

KEY POINTS

- Effective regulation and governance of the pharmaceutical sector is key to effective delivery of healthcare. In the Greater Mekong Subregion (GMS), substandard or falsified medicines detected in the supply chain are fueling resistance to artemisinin combination therapies, the most effective treatment for falciparum malaria. This resistance is undermining the region's drive to eliminate malaria as a public health threat by 2030.
- National regulatory agencies (NRAs), who are the gatekeepers of the medical product supply chain, lack the resources needed for effective regulation within their respective jurisdictions.
- International collaboration and the implementation of common standards and activities will help the NRAs increase their capacity and improve regulatory effectiveness, leading to better public health outcomes.
- The Asian Development Bank (ADB) engaged the Centre of Regulatory Excellence (CoRE) at the Duke–National University of Singapore Medical School to assess the capacity gaps in the GMS NRAs. To address the identified needs, CoRE worked with GMS NRAs to develop national capacity development plans and, by comparison of needs, the regional roadmap for regulatory systems strengthening in the GMS.
- To foster ongoing regional collaboration, the Asia Pacific Regional Regulatory Partnership for Malaria Elimination (RRPME) has been established in partnership with ADB, to engage regulatory stakeholders and technical partners to support coordination of regulatory strengthening activities.

Strong Regulation of Medical Products: Cornerstone of Public Health and Regional Health Security

Susann Roth
Senior Social Development Specialist
Sustainable Development
and Climate Change Department
Asian Development Bank

Sonalini Khetrupal
Health Specialist
Sustainable Development and Climate
Change Department
Asian Development Bank

Douglas Ball
Regulatory Specialist

Valerio Reggi
Regulatory Specialist

Jane Parry
Specialist Public Health Writer

GATEKEEPERS OF THE MEDICAL PRODUCT SUPPLY CHAIN

National regulatory agencies (NRAs) are the gatekeepers of the supply chain of medical products such as pharmaceuticals and medical devices. It is through registration with an NRA that a manufacturer brings products to market. Post-marketing surveillance of how those products perform and impact patient safety—including how quality is maintained in storage and distribution, and adverse events associated with their use—also falls under the agency's remit, as does inspection of manufacturing facilities and regulation of product promotion and advertising. At the same time, the value chain for medical products is becoming increasingly globalized. In pharmaceutical manufacturing, for example, active ingredients may be sourced from multiple countries for medicines production in another, before being globally distributed. A weakness in one part of the supply chain can have adverse consequences for patients thousands of miles away.

When the medical products gatekeeper is weak the population is vulnerable to harm from unregulated supplies, including substandard and falsified (“fake”) medicines and devices, often with links to organized crime.¹ This issue affects many countries: the World Health Organization (WHO) estimates that only 30% of NRAs worldwide

¹ World Health Organization (WHO). 2017. *WHO Global Surveillance and Monitoring System for Substandard and Falsified Medical Products*. Geneva.

are strong enough to provide adequate oversight of the medical product supply chain.² In Asia and the Pacific, most NRAs do not have sufficient infrastructure and human capital to perform their gatekeeper role effectively.³

Disease control and prevention, already a challenging task in resource-constrained environments, is adversely affected by weak regulation. For example, in Asia and the Pacific as a whole, and the Greater Mekong Subregion (GMS) in particular, NRAs are not yet well equipped to support the elimination of malaria, a goal that governments across the region are committed to achieving by 2030.⁴ Unregulated medicines in the supply chain, including fake and substandard medicines, are fueling resistance to artemisinin combination therapies, the key and most effective treatment for malaria. This is undermining the region's drive to achieve elimination of malaria as a public health threat by 2030. Inadequate resources also impact NRAs' capacity to provide fast access to new medicines of high public health priority, such as antimalarial medicines.

GLOBAL TREND TOWARD CONVERGENCE AND MUTUAL RELIANCE

It is not realistic to expect all NRAs to develop the same capacity to assess medical products, provide reliable product information and effectively implement post-approval surveillance. WHO and well-resourced NRAs are promoting a movement towards convergence of regulatory practices and reliance on each other's assessments and policies. NRAs are being encouraged and supported to move towards common standards for medical product manufacturing processes and regulatory assessment criteria, so that they can rely on each other's product registration. Thus, criteria and reports used in one jurisdiction to deem medical products fit for entry into the market can then be accepted by another, without the need to duplicate a large part of the assessment work that underpins the registration process.

For countries to engage with their counterparts to work towards convergence and reliance, they first have to know their own state of play, identify the specific gaps in their registration and surveillance systems and lay out a road map to address them. In the GMS, understanding the state of NRAs and working with them to improve their operations was a key component of the

Asia Development Bank (ADB) Regional Malaria and Other Communicable Disease Threats Trust Fund (RMTF). From October 2015 to December 2017, ADB engaged the Duke-National University of Singapore Medical School's Centre of Regulatory Excellence (CoRE) to address this gap in knowledge and work with GMS countries to strengthen their regulatory systems, and strengthen the countries' ability to eliminate malaria.⁵

MAPPING REGULATORS' GAPS AND NEEDS

CoRE developed a regulatory system profiling instrument (RSPI) (Box 1), using available literature and existing instruments including the WHO Global Benchmarking Tool, to map NRA needs and capacity gaps in the GMS.⁶

When NRAs were assessed using the RSPI, common issues and gaps across the countries surveyed emerged. In terms of funding and resources, NRAs have inadequate human capital, information and communication technology (ICT) infrastructure, and quality laboratory services for testing of medicines and medical devices. Common gaps in process governance were quality management systems, inadequate management of conflicts of interest within management, and suboptimal processes for ensuring transparency, accountability and communication. In order to develop staff and improve the competency of the NRA, more formal, structured training is needed, together with diversification of skill sets, greater exposure to best practice from other jurisdictions, and greater alignment with global standards and best practice.

These findings concur with existing evidence on the state of NRAs in the region, which indicates that human resource constraints are exacerbated by insufficient recognition for the skill set involved, lack of exposure to best practices in regulation, and insufficient knowledge to advocate for greater government investment in regulation.⁷ NRAs are typically perceived as set apart from the public health system, rather than central to it. This ignores the fact that the regulation of medical products, if properly implemented, protects public health and can generate data that are of integral value to health care delivery systems. In the absence of effective international collaboration, registration of the same product in neighbouring countries is burdened with unnecessary

² WHO. 2018. *Towards Access 2030*. WHO Essential Medicines & Health Products Annual Report 2017. Geneva. <http://apps.who.int/iris/bitstream/handle/10665/272972/WHO-EMP-2018.01-eng.pdf?ua=1>.

³ John C. W. Lim. 2018. *Strengthening Health Products Regulatory Systems to Enhance Access to Quality Health Products in the Asia-Pacific*. *Therapeutic Innovation & Regulatory Science*, 12 April. California: SAGE Publications.

⁴ Ministers of Health and Delegates at the High-Level Meeting to Accelerate Elimination of Malaria in the Greater Mekong Subregion. 2017. *Ministerial Call for Action to Eliminate Malaria in the Greater Mekong Subregion before 2030*. Nay Pyi Taw. <http://malariaweek.org/upload/day-5/GMS%20CFA%20Dec%208%20rev.pdf>.

⁵ Duke-NUS Medical School Centre of Regulatory Excellence (CoRE). 2016. *Asian Development Bank (ADB) Project*. Singapore. <https://www.duke-nus.edu.sg/core/page/asian-development-bank-adb-project>.

⁶ WHO. 2017. *WHO Global Benchmarking Tool for Evaluation of National Regulatory Systems*. Geneva. <http://www.who.int/medicines/regulation/benchmarking-tool/en/>.

⁷ Leong J, Vogel S, Lim J. Regulatory gaps—Industry's perspectives on Asia's regulatory authorities. Paper presented at: DIA 51st Annual Meeting: 14–18 June 2015; Washington, D.C.

Box 1: The Regulatory System Profiling Instrument

The regulatory system profiling instrument (RSPI) comprises a set of questionnaires, to be completed by the national regulatory agency in a process of self-assessment. The findings are validated by in-country interviews, and supplemented with the results of meetings and group discussions with stakeholders in the regulatory system, including industry and private sector players, the Ministry of Health, and academia.

Designed to be shorter and quicker to use than the World Health Organization (WHO) tool, the RSPI takes only three days to administer and complete. It is largely self-reported, unlike the WHO tool, which requires some documentary verification. However, it uses the same domains as the WHO tool in assessing needs across the following regulatory functions:

- product registration (assessing and authorising products to be on the market based on evidence of efficacy, safety and quality);
- licensing of medical product establishments (assessing and authorising premises where medical products may be manufactured, distributed, and sold);
- inspections of medical product establishments (on-going inspections of medical product establishments to ensure they maintain standards);
- post-marketing surveillance (sampling samples on the market to ensure they are still of good quality and from licensed sources);
- medical product vigilance and pharmacovigilance (assessing the ongoing safety of medical products on the market);
- control of promotion and advertising (overseeing and controlling the means that companies use to promote their medical products); and
- regulatory quality control testing (laboratory support to test the quality of medical products during market authorization and post-marketing surveillance).

complications for manufacturers, because different NRAs tend to repeat assessments and inspections already performed by others and tend to impose country-specific requirements, despite the availability of regional regulatory guidelines, such as the Association of Southeast Asia Nations (ASEAN) Common Technical Dossier and Requirements.⁸

A ROAD MAP FOR IMPROVING REGULATION

To address these gaps, CoRE worked with NRAs in the GMS to develop national capacity development plans, and, following a comparison of needs, the Regional Roadmap for Regulatory Systems Strengthening in the GMS, to address common priorities across the countries (Figure 1). Technical partners and funding agencies can use this to identify which of the needs fall within their interests and ensure that they are not overlapping with activities of other partners, whilst the NRAs can use the plans to inform their strategic development, discuss their needs with technical agencies and develop proposals for funding. Nationally, as well as calling for regulatory training, the roadmap takes a holistic approach to regulatory systems strengthening, by promoting better organizational governance and communication with external stakeholders. Regionally, the roadmap enables GMS NRAs and other stakeholders to track wider goals for the region and encourage ongoing progress towards enhanced regulatory capacity.

The Regional Roadmap focuses on what is needed for malaria elimination, but it also serves much bigger, over-arching goals of universal health coverage (UHC) and health systems strengthening. The roadmap has three priorities. The first is more effective regulatory processes, and implementing quality management systems. The second is new frameworks to enhance regulatory effectiveness and efficiency (employing fast-track processes for medical products of higher public health need and adopting regulatory work-sharing and joint assessments among NRAs). The third is stronger post-market surveillance and control (through risk-based approaches, improved vigilance activities, and multi-stakeholder collaboration to prevent, detect, and remove substandard and falsified medical products). All of these support UHC and stronger health systems overall, and all require investment in NRAs, especially in human resources and ICT.

ADB AND STRONGER REGULATORY SYSTEMS

ADB, as part of its remit to invest in the health sector, continues to support its developing member countries to improve pharmaceutical regulation and strengthen their health systems. Under the umbrella of the RMTF, from 2013 to 2018, ADB supported regional capacity development for medical products regulation, including collaboration with WHO to support country reporting into the WHO global database of substandard and

⁸ Asia Partnership Conference of Pharmaceutical Associations Regulations and Approvals Expert Working Group. 2014. *Identification and Clarification of the Differences in Regulatory Requirements between Asian Economies*. Analysis report. Tokyo. 10 April; Pharmaceutical Product Development. 2012. *Establishing a Regulatory Drug Development Strategy for Asia Pacific*. White paper. North Carolina. July.

Figure 1: Regional Roadmap for Regulatory System Strengthening in the Greater Mekong Subregion



IT = information technology.
Source: Authors.

falsified medical products. ADB also worked closely with the Myanmar NRA to transform its regulatory system and process (Box 2). This work by ADB in Myanmar serves as a useful case study in how ICT and training can transform an NRA.

ADB has also invested in numerous projects covering integrated information systems for better quality control of the supply chain, improved cross-border coordination, and collaboration between border control, customs and regulatory agencies. In the broader area of ICT in the health sector, ADB has fostered convergence of digital health standards to comply with international information standards, which is crucial for cross-border collaboration and mutual reliance between regulators. ADB's efforts benefited from working with countries through a multi-dimensional trust fund with a clear remit to tackle malaria and other communicable diseases. The trust fund structure enabled regional, rather than just national, information gathering, and accelerated joint action between national counterparts toward a common goal. It was a catalyst for sustainable results, which ADB is taking forward through its other health-sector projects.

LESSONS LEARNED: HOW TO STRENGTHEN MEDICAL PRODUCT REGULATION

NRAs should be a cornerstone of UHC, but for that goal to be realized, the agencies must be better integrated into the public health system, and be seen by other players as relevant agencies with unique skills and a valuable data set that can be shared for the benefit of other parts of the health system. NRAs need to invest more in people, processes, technology, and communication, and ADB's experience in the medical regulatory environment points to several key lessons learned in how this can be achieved. First, regional and national digital health standards must be in place so that countries can share data. Second, NRAs need to introduce an integrated regulatory information management system (IRIMS) (Box 3), as was implemented in Myanmar. Third, NRAs are a key part of the global value chain and should be empowered to ensure that this value chain properly serves the population (Figure 2), supports UHC, and promotes regional health security.

Box 2: Moving Medical Product Regulation Online in Myanmar

In 2017, under the Asian Development Bank (ADB) Regional Malaria and Other Communicable Disease Threats Trust Fund, an ADB consultant was embedded in the Food and Drug Administration (FDA), Myanmar, the country's national regulatory agency. At that time, Myanmar's medical product registration process relied on a cumbersome, paper-based registration application with some data input into a scanty Excel file. This system was taxing the human resource capacity of the FDA to the limit.

Being embedded within the FDA, the consultant was able not only to develop a deep understanding of how the current system operated, but also to build trust with staff. These proved to be valuable assets when it came time to assist the FDA in addressing its priority needs, and move away from a paper-based process to a fully online system. The consultant was able to secure buy-in for the changes he proposed, and by mid-2018, an online-only product registration application process was in place, including the training of private sector applicants. As part of the process of establishing an integrated regulatory information management system, the FDA's online databases were linked to those for the management of facility inspections and of quality control laboratories.

Now the national quality control laboratory and inspectors are able to link to an online database to get the information they need from medicine registration dossiers. Inspectors can use a tablet-based system to connect to the central registration database and find out which products are registered, and to directly upload images and

videos of the facilities they are inspecting, along with the inspection reports and follow-up actions.

This online regulatory information management system was developed with open-source software. As all source code is made available to the FDA, hosting the system does not require ownership of a data center and will entail an annual maintenance cost of less than \$20,000 after ADB support ends.

The FDA, working with the consultant, also reviewed its list of approved products and compared the listed products with those on the lists used by reference authorities—the European Medicines Agency and the regulatory agencies of Australia, Canada, the United Kingdom, and the United States. The process revealed medicines not registered in any of these reference countries, as well as banned and obsolete products. After this review, the online medicine registration system was set up to automatically trigger an alert whenever products with banned or obsolete active ingredients were submitted for registration. Product information documents, which describe a medicine's indications, contraindications, dosages, and warnings, will also rely on reference texts obtained from Australia's Therapeutic Goods Administration and the British National Formulary.

Although such a major change is usually simpler to bring about in a setting like Myanmar, where no complex system is in place, the impact of the ADB project is also being felt elsewhere in Asia. The project attracted the interest of the NRAs in Cambodia, Thailand, the Philippines, and Viet Nam.

REGIONAL REGULATORY PARTNERSHIP FOR MALARIA ELIMINATION IN ASIA AND THE PACIFIC

Achieving these goals demands stakeholder collaboration, particularly between donor agencies, bilateral lenders, and other financing institutions, to ensure that investments in regulatory systems strengthening achieve the maximum possible impact and do not create overlapping and increased demands on the NRA. To foster ongoing regional collaboration, the Asia Pacific Regional Regulatory Partnership for Malaria Elimination (RRPME) has been established to engage the support of regulatory stakeholders and

technical partners in regulatory capacity building. The RRPME brings together ADB, the Asia Pacific Leaders Malaria Alliance, CoRE, national stakeholders, and regulators from outside the region, including Australia's Therapeutic Goods Administration as a founding member, the United States Pharmacopeial Convention (USP), and WHO, and its work plan incorporates the recommendations of the GMS regional road map. However, the RRPME does not only cater to the GMS. Indonesia and Malaysia have also taken part, as have India and Papua New Guinea. Their common goal is to help eliminate malaria by building regulatory capacity and ensuring that further needs assessment and training can be more specific and focused.

Box 3: Integrated Regulatory Information Management System

An integrated regulatory information management system (IRIMS) is a digital platform that processes, stores, retrieves, and shares information about regulatory activities. It enables effective information exchange, coordination, and implementation across all key medicine regulatory functions, through a permanently established connection. These functions include product registration; company licensing; quality testing; inspection of manufacturers, wholesalers, and retail outlets; monitoring of importations and manufacturing output; and post-marketing monitoring of the quality and safety of medicines. An example of an IRIMS is Myanmar’s online registration database linked to quality control testing and inspection of retail outlets. Key to a successful IRIMS is standardization of terminology as well as the establishment of a unique code (or registration number) assigned to each individual pack size and type for each authorized product. The same approach is used for products authorized for marketing and products admitted through special access schemes such as donations, disease control programs, or compassionate-use programs. The starting point of an IRIMS is invariably the medicine registration database. If this is properly set up, all the other regulatory functions will be able to link to it, obtain data, and complement the database with their own data and output (see figure).

The key benefits of an IRIMS are:

- enhanced capacity to protect public health through faster exchange of information and more efficient regulatory work;
- reduced staff costs, thanks to automation of repetitive tasks such as preparation of letters, certificates, and internal reports;
- increased visibility and credibility of the regulatory authority within the public health community;
- increased capacity to filter out products with inadequate safety, efficacy, or quality documentation; and
- increased capacity to support the work of other government institutions (such as pharmaceutical procurement and distribution programs) by providing timely and reliable data to inform choices and decisions.

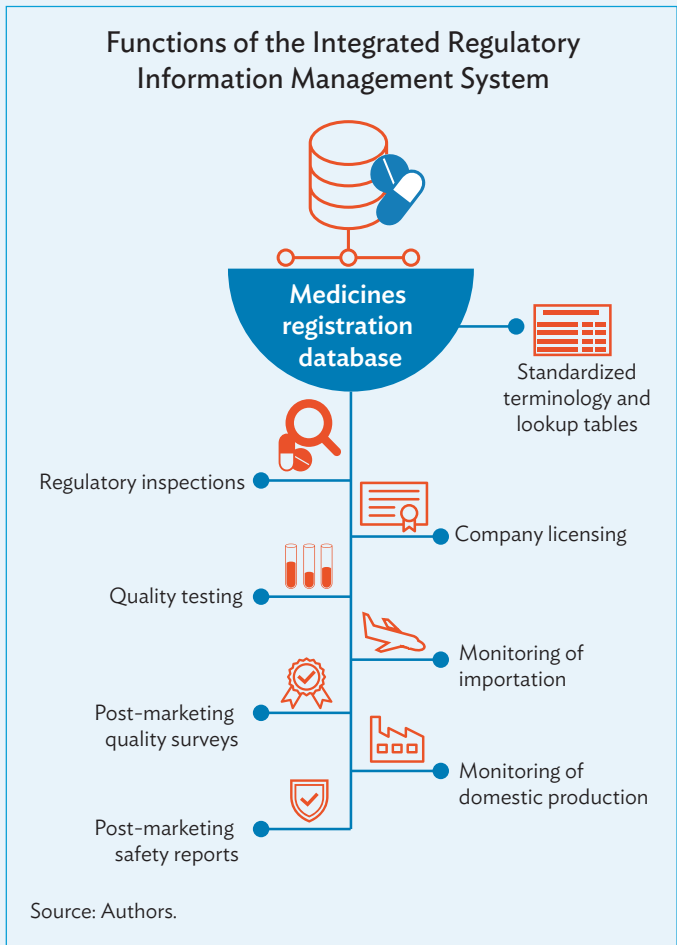
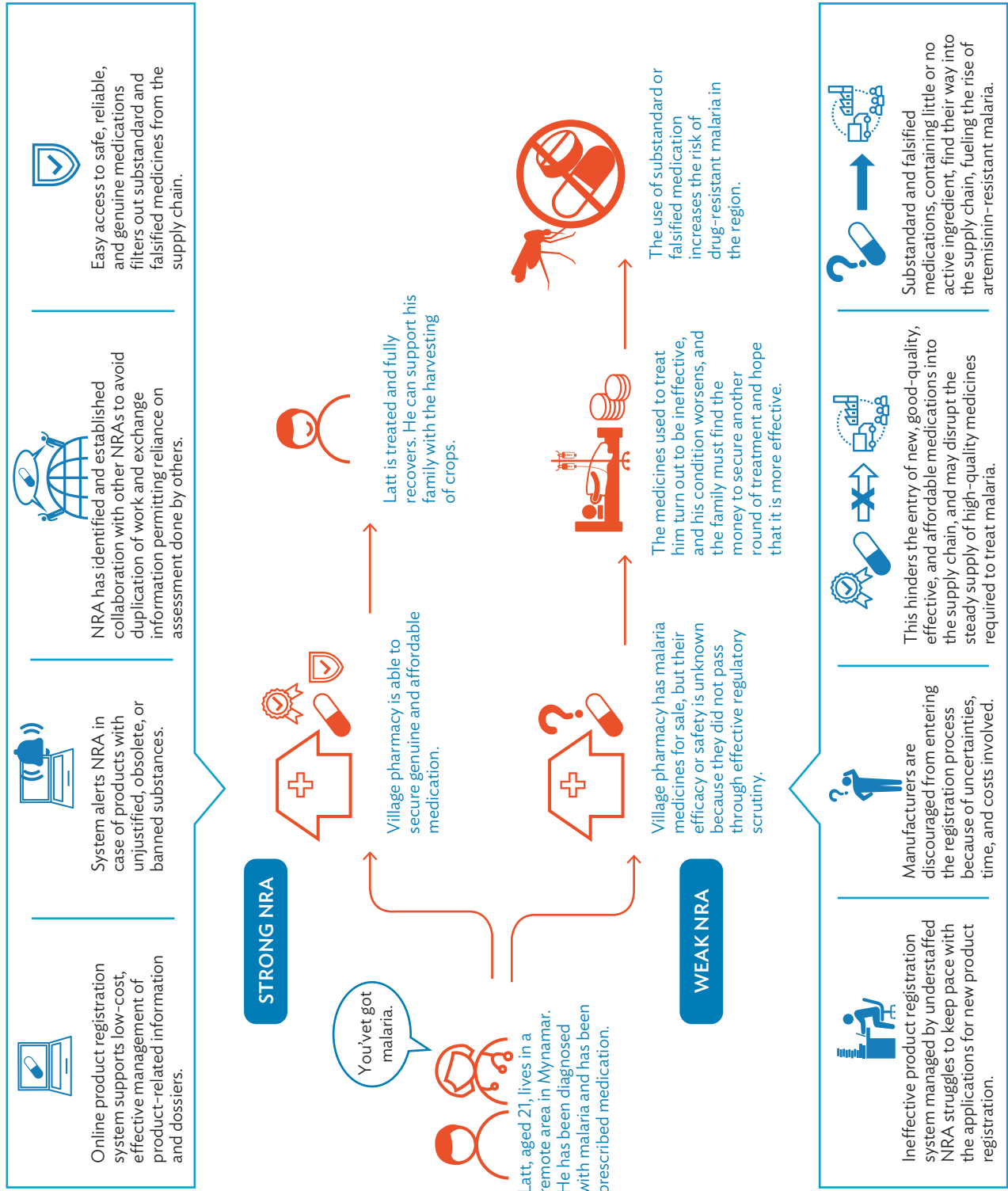


Figure 2: The Human Face of Medical Product Regulation



NRA = national regulatory agency.
Source: Authors.

About the Asian Development Bank

ADB is committed to achieving a prosperous, inclusive, resilient, and sustainable Asia and the Pacific, while sustaining its efforts to eradicate extreme poverty. Established in 1966, it is owned by 67 members—48 from the region. Its main instruments for helping its developing member countries are policy dialogue, loans, equity investments, guarantees, grants, and technical assistance.

ADB Briefs are based on papers or notes prepared by ADB staff and their resource persons. The series is designed to provide concise, nontechnical accounts of policy issues of topical interest, with a view to facilitating informed debate. The Department of Communications administers the series.

The views expressed in this publication are those of the authors and do not necessarily reflect the views and policies of ADB or its Board of Governors or the governments they represent. ADB encourages printing or copying information exclusively for personal and noncommercial use with proper acknowledgment of ADB. Users are restricted from reselling, redistributing, or creating derivative works for commercial purposes without the express, written consent of ADB.

Asian Development Bank
6 ADB Avenue, Mandaluyong City
1550 Metro Manila, Philippines
Tel +63 2 632 4444
Fax +63 2 636 2444

www.adb.org/publications/series/adb-briefs



Creative Commons Attribution 3.0 IGO license (CC BY 3.0 IGO)

© 2018 ADB. The CC license does not apply to non-ADB copyright materials in this publication.

<https://www.adb.org/terms-use#openaccess> <http://www.adb.org/publications/corrigenda> pubsmarketing@adb.org