such as medication errors, are known collectively as PV. Many LMICs lack functional systems to effectively carry out PV to ensure patient safety and confidence in the health care system.

MTaPS supports LMICs to build or strengthen PV systems guided by the GBT, with the overall goal of supporting countries to achieve maturity levels 3 for PV on the GBT. This approach includes:

- Supporting countries to establish the legal and regulatory framework for PV
- Strengthening governance structures through safety advisory committees
- Improving the demand, supply, and use of country-level safety data for clinical and regulatory decision making
- Strengthening the processes for risk identification and characterization, risk assessment/evaluation, risk minimization, and safety communication
- Helping establish systems to actively monitor the safety of new and/or high-risk medicines and vaccines, including for COVID-19
- Strengthening stakeholder engagement, coordination, and communication

MTaPS conducted a situational analysis in **Nepal** to identify strengths, weaknesses, opportunities, and threats for building a PV program. Nepal's GBT assessment results formed the basis for the PV strategy with a focus on achieving maturity level 3 by strengthening the PV system. MTaPS also provided support in drafting regulations, guidelines, SOPs, and risk communication plans for strengthening the national PV program.

MTaPS is helping **Bangladesh's** DGDA expand its PV program nationally, including building capacity on how to evaluate adverse drug events and report safety data to WHO's database, VigiFlow; causality assessment; and good vigilance practices. MTaPS is also supporting the DGDA to develop good vigilance practice guidelines and update the national PV guideline, including different procedures and plans. For PV of COVID-19 vaccines, MTaPS supported the DGDA in the development of a national PV protocol, tools, and an electronic reporting system. MTaPS is providing technical assistance as part of the safety surveillance cell of the DGDA by facilitating adverse events following immunization (AEFI) evaluation and regulatory decision implementation. MTaPS also supported the government in the development of an active safety surveillance protocol.

In **Kenya**, MTaPS continued to provide technical assistance to the National Vaccine Immunization Program (NVIP) and PPB related to PV and monitoring of AEFI by developing the Targeted Spontaneous Reporting Protocol for COVID-19 Vaccines, the Cohort Event Monitoring Protocol for COVID-19 Vaccines, and a mobile application and Unstructured Supplementary Service Data (USSD)[12] code to support reporting of AEFI through the web-based Kenya Pharmacovigilance Reporting System (PVERs). MTaPS, in collaboration with the NVIP and PPB, conducted trainings of health care providers on PV, targeted spontaneous reporting (TSR), and AEFI investigations, with 236 health care providers trained on TSR and 394 on AEFI investigation. MTaPS also supported a rapid orientation on PV and AEFI monitoring for 1,238 trainers and vaccinators to support multiple COVID-19 vaccine deployments.

In **Mozambique, Rwanda,** and the **Philippines**, MTaPS is supporting the rollout of the Pharmacovigilance Monitoring System (PViMS), a web-based application that identifies signals for monitoring medicine safety covering the entire data collection and analysis process. The Rwanda FDA used PViMS to collect information on adverse effects during a mass campaign for an Ebola vaccine, and MTaPS trained both

[12] USSD is a global system for sending text messages using codes consisting of characters available on a mobile phone.

Rwanda FDA staff and health care service providers from public and private health facilities on PV and how to use the tool. Lessons learned from implementing PViMS will be used to support broadening its use in other countries such as **Bangladesh**, **Burkina Faso,** and **Nepal**.

MTaPS is helping the FDA in the **Philippines** increase the effectiveness of its PV system with the development of a good governance framework, clear structures, and a comprehensive national PV policy that includes both active and spontaneous surveillance. MTaPS conducted a workforce assessment and development plan for PV structures, functions, and skill set requirements that the Department of Health and the FDA are using to identify and address workforce challenges related to institutionalizing the national PV system. In addition, MTaPS conducted a knowledge, attitudes, and practices survey of health practitioners to help identify barriers to monitoring and reporting adverse drug events. With MTaPS' support, the Philippines Department of Health developed a simple monitoring and evaluation tool for PViMS for active drug safety monitoring (aDSM) of second-line TB medicines. MTaPS and the Department of Health conducted supportive supervision on the use of PViMS in reporting adverse events for patients enrolled in aDSM. Proper monitoring of aDSM data reporting through PViMS will help build the safety profile of second-line TB commodities to improve patient safety.

In **Burkina Faso**, MTaPS is working with the NMRA and the National Malaria Control Program to establish and implement an active safety surveillance system for Pyramax following its adoption for the treatment of uncomplicated malaria in October 2021. In **Jordan**, MTaPS is supporting the Pharmacy and Clinical Pharmacy Directorate to strengthen the technical and systematic functions of COVID-19 vaccines safety surveillance. MTaPS in **Rwanda** has continued to support the Rwanda FDA and the Rwanda Biomedical Center to establish and implement an active safety surveillance system for the newly introduced dolutegravir-based antiretroviral regimens and to further strengthen the existing spontaneous safety reporting system. MTaPS has trained 20 health care providers from the implementing health facilities on the protocol, tools, and consent form for active safety surveillance. Supervisory visits and WhatsApp groups provide participants with ongoing support. Continuous monitoring of data quality and participant follow-up indicate the uptake and application of skills acquired during training.

Ensuring Stronger Medicines Regulatory Capacity through Regional Regulatory Harmonization

MTaPS has supported regional regulatory harmonization as an important platform to improve NMRA efficiency. In collaboration with its core partner the African Union Development Agency–New Partnership for Africa's Development (AUDA-NEPAD), MTaPS has worked with several regional economic communities and initiatives, including the African Medicines Regulatory Harmonization Initiative implemented through the East African Community (EAC), Economic Community of West African States (ECOWAS), West African Health Organization (WAHO), and Intergovernmental Authority on Development (IGAD), to harmonize processes, tools, and approaches related to PV regulations, regulatory inspections, and regulatory information management.

For example, MTaPS collaborated with WAHO to develop a regional web-based platform for improving PV systems in the ECOWAS region. The platform will collect and collate regional data and information on PV-related findings from the WHO GBT and aggregate data on PV indicators such as adverse drug events and other reports such as risk management plans. The platform will enable member states to exchange information and experiences and will serve as a one-stop portal at the national and regional levels for monitoring the status of PV systems in Africa. In Asia, MTaPS worked with several regional and other stakeholders to design and implement an online course on GMP. After piloting the course with medical product manufacturers in India, it will be rolled out to other South-East Asia Regulatory Network member states. MTaPS is also developing strategic guidance on digitization of regulatory information management systems at the continental, regional, and national levels in preparation for the operationalization of the African Medicines Agency.

MTaPS has worked closely with the IGAD and EAC Secretariats and respective IGAD/EAC member/partner state focal persons on the medicine regulatory

harmonization agenda. MTaPS provided support to the IGAD and EAC Secretariats to convene quarterly meetings of the PV expert working groups (EWGs) to discuss activity implementation, monitor progress, and support the development and adaptation of regional documents. The EAC PV EWG developed harmonized SOPs to operationalize the EAC PV compendium and drafted a curriculum for in-service training of health care workers on PV. MTaPS supported the IGAD EWG to review and validate a baseline assessment of the PV system in member states and developed a plan for an IGAD-led PV in-service training curriculum, which was adapted from the EAC and other relevant global, regional, or country-specific curricula. The curriculum development was followed by a training of trainers and health workers at cross-border areas.

MTaPS also collaborated with the IGAD and EAC Secretariats to assess local pharmaceutical manufacturers' capacity to adhere to Good Regulatory Practices (GRP). MTaPS engaged local manufacturers to discuss the sustainability of support on regulatory compliance and build capacity on GRP principles, PV, and safety monitoring as well as how to address existing gaps and challenges related to regulatory compliance. MTaPS and the Pharmaceutical Society of Kenya convened an online training with more than 500 participants focused on strengthening regulatory systems and compliance for local manufacturers, PV, and safety monitoring as well as challenges and solutions for ensuring good regulatory compliance. A follow-up professional development session sensitized participants on the importance of compliance to good regulatory practices. A technical exchange network on regulatory compliance was also established to support information sharing and best practices over the long term.

DEVELOPING THE CAPACITY OF REGIONAL CENTERS OF REGULATORY EXCELLENCE TO PERFORM KEY REGULATORY FUNCTIONS

AUDA-NEPAD founded 11 regional centers of regulatory excellence (RCOREs) specializing in different interconnecting themes to better manage knowledge and meet the continent's capacity-building needs in regulatory systems. MTaPS developed a monitoring and evaluation tool to help the RCOREs improve their ability to train officials in medical product regulation. MTaPS has since used the tool to assess the RCOREs' performance, which informed the baseline for routine monitoring and evaluation. In **Kenya**, MTaPS supported training of the PPB Pharmacovigilance Expert Review and Advisory Committee, the national regulatory authority, and the designated RCORE for PV and post-market surveillance in the EAC and IGAD regions to build capacity in using PV data for decision making.

MTaPS, IGAD, and PPB staff providing mentorship at a cross-border community/retail pharmacy. Photo credit: MTaPS Kenya

ENSURING THE QUALITY OF SUB-NATIONAL MEDICAL PRODUCT PROCUREMENT IN MTAPS-SUPPORTED COUNTRIES

Sub-national procurement of medicines and commodities occurs for many reasons—from overall decentralization to averting stock-outs—and MNCH medicines are often procured this way. However, the lack of strict procurement and quality control procedures at the sub-national level makes it challenging to ensure product quality. A robust prequalification scheme for suppliers allows local entities such as health facilities to have confidence in the commodities they procure. Moreover, because quality assurance beyond physical inspection is rarely feasible at the sub-national level, a strong NMRA with robust port of entry and post-market surveillance systems for quality is crucial.

MTaPS interviewed state and regional stakeholders in **Nigeria** and **Tanzania** (and later in **Liberia**) to document the mechanisms they use to guarantee the quality of medical products procured sub-nationally for public-sector health care facilities, identify best practices, and share lessons learned. The redesign of Nigeria's local procurement mechanism, which allows the state central medical store to procure from prequalified vendors, increased the availability of essential medical products, especially at health facilities that can procure directly from the state store. Tanzania's innovative prime vendor scheme also improved availability after the central medical store's fulfillment rate had dipped to 60%; however, facilities' late payments to the prime vendors were threatening its sustainability.

In **Nepal**, MTaPS conducted a mapping in four provinces of decentralized procurement practices to identify problems and opportunities, which were presented at a large stakeholder conference. Based on the findings and informed by best practices from Indonesia, New Zealand, South Africa, and Tanzania, a set of recommendations resulted from the conference deliberations, including establishing a framework agreement to allow aggregation of demand for better pricing and assured quality while maintaining procurement responsibilities at decentralized levels as well as strengthening good storage and distribution practices of wholesalers. MTaPS will help the government consider these recommendations for inclusion in strategy development and planning to improve subnational procurement with the goal of improving access to safe, effective, affordable, and quality-assured medical products for women and children.

Select Country Achievements

MTaPS has supported LMICs in strengthening their regulatory systems to ensure access to safe, effective, affordable, and quality-assured medical products. Selected achievements include:

- In **Rwanda**, MTaPS supported the Rwanda FDA in validating two regulations, eight guidelines, and six SOPs. In addition to addressing critical regulatory gaps, the new regulations and guidelines provide for fast-tracked registration of prioritized categories of medicines, such as antiretrovirals, and the recognition of collaborative assessments with WHO and NMRAs within the EAC. MTaPS also collaborated with the Ministry of Health, the Rwanda FDA, and the National Pharmacy Council to develop accreditation standards for improving pharmaceutical services at private and public hospitals and pharmacies, which were approved in July 2020.
- MTaPS provided technical support to the regulatory authority in **Mozambique** in drafting regulations and guidelines for medical products registration, regulatory inspections, licensing of medical product establishments, PV, pharmacy practice, and price control to enable the country to implement its 2017 medicine law and address important gaps identified in the 2018 GBT assessment. At the request of the ANARME, IP, MTaPS helped to finalize the Regulation on the Distribution, Import, and Export of Medical Products, which further regulates the pharmaceutical sector by securing the pharmaceutical supply chain to ensure the quality and safety of medical products from manufacture through distribution channels to the end user. Additionally, assessors from the ANARME, IP, were trained in assessing bioequivalence studies to facilitate their evaluation of oral generic medicines.
- As part of MTaPS' support in establishing a QMS in **Nepal**, the DDA drafted GPP and GSDP guidelines. In collaboration with DDA inspectors and stakeholders, MTaPS revised and completed a pilot test of the electronic inspection tool for GPP inspections. Introduction of WHO GPP and GSDP inspections will improve service provision, patient care, and quality assurance of products that are procured at different levels of the system. In addition, with MTaPS' support Nepal has completed the WHO recommended competency mapping of the DDA with a training plan as per the recommendations.
- In **Bangladesh**, MTaPS supported the development of an electronic inspection and

licensing system for retail drug outlets. The system has been accepted by the DGDA for piloting in two sub-districts, followed by a planned countrywide scale-up. Overall, the inspection and licensing system will help optimize pharmacy inspection and licensing to provide better regulatory and quality outcomes from the DGDA in a cost-effective way.

- In **Kenya**, MTaPS supported the development of a mobile application and USSD code to support reporting of AEFI and adverse events through the PVERs. The mobile application and USSD will also support reporting of sub-standard falsified products, medication errors, and adverse events from medical devices and blood products.

Lessons Learned

- Stakeholder engagement, coordination among government institutions, and a clear roadmap for development are important steps in establishing an effective regulatory framework for medical products. As an example, in **Rwanda** and **Mozambique**, MTaPS worked in close collaboration with a range of government stakeholders to support national regulatory authorities in developing concrete and strategic action plans for strengthening regulatory systems and streamlining registration. Despite being an autonomous organization, coordination among the Rwanda FDA and other government institutions such as the National Pharmacy Council, Rwanda Biomedical Center, Ministry of Health, and Rwanda Medical and Dental Council was critical in aligning technical requirements in the development process of medical product regulations.
- Updating laws and regulations in line with international standards can help support countries in building efficient regulatory systems and improving access to quality-assured medical products. In **Mozambique**, MTaPS supported the ANARME, IP, to draft the Regulation on the Distribution, Import, and Export of Medical Products to be in compliance with WHO's Good Distribution Practices and to ensure that imported and distributed medical products meet safety and quality standards.
- While opportunities to speed up registration processes exist, it is essential to address the lack of legal provisions of national regulatory authorities to use mechanisms such as the recognition of regulatory decisions made by stringent regulatory authorities or reference authorities. MTaPS worked with the regulatory authority in **Rwanda** to develop regulations for registration of medical products that include provision for reliance on stringent regulatory or reference authorities. As a result, the Rwanda FDA was able to expedite the registration of 12 medical products through reliance on stringent regulatory authorities. In **Nepal**, the revision of the drug law includes mechanisms to allow reliance on regulatory decisions made by other reference authorities.
- Fostering regional and international collaboration through reliance, recognition, and harmonization improves regulatory efficiency. While harmonizing medicines regulation can take a long time, regional convergence can be achieved through information exchange, work sharing, and the use of common technical guidance, which can advance larger-scale harmonization efforts. MTaPS' engagement with well-established organizations at the regional level provides an important platform to implement interventions that move regulatory harmonization forward. For example, exchange of information and learnings among the **IGAD/EAC** has supported the harmonization of PV tools and processes (e.g., PV curriculum, SOPs) for monitoring the safety of medical products.
- Prioritizing consultation with key stakeholders promotes inclusion in the activity design process. MTaPS consulted with the 15 **ECOWAS** countries to design a survey on PV harmonization; the survey produced rich insights into what data countries are willing to share and in which areas countries need PV support, such as basic data collection and signal generation and assessment. The survey showed that countries are willing to share aggregated data related to their PV work and to collaborate and learn from one another on how to strengthen their individual PV systems.

- Establishing and implementing a robust QMS ensures that NMRAs follow a consistent methodology for carrying out key regulatory functions. MTaPS' experience from implementing QMS in **Mozambique, Rwanda, Bangladesh,** and **Nepal** has demonstrated that high-level commitment and a well-supported and dedicated quality team is essential for driving the process.

Conclusion

MTaPS recognizes that a regulatory system's ultimate purpose is to provide access to safe, effective, affordable, and quality-assured medical products to citizens. MTaPS has supported LMICs in strengthening regulatory systems through a systematic approach that assesses the problem, prioritizes key actions, supports implementation, and re-evaluates for continuous improvement. As a result, many MTaPS-supported LMICs have made progress on the regulatory system maturity scale, as measured by the WHO GBT. Continued investment and political commitment is needed to sustain these gains.

Publications

MTaPS publications aim to shape decision maker thinking on developing approaches to building and maintaining regulatory systems in LMICs. More information and resources are available on the regulatory systems and pharmacovigilance sections of the MTaPS website.

Guzman J, O'Connell E, Kikule K, et al. The WHO Global Benchmarking Tool: a game changer for strengthening national regulatory capacity. BMJ Global Health 2020;5:e003181

Twesigye G, Hafner T, Guzman J. Making the investment case for national regulatory authorities. J Pharm Policy and Practice 14, 16 (2021). https://doi.org/10.1186/s40545-021-00299-7

Technical Brief: Improving Access to MNCH Medical Products: Considerations for Effective Registration Systems

Fact sheet: Supporting Pharmaceutical Regulatory Systems

Fact sheet: Strengthening Medicines Safety: Pharmacovigilance Systems

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