KEY POINTS

• Medicines regulation should ensure that only products of proven quality, safety, and efficacy are on the market. In developing member countries in Asia and the Pacific a large proportion of health care is paid for out-of-pocket and low quality, ineffective medicines are expensive for both patients and health systems.

• Weak regulatory agencies threaten national and regional health security. Stronger regulatory capacity has system-wide public and private sector benefits due to improved treatment outcomes, lower treatment costs, reduced antimicrobial resistance, lower availability of substandard and counterfeit medical products, and faster marketing authorization applications for new medicines.

• In the Association of Southeast Asian Nations (ASEAN) region this is particularly relevant where development of resistance to artemisinin-containing combination therapies threatens to derail malaria elimination efforts.

• National medicines regulatory authorities (NMRAs) vary in capacity and need to work together to provide effective regulation and maximize use of resources. Regulatory collaboration and harmonization can improve operational efficiency and speed up market access for medicines of public health importance and new, advanced therapies.

• Donors and governments acknowledge the importance of regulatory strengthening and convergence. Regional initiatives in Asia and the Pacific can help to strengthen those NMRAs with lower capacity, with harmonization in the longer term.

BETTER REGULATION OF MEDICINES MEANS STRONGER REGIONAL HEALTH SECURITY

STRENGTHENING AND CONVERGENCE OF NATIONAL REGULATORY AGENCIES HAS BENEFITS BEYOND COUNTRY BORDERS

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Target audiences:
• Nonregulatory experts
• Ministry of Health decision makers
• Ministry of Finance experts
• ADB staff

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NATIONAL MEDICINES REGULATORY AUTHORITIES: PROTECTING PUBLIC HEALTH

Medicines are safely used every day to treat diseases, but there have been enough adverse events and even large-scale human disasters over the years to prove that medicines also carry risks. Daily adverse events may or may not be reported but evidence of harm can lead to regulatory change. It is often high-profile tragedies that bring about stricter regulation. National medicines regulatory authorities (NMRAs), such as the US Food and Drug Administration (FDA) developed from the initial moves to control the development and sale of medicines following such incidents. This concept subsequently became established in most developed countries and it is a form of regulation that differentiates medicines from other consumer goods.

The three common pillars of medicines regulation are quality, safety, and efficacy (Figure 1). Only medicines that can satisfy these three criteria should be allowed onto the market. Companies wishing to sell a pharmaceutical or other regulated health care commodity are required to submit evidence in the form of a dossier to the NMRA that their product meets the requirements of each of these criteria for marketing authorization to be granted.

Figure 1: The Three Pillars of Medicines Regulation

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**Quality**

Product produced consistently to the same standards and specifications:

- Contains the correct amount of active ingredients
- Maintains quality through the shelf life of the product
- Designed to release its active ingredients appropriately
- Maintains its integrity and does not allow the growth of any harmful ingredients or bacteria.

**Safety**

Evidence from clinical trials of favorable risk-benefit profile:

- Preclinical testing in animals and culture models suggest safe and not carcinogenic
- Early clinical studies in human volunteers show short-term safety; the absorption, distribution, metabolism and excretion of the drug is measured to “inform dosing”
- Later clinical trials show safety and side effects when the drug is formulated and tested in actual patients for longer periods of time.

**Efficacy**

Pre-marketing requirements:

- Demonstrate that the medicinal product is effective (more effective than placebo; at least as effective as current standard of care) for the intended use
- Show efficacy in relatively large-scale clinical trials using patients for whom the medicine is intended to be marketed, for long periods of time, using appropriate end points.

Post-marketing:

- Inspections to ensure manufacturers maintain Good Manufacturing Practice (GMP) and that distributors and retailer manage and store products appropriately
- Reporting of product defects and periodic quality control testing of random samples from the market

Post-marketing:

- Reporting system for side effects and adverse events and updating safety profiles (pharmacovigilance)

Post-marketing:

- Reporting system for product defects and treatment failures

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2 Two such disasters—the mass poisoning due to diethylene glycol (antifreeze) as a solvent in a sulfanilamide antibiotic elixir in the US in 1937 and the limb malformations resulting from the use of thalidomide as an anti-nausea agent during pregnancy in Europe and other countries in the late 1950s and early 1960s—both led to greater oversight of the safety of medicines. Tragedies still happen in the face of poor regulatory oversight, such as the deaths of over 151 people from contaminated heart medicines in Lahore in 2012.
To ensure that medicines and other health products meet these criteria and to support their appropriate use, NMRAs have a number of recognized functions. These include licensing, control and monitoring of the manufacture, import, export, distribution, promotion, and advertising of medicines; assessing the safety, efficacy, and quality of medicines; and inspection and surveillance along the entire supply chain. NMRAs collect and analyze post-marketing data on adverse reactions, provide independent information on medicines, and approve and monitor clinical trials.3

Appropriate medicines regulation and a functioning NMRA help to ensure that quality, safe, and effective medicines are available on the market and are appropriately promoted. As the development, manufacture, and trade of medicines has become global, there is a clearly recognized need for collaboration among regulatory authorities.

There have been enough adverse events and even large-scale human disasters over the years to prove that medicines also carry risks.

**WEAK REGULATORY AGENCIES THREATEN NATIONAL AND REGIONAL HEALTH SECURITY**

While the basic tenets and functions of medicines regulation are common, the resources and capabilities of NMRAs can vary widely. The US FDA is well resourced with over 14,000 staff, including more than 3,000 in its Center for Drug Evaluation and Research alone. Smaller regulators in low-income countries must make do with far less firepower — approximately 20 staff in the Lao People’s Democratic Republic for example, who also have other duties in addition to regulation—and yet may still have to regulate hundreds of local and international manufacturers and thousands of domestic pharmaceutical establishments. In addition to suboptimal financing, political interference and lack of transparency are among the many possible causes of a dysfunctional NMRA (Figure 2).

A weak or poorly functioning NMRA can impact on public health goals as well as private investment and domestic industrial objectives. Poor capacity can lead to long delays in the assessment of marketing authorization applications for medicines and

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health products. This can deter pharmaceutical companies from marketing their products in the country and also foster corruption as a means to bypass or to benefit from the bureaucratic delays.

Conversely, a weak regulatory environment that does not act as an effective barrier, promotes the manufacture and sale of low-quality, potentially ineffective and unsafe medicines. These include counterfeit medicines, which adversely affect public health as well as discouraging quality manufacturers due to the competition of cheaper (and often poorer quality) products and potential risks to their brand (Figure 3).

Poor capacity can lead to long delays in the assessment of marketing authorization applications.

Figure 3: Effects of Weak NMRA Capacity and Function

Area of Regulatory Weakness

Circulation of low-quality medicines and inconsistent enforcement of manufacturing standards

Weak licensing process for businesses and products

Inadequate reporting of adverse events and inadequate recall mechanism

Sale of prescription medicines over the counter

Inadequate information provided with medicines

Unethical marketing practices

Lack of oversight for clinical trials

Potential Systemic Effect

Lack of confidence in medicine quality and preference for more expensive branded or imported medicines

Fewer products on the market, potential delays in access to medicines

Reliance on adverse event data from developed countries, with potentially disastrous health impacts

Risk of irrational use of a medicine or use in cases where it is contraindicated, with negative impacts on individual’s and public’s health e.g. drug resistance, adverse reactions

Overuse and inappropriate use of certain medicines

Reduction of in-country clinical trials by pharmaceutical companies and trial data that is unacceptable to regulatory authorities; harm to patients

The potential adverse consequences of NMRAs with limited capacity underline the need for countries and development partners to support their strengthening. In the Association of Southeast Asian Nations (ASEAN) region this is particularly relevant with the development of resistance to key antimalarial medicines. Resistance to artemisinin-containing combination therapies (ACTs) threatens to derail malaria elimination efforts. Should the resistance spread to Africa it could set back the recent gains made against the disease. Proven ineffective medicines and substandard and counterfeit products remain on the market in Asia and the Pacific and regulatory bureaucracy can delay access to innovative therapies that may be developed. Tuberculosis, hepatitis, and other communicable and noncommunicable diseases face similar challenges.

The quality of medicines on the market can be improved and substandard and counterfeit products identified and removed through a number of actions. These include:

- streamlining market authorization processes
- developing transparent procedures for marketing authorization and to review and monitor quality of products
- collaborating and worksharing with other NMRAs, with reliance on their reports
- increasing the NMRA workforce and retaining trained personnel
- raising the standards of Good Manufacturing Practice applied to domestic and international manufacturers
- developing risk-based inspection and related post-marketing surveillance activities.

This would have system-wide benefits in both public and private health systems due to improved treatment outcomes, and lower costs from treating the increased morbidity due to substandard and counterfeit medicines, in addition to wider public health benefits, e.g. reduced antimicrobial resistance (Figure 4). These actions would also encourage private sector investment in quality pharmaceuticals and crowd out low-quality manufacturers. They may also have impact beyond borders in terms of lower availability of substandard, falsified and counterfeit medical products. Stronger regulatory capacity leads to better oversight of local clinical trials to support marketing authorization applications for new medicines. This is important in the Asian context where the share of global clinical trials rose from 5.9% of the total global volume in 2005–2007 to 9.7% in 2011.4 Harmonization and convergence of regulatory requirements can overcome national requirements for new medicines to be tested in local populations.

The case for increased investment in NMRA strengthening and capacity development is clear, but NMRAs in low- and middle-income countries cannot and should not be expected to function in all aspects at the same level as those in high-income countries. Moreover, collaboration between NMRAs enables them to share experiences, avoid duplicative efforts, maximize resources, and concentrate on critical functions.

THE CASE FOR REGIONAL REGULATORY CONVERGENCE AND HARMONIZATION

Globalization means regulation is no longer a purely national responsibility

Medicines regulation was previously seen as a purely national responsibility. However, regional and global regulatory convergence and harmonization are important to increase the efficiency of medicines regulation with important benefits for the public and private health sectors.

The globalization of pharmaceutical production and distribution means that individual ingredients are produced and various stages of production for a finished product are completed in multiple countries. Conversely, a company making an application for marketing authorization of a product in multiple jurisdictions may be faced with slightly different standards for the same criterion in each country. This leads to duplication of effort by both NMRAs and industry players.

This wastes resources for the NMRAs, and increases costs for pharmaceutical companies which have to develop different dossiers for each country, and even conduct extra clinical trials to meet the needs of one NMRA. This has led to the initial efforts at regulatory harmonization.

Regulatory harmonization and convergence

Regulatory harmonization typically relates to the development of common technical requirements, standards, and guidelines for quality, safety, and efficacy in the regulation of pharmaceutical products. It involves the development of common documentation and alignment of legal frameworks to adopt this documentation and it requires collaboration and trust between NMRAs. Final decision-making is still the remit of each NMRA, but this process can still pave the way for recognition of each authority’s decisions, or lead to a centralized registration procedure as is the case in the European Union. Regulatory convergence refers to a more general process whereby regulatory requirements between countries become more and more similar over time due to increased collaboration and common moves to adopt international best practice.

The globalization of pharmaceutical production and distribution means that individual ingredients are produced and various stages of production for a finished product are completed in multiple countries.

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Harmonization is cost-effective

International moves towards regulatory harmonization and convergence have increased in recent decades. Collaboration and cooperation between NMRAs is no longer seen as optional but rather as essential to increase efficiency in medicines regulation to the benefit of public health. This is evident in the increasing collaborations between what are considered relatively well resourced and “stringent” NMRAs through organizations such as the International Conference on Harmonization, the International Coalition of Medicines Regulatory Authorities5, and the Heads of Agencies Consortium.6

Regulatory collaboration and harmonization are also evident in lower-income countries. The African Medicines Regulatory Harmonization Initiative, launched in 2009, has spawned harmonization activities in the East African Community and between the NMRAs of Zambia, Zimbabwe, Botswana and Namibia (the ZAZIBONA process) among others. These employ a collaborative approach for registration of generic products to speed access to essential medicines and ensure efficient use of resources through work-sharing. The Pan American Network for Drug Regulatory Harmonization has also initiated harmonization activities in the Americas for small molecule i.e. nonbiological, less

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**Figure 4: Benefits of NMRA Capacity Development**

- **Reduced** antimicrobial resistance
- **Improved** treatment outcomes
- **Increased** export opportunities for domestic pharmaceutical manufacturers
- **Better** oversight of clinical trials
- **Incentives** to produce quality-assured pharmaceuticals
- **Increased** confidence in health system and medicines
- **Removal** of substandard and counterfeit medical products from the market

*NMRA* = national medicines regulatory authority.
Source: Authors.

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complex medicines. Such initiatives are supported by the WHO collaborative registration process for WHO prequalified products that can result in accelerated national market approval in less than three months. Thus harmonization initiatives can speed access to medicines of public health importance and free resources for other NMRA priority functions.

Pharmaceuticals are becoming ever more complex

Reliance on NMRA with strong capacity is increasingly necessary with the advent of advanced, more complex therapies such as biotherapeutics, gene therapies, and the biosimilars (“generic” versions of biological therapies that involve complex molecules and manufacturing processes). Smaller NMRA are unlikely to have the expertise and capacity to assess the dossier for such medicines and they will need to rely more on other NMRA assessments.

This effort of regulatory harmonization requires support for regional cooperation beyond the health sector. This includes advocacy and awareness-raising among ministries of foreign affairs, finance, commerce, and industry. It also requires investments for capacity development and support for policy dialogue.

WHO is closely involved in support for regulatory strengthening and harmonization activities. It develops common standards for pharmaceutical processes and regulation and supports regional harmonization networks. It has been instrumental in the establishment of the African Medicines Regulatory Harmonization Initiative and involves regulators from less developed NMRA in its regulatory strengthening programs, particularly the Prequalification Programme (WHO). Regulatory convergence will help lead to the rapid introduction of prequalified generic formulations for new products such as direct-acting antivirals medicines for hepatitis C and cancer medicines that the WHO Essential Medicines List now encompasses.

REGULATORY HARMONIZATION AND CONVERGENCE IN ASIA

ASEAN NMRA show a range of capacities from the highly developed and relatively well-resourced Health Sciences Authority of Singapore to those of the lower-income countries like Myanmar and the Lao People’s Democratic Republic. There is great opportunity for sharing expertise and building capacity.

ASEAN, through its Pharmaceutical Products Working Group in particular, has developed its own guidelines on technical requirements and what information marketing authorization applications should include. These are similar to those of the International Conference on Harmonization. In addition to these, a mutual recognition arrangement for Good Manufacturing Practice inspections has been established. NMRA within ASEAN can be approved as one of the Good Manufacturing Practice inspection authorities, in which case any inspection will be recognized by the agencies of the other ASEAN nations. They are also looking at how, for more advanced and complex medicines, the regulatory review done by Health Sciences Authority of Singapore could be accepted or at least used by the other NMRA that do not have the expertise for such health products.

The Asia-Pacific Economic Cooperation (APEC) Life Sciences Innovation Forum has a Regulatory Harmonization Steering Committee which aims to promote a coordinated approach to medical product regulatory harmonization and capacity-building efforts within the APEC region. The aim is to achieve regional convergence on regulatory approval procedures for medical products by 2020. It intends to achieve this through research on harmonization policies and best practices, training, fostering information exchange and collaboration, and disseminating relevant information.

The establishment of the Centre of Regulatory Excellence (CoRE) at the Duke–National University of Singapore campus offers a tremendous opportunity to support regulatory harmonization and convergence. It can foster capacity development through training activities to strengthen competencies and leadership in regulation; provide expert insight into opportunities for policy and systems innovations and improvements; and foster the networking of regulatory agencies. CoRE is currently undertaking a landscape analysis of medical product regulation in the ASEAN region with a view to providing targeted capacity development activities, funded by ADB.

There are benefits for public health, and stronger, more efficient and transparent medical product regulation will benefit the private sector. This in turn will lead to greater confidence in the health system and the quality of pharmaceuticals, more rapid access to the market for existing and new products, growth in the pharmaceutical market, and greater investment in the pharmaceutical sector. Providing efficacious and quality pharmaceuticals contributes to lower health care costs. Patients or other payers do not waste money on ineffective pharmaceuticals and medical devices, thereby reducing private and public health care costs. This is particularly important in the context of ensuring the financial sustainability of social health insurance schemes. To sustain these benefits beyond the short term it will be necessary for governments to invest in NMRA’s capacity strengthening, for development partners to include NMRA’s investments in health sector projects and reform programs and support and promote regional cooperation on regulatory practices.

Providing efficacious and quality pharmaceuticals contributes to lower health care costs.
The importance of regulatory strengthening and convergence in Asia has been acknowledged by donors and some of the better-resourced NMRA in the region. The World Bank and Bill & Melinda Gates Foundation have been supporting harmonization initiatives within Africa and the former is currently undertaking a study of selected Asian country pharmaceutical regulatory systems to provide an assessment of convergence and harmonization opportunities. Singapore and ADB are supporting the activities of CoRE to promote regulatory excellence in the region. The Asia Pacific Leaders Malaria Alliance has also highlighted the need for regulatory strengthening to address the concerns of resistance to artemisinin in the fight against malaria.

**THE WAY FORWARD**

There is a pressing need to support NMRA strengthening in the region and also to support regional initiatives that will lead to greater convergence and harmonization. NMRA with limited capacity need help in strategic leadership and planning so that they concentrate on value-added tasks rather than repeating work done by other agencies. Supporting the work of CoRE as a training and collaboration hub can help bring in the opinions and ideas of the private sector.

Actions that countries can begin to take now include:

**Increase the transparency of regulatory authority processes and decisions**

Put an updated list of registered medicines into the public domain, set target deadlines for regulatory decisions on registration, licensing and other functions and provide public disclosure of regulatory decisions.

**Increase the efficiency of the registration processes**

NMRA can expedite the registration processes for medicines of high public health importance through, for example, making use of the WHO collaborative registration process, or utilizing the assessment of a reference regulatory authority for new or complex products upon which to base their marketing authorization decision.

**Increase communication and cooperation between NMRA**

Practical measures include bilateral sharing of personnel, i.e., working for a period in another NMRA, and conducting joint assessments of a product’s quality, safety, or efficacy, thus establishing confidence in each others’ procedures, building up to reliance on the reports and decisions of these NMRA so as not to repeat the same work.

**Increase financing and political commitment**

This entails high-level recognition that an NMRA needs to be strengthened and financed appropriately and planning for this made in coordination with Ministry of Health budgets and plans. NMRA should have long-term development plans to guide capacity development and coordinate the input of government and donors with a view to establishing a sustainable financing mechanism that will allow the NMRA to perform to internationally accepted standards.

**Improved post-marketing surveillance**

Targeted regular inspections of manufacturers and along the supply chain can remove poor quality medicines from the market, while better collaboration with other NMRA and with other authorities in the country can help to address the issue of substandard and counterfeit health products.

In the process, countries will have fewer substandard, spurious, falsely-labeled, falsified and counterfeit medical products events to contend with. There will be better treatment outcomes due to reduced usage of ineffective medicines, which in turn will save the public health system money. Moreover, the private sector will have increased confidence to engage in the pharmaceutical industry. While support for harmonization and convergence may not be seen as a priority in-country due to constrained resources, these measures can all contribute to regulatory strengthening, and serve the ultimate long-term goal of regulatory convergence in the region.

NMRA with limited capacity need help in strategic leadership and planning so that they concentrate on value-added tasks rather than repeating work done by other agencies. Supporting the work of CoRE as a training and collaboration hub can help bring in the opinions and ideas of the private sector.
## Appendix

### Selected Partners and Organizations Involved in Regulatory Harmonization and Convergence in the Southeast Asia Region

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<th>Activities</th>
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<tr>
<td>APEC Regulatory Harmonization Steering Committee (RHSC)</td>
<td>Conducting research on harmonization policies and best practices, training, information exchange</td>
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<tr>
<td>Asia Pacific Leaders Malaria Alliance (APLMA)</td>
<td>High-level forum to provide leadership and policy to address malaria in the region including regulatory strengthening and action as advised by the Access to Quality Medicines and other Technologies Task Force (AQMTF)</td>
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<tr>
<td>ASEAN Pharmaceutical Products Working Group (PPWG)</td>
<td>Leading harmonization and mutual recognition efforts in the ASEAN region</td>
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<tr>
<td>Asian Development Bank</td>
<td>Supporting regulatory capacity building and convergence to address artemisinin resistance in the Greater Mekong Subregion</td>
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<tr>
<td>Centre of Regulatory Excellence (CoRE)</td>
<td>Providing a platform for interaction and training on regulatory leadership and regulatory science</td>
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<tr>
<td>World Bank</td>
<td>Conducting baseline assessments of regulatory systems and scope for regulatory harmonization in selected countries</td>
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<tr>
<td>World Health Organization (WHO)</td>
<td>Setting norms and standards, supporting regulatory strengthening, providing leadership, building capacity and implementing a tool to assess regulatory capacity and processes. Specific initiatives for medical products to respond to epidemics.</td>
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<td><strong>Governments and national medicines regulatory authorities</strong></td>
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<td>Australia – Therapeutic Goods Administration (TGA)</td>
<td>Training of regulators in Pacific Islands, supporting work-sharing initiatives</td>
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<td>Japan – Pharmaceutical and Medical Device Agency (PMDA)</td>
<td>Bilateral support to selected NMRAs in the region</td>
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<tr>
<td>Malaysia – National Pharmaceutical Control Bureau (NPCB)</td>
<td>WHO Collaborating Centre for Regulatory Control of Pharmaceuticals; ASEAN regional training centre for quality control of pharmaceuticals; capacity building of regional NMRAs in quality assurance and regulation of medicines</td>
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<tr>
<td>Singapore – Ministry of Health and Health Sciences Authority (HSA)</td>
<td>Supporting CoRE to improve regulatory practice in public and private sectors</td>
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<tr>
<td>Republic of Korea – Ministry of Food and Drug Safety (MFDS)</td>
<td>Bilateral support to selected NMRAs in the region</td>
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Better Regulation of Medicines Means Stronger Regional Health Security
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ADB’s vision is an Asia and Pacific region free of poverty. Its mission is to help its developing member countries reduce poverty and improve the quality of life of their people. Despite the region’s many successes, it remains home to the majority of the world’s poor. ADB is committed to reducing poverty through inclusive economic growth, environmentally sustainable growth, and regional integration.

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