



REGULATORY SYSTEM MODELS FOR SMALL STATES/MARKETS WITH LIMITED RESOURCES: CONCEPT NOTE AND RECOMMENDATIONS

Ninth Conference of the Pan
American Network for Drug
Regulatory Harmonization
(PANDRH)

San Salvador,
24 to 26 October, 2018

PAHO

PANDRH Pan American Network for Drug Regulatory Harmonization



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ABBREVIATIONS

CARPHA	Caribbean Public Health Agency
CARICOM	Caribbean Community
CRS	Caribbean Regulatory System
GBT	Global Benchmarking Tool
GDP	gross domestic product
NRA	national regulatory authority
NRAr	national regulatory authority of regional reference
PAHO	Pan American Health Organization
PANDRH	Pan American Network for the Harmonization of Pharmaceutical Regulation
WHO	World Health Organization

SUMMARY

Regulatory systems are an essential part of well-functioning health systems and critical to the achievement of universal access to health and universal health coverage. Therefore, there is increasing focus on strengthening medical product regulatory systems around the world, which has been the priority of the Pan American Network for Drug Regulatory Harmonization (PANDRH).

The Pan American Health Organization/World Health Organization (PAHO/WHO), as PANDRH's Secretariat, has drafted this concept note to help Member States with limited resources develop approaches to strengthen regulatory systems to assure safe, quality, and effective medicines for people in the Americas.

For the purpose of this document, “limited resources” refers to a series of characteristics that pose obstacles to the development of a regulatory system. The limitation on resources can refer to limited financial resources in the context of small and/or low income economies, but also to settings in which the size of the population and/or the market dynamics impede or do not permit the development of a regulatory system such as those classically found in large economies with robust regulatory capacity.

This document focuses on ways to strengthen regulatory capacities in such settings by prioritizing the most critical regulatory functions and taking advantage of efficiencies that will enable systems to do more with less. A few terms are used hereafter, including “small state,” “small market,” and “small state regulatory system” but, as mentioned before, these recommendations may also apply to lower income economies. Although the World Bank defines a small state as a country with a population of 1.5 million or less, PAHO uses the same term in this document but does not set a numerical threshold. Likewise, PAHO uses the term “small market” to refer to the pharmaceutical market of a small state.

The aim of this document is to spotlight the regulatory challenges faced by small states with limited resources, especially in light of mandates to strengthen regulatory systems in the Americas and globally, and to ensure all peoples have access to quality medicines through the implementation of certain essential regulatory functions. It offers theoretical and practical advice about the adoption of key efficiencies to strengthen small state regulatory systems. It is also a call to action for PANDRH stakeholders, including governments, industry, and donors, to strengthen small state regulatory systems in the future.

BACKGROUND

There is increasing focus on strengthening medical product regulatory systems around the world. Regulatory systems are an essential part of well-functioning health systems and critical to the achievement of universal access to health and universal health coverage. An overarching vision and mandate for regulatory systems is outlined in Sustainable Development Goal 3, Target 3.8, and stipulates that United Nations Member States

should, “Achieve ... access to safe, effective, quality and affordable essential medicines and vaccines for all.”

In other words, governments should have in place, or be working to put in place, systems that can assure access to quality medicines for everyone. Functional regulatory systems are a requisite to doing so. The increasing focus on regulatory systems is in part due to a convergence of challenges, including the globalization of manufacturing and supply chains, the proliferation of new and complex medicines and other health technologies, the varying quality spectrum of medicine sources around the world, and efforts to improve access to safe and affordable medicines against a backdrop of scarce resources and the need to do more with less—such as adopt efficiencies, leverage resources, and collaborate across authorities and institutions.

PAHO Member States have been at the forefront of regulatory systems strengthening through the adoption and implementation of Resolution CD50.R9.¹ Agreed on in 2010, it represents a first of its kind related to the subject, and calls on Member States to strengthen their regulatory systems and creates a regional approach for supporting countries to develop their capacities. The approach is predicated on assessment using an internationally recognized WHO tool,² adapted by PAHO, which benchmarks national capacities. Systems that reach the highest level of capacity (level 4) are designated as “functional” and thus, “National Regulatory Authorities of Regional Reference” (NRAr), which have the responsibility to support regional efforts toward regulatory systems strengthening, among other responsibilities. As of January 2020, PAHO has assessed 27 of 35 (77%) systems and designated 8 (23%) authorities as meeting the standards of NRAr.³ Other regulatory authorities have undergone substantial improvements in capacity through the assessment process as well. Such authorities have taken advantage of the assessment findings to establish institutional development plans that address challenges through PAHO and NRAr support. The momentum on regulatory system strengthening had one peak in 2014 via World Health Assembly Resolution 67.20,⁴ which reaffirmed the importance of regulatory system strengthening as a public health priority at the global level, and encouraged WHO Member States to go through the assessment and institutional development plan process to strengthen their systems.

Despite the many gains in regulatory systems strengthening, data show there is still much work to be done. Figure 1 explores the status of regulatory capacity in the Americas in broad terms by categorizing the degree to which states possess legal foundations and organizational structures to operate comprehensive regulatory systems⁵ based on PAHO assessment data and WHO Pharmaceutical Country Profiles. Four distinct groups emerge. Roughly a quarter have attained reference status. A group of countries (37%) possess the legal

1 Pan American Health Organization. Strengthening national regulatory authorities for medicines and biologicals [Internet]. 50th Directing Council of PAHO. 62nd Session of the Regional Committee of WHO for the Americas; 27 Sep–1 Oct 2010; Washington, D.C.: PAHO; 2010 (Resolution CD50.R9). Available from: <http://new.paho.org/hq/dmdocuments/2010/CD50.R9-e.pdf>

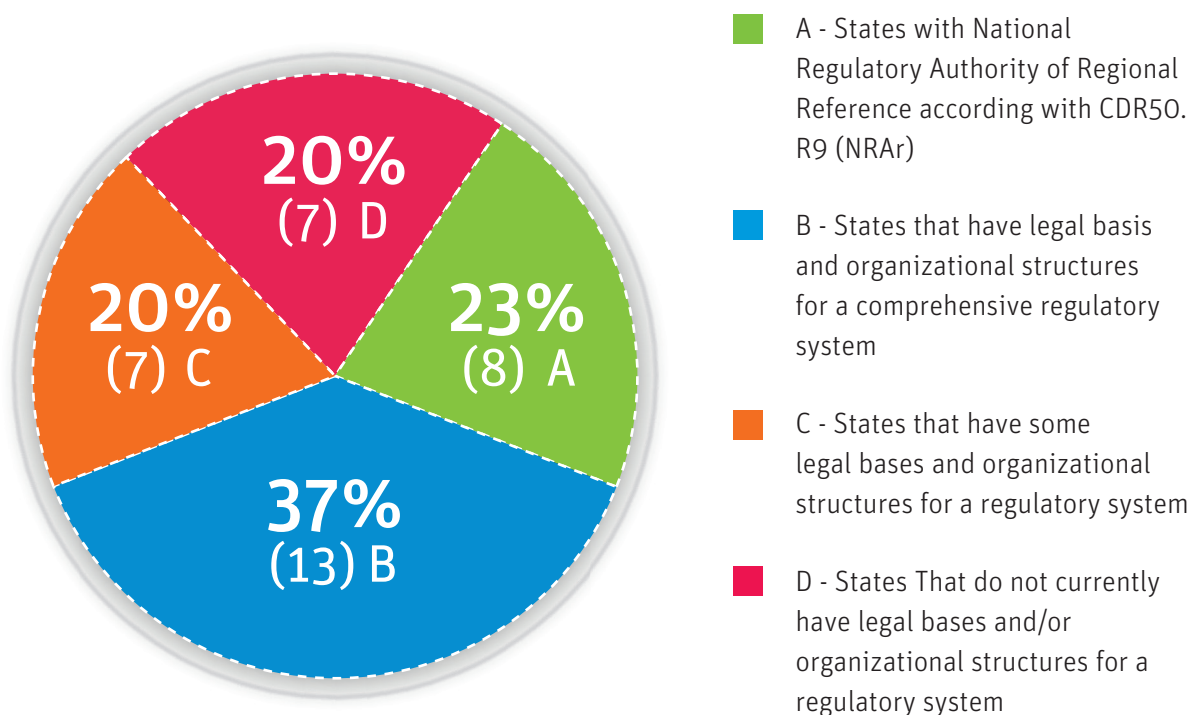
2 WHO Global Benchmarking Tool (GBT) for evaluation of national regulatory systems. Available from: http://www.who.int/medicines/regulation/benchmarking_tool/en/

3 PAHO NRAr are: Argentina, Brazil, Canada, Chile, Colombia, Cuba, Mexico, United States

4 World Health Organization. Regulatory system strengthening for medical products. [Internet]. 67th World Health Assembly; 24 May 2017; Geneva, Switzerland. Geneva: WHO; 2014 (Resolution WHA 67.20). Available from: http://apps.who.int/gb/ebwha/pdf_files/WHA67/A67_R20-en.pdf

5 Regulatory system recommended functions are: regulatory system; registration and marketing authorization; licensing of establishments; market surveillance and control; vigilance; clinical trials oversight; regulatory inspection; laboratory testing; NRA lot release (PAHO/WHO).

foundations and organizational structures to have a comprehensive system. Another 20% of states possess some of the legal foundations and organizational structures to have a regulatory system. A final group of 20% do not currently have the legal bases and/or organizational structures for a regulatory system. There are additional PAHO Member States that would come under the latter category if territories were considered.



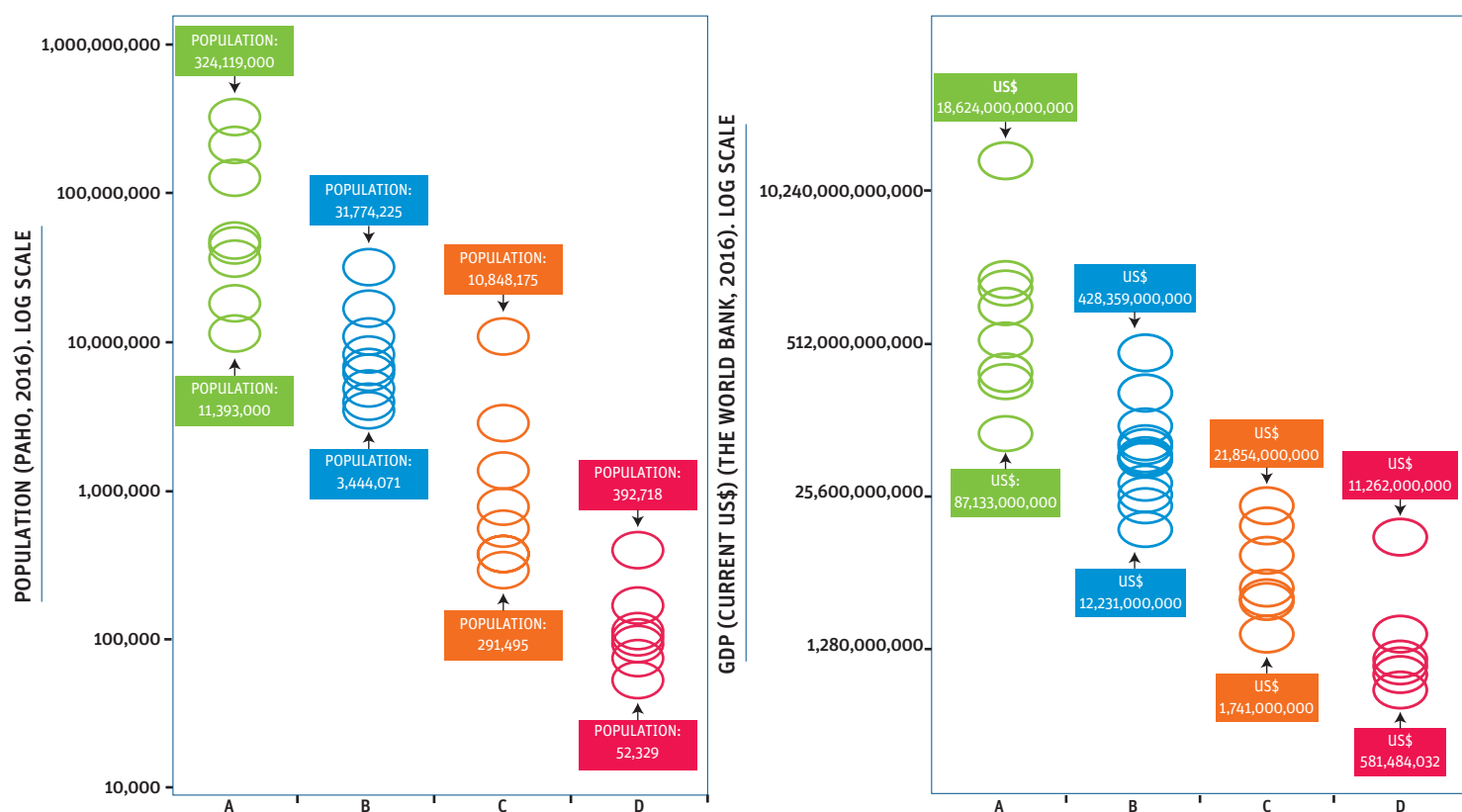
Source: Preston C, Freitas Dias M, Peña J, et al. Addressing the challenges of regulatory systems strengthening in small states BMJ Global Health 2020;5:e001912.

The good news is that in aggregate, NRAr cover about 82% of the population of the Americas, and states with legal and organizational frameworks for a comprehensive system cover another 16%. This means that about 2% of the population of the Americas falls under systems that have some or no legal and/or organizational frameworks for regulatory systems. However, this is roughly 18 million people.

The 40% of countries that have some or no legal framework and/or organizational structure are important to understand, because unique approaches are needed to effectively strengthen their regulatory capacity. Having a small population appears to be highly associated with having some or no legal framework and/or organizational structure. Thirteen of the 14 states with some or no legal and/or organizational structures for regulatory systems make up the smallest population states in the Americas (~93%). Smaller economies are also associated, and similarly, 13 of the 14 states having some or no legal and/or organizational structures for regulatory systems also constitute the smallest gross domestic product (GDP). Figures 2A and 2B show a clear association across these groupings of states by regulatory capacity and population and GDP, with capacity tending to decrease as population and GDP decrease. This is partly a commentary on the resource requirements for regulatory systems in the form of people and financing. The ones with more capacity tend

to have more people and financing. However, it is important to say that there are of course exceptions to these associations.

Figures 2A and 2B. Regulatory system capacity based on population and GDP in the Americas (N = 35)



Source: Preston C, Freitas Dias M, Peña J, et al. Addressing the challenges of regulatory systems strengthening in small states BMJ Global Health 2020;5:e001912.

GENERAL CONSIDERATIONS FOR REGULATORY SYSTEM STRENGTHENING

WHO has published a large amount of material relating to the development and strengthening of regulatory systems. These are outlined in documents dating back decades, such as Guiding Principles for Small National Drug Regulatory Authorities,⁶ but also more recent publications such as the WHO “Blue Book,” which is a manual for the development of marketing authorization⁷ functions for multisource (i.e., generic) products.⁸

At a general level, WHO recommends that all states be able to assure that medicines and other health technologies used locally are safe, quality, and effective. This is typically a function carried out by governments through their ministry of health and specifically through their regulatory system, which should operate within the context of defined national medicines and health technology policy/legal frameworks, and in conjunction with interested public bodies.

In response to the Resolution WHA 67.20, WHO, along with Regional Offices and Member States supported the development of the Global Benchmarking Tool (GBT) to evaluate national regulatory systems to solidify assessment indicators across different product categories and include a system for interpreting regulatory capacity through a schema known as maturity levels.

INHERENT CHALLENGES OF SMALL STATES AND SMALL MARKETS

Successful approaches of larger regulatory systems do not necessarily translate to small markets, which face a unique set of inherent challenges, including from both the regulator and market perspectives.

Regulator Challenges

For the regulator, small populations mean limited human resources because there is a smaller group of people with competences, skills, and experience to draw from. In many cases, small state health authorities may employ only a few people, which stands in contrast to the hundreds or thousands of people employed by larger authorities. Further, laws and policies in small states can be outdated and limited in scope, and/or

6 Guiding principles for small national drug regulatory authorities. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations, thirty-first report. Geneva: WHO; 1990 (WHO Technical Report Series, No. 790). Annex 6.

7 The terms “marketing authorization,” “registration,” and “approval” are used synonymously and refer to the authorization of a product for legal sale in the market by the government body entrusted with these responsibilities.

8 World Health Organization. Marketing authorization of pharmaceutical products with special reference to multisource (generic) products: a manual for National Medicines Regulatory Authorities (NMRAs) – 2nd ed [WHO Blue Book]. Geneva: WHO; 2011.

may not reflect current thinking in terms of approaches that will enable regulatory efficiencies.

A number of the small states in the Americas do not have the legal underpinnings for regulatory systems, making it difficult to set standards that the industry should follow. Of the small states that do have the legal basis for regulatory systems, there are difficulties in conducting recommended functions like marketing authorization, post market surveillance, and pharmacovigilance due to several reasons that usually include the deficits in their structure and their standards.

Small state authorities tend not to have a fully developed medicines registration process in place, or if they do, struggle with processing dossiers for marketing authorization. For example, there are cases where backlogs of dossiers have built up over the course of years, impacting market entry and eventually, access to medicines. Post market surveillance and pharmacovigilance functions are also not exercised, or are limited, since reporting by vital sectors, including health workers, is minimal. Further, there is a lack of procedures for assessing reports, guaranteeing traceability of products, and for taking necessary regulatory actions. Ability to carry out other recommended regulatory functions, such as clinical trials oversight, inspections, and laboratory testing is also limited or does not exist.

Market Challenges

From the market perspective, the small populations present in these states result in very small markets, which are characterized by a low volume of products being traded. Moreover, these states are in many cases insular or hard to reach.

Unlike larger economies and countries that benefit from the proximity to larger pharmaceutical markets, small states do not generate the business incentives to operate efficiently and thus, small markets have a hard time attracting the types of companies that can comply with stricter regulations. Some companies, for instance, may choose not to sell their products in the market, creating availability issues, or they may sell more expensive or different versions.

Other challenges are that the front-line actors in small state markets tend to be intermediaries such as importers and distributors, with the manufacturer operating at a distance. In some cases, distributors act as international trading agents of medicines and other products with no specific capacities to handle health products. These entities are sometimes not as familiar with, or do not have access to, the detailed regulatory information held by the manufacturer. As a result, when small markets move to increase their regulatory standards, there may be opposition that can include either an unwillingness and/or inability to produce the requested documentation or other compliance materials.

The interface with such intermediaries can also present problems when substandard or falsified medicines are identified. The manufacturer knows more about its internal quality assurance systems and vulnerabilities than the intermediary, and can assess the situation and take corrective action with greater ease and speed.

The lack of incentives to operate in the market can also translate into less financing for the regulatory

system. User fees for processing marketing authorization applications are a very common way to finance regulatory system activities. However, in many markets in the Americas, particularly the small ones, fees can range from US\$ 50–150 per dossier, for example. This stands in stark contrast to the tens to hundreds of thousands of dollars charged by larger markets.

The few human resources and minimal financing creates a vicious cycle of inability to process and respond to industry expectations for accountable timelines and performance goals. This spurs more difficulties in the industry/regulator interplay and creates situations where unscrupulous actors can bypass official regulatory channels.

DEFINITIONS OF KEY APPROACHES TO ENHANCE REGULATORY EFFICIENCIES IN SMALL STATES/MARKETS

The following are definitions and descriptions of currently used approaches that can enhance regulatory efficiencies in small states/markets:

Regionalization

According to a recent publication, a regionalized approach is one in which regional entities (e.g., countries or organizations) with similar characteristics (e.g., histories, cultural values, languages, geographic location, economic conditions, etc.) combine their resources, harmonize disparate rules and processes, and/or rely on and share common information and policies to establish a collective system that is stronger and more efficient than what would be feasible individually.⁹ The concept is becoming increasingly common around the world, particularly in economic communities, and regionalization exists in Europe, Africa, the Middle East, and Asia. Resolution WHA 67.20 calls on Member States to use regionalization to strengthen regulatory systems when possible.

Reliance and Recognition

According to WHO, “reliance” occurs when a regulatory system uses information and/or evaluations performed by a different institution to reach its own decisions.¹⁰ Another important term, “recognition”, falls under the umbrella of reliance, but is a specific form, and occurs when a regulatory system adopts the decision of another trusted entity. Recognition may be unilateral, bilateral, or multilateral, and may be the subject of a policy or legal agreement.

9 Preston C, Chahal HS, Porrás A, Cargill L, Hinds M, Olowokure B, et al. Regionalization as an approach to regulatory systems strengthening: a case study in CARICOM member states. *Rev Panam Salud Publica*. 2016 May; 39(5):262–8. Available from: <https://iris.paho.org/xmlui/handle/123456789/28526>

10 World Health Organization. Good regulatory practices: guidelines for national regulatory authorities for medical products. Working document QAS/16.686, Oct 2016. Available from: https://www.who.int/medicines/areas/quality_safety/quality_assurance/GoodRegulatory_PracticesPublicConsult.pdf

Numerous authorities in the region practice some form of reliance, and a common application of reliance is in the marketing authorization function, where for example, a regulatory system may use the results of another's assessment report to help make a decision about approval of a particular product. It is important to have clear criteria for the selection of partners/products on which to rely.

There are a variety of ways to make these decisions, but many are based on an assessment of the regulatory system to perform certain functions very well. PAHO uses the term “trusted authority” to refer to this concept. The publication *Regulatory Reliance Principles: Concept Note and Recommendations* offers a fuller discussion of this subject.¹¹

Fast-Track/Accelerated Reviews

Many regulatory authorities employ pathways to fast-track the review and approval of products in order to speed access to qualified medicines.¹² This is typically done for products that offer a breakthrough in treatment and/or advantage to public health. It is also increasingly occurring as a form of reliance in situations where products have been approved by trusted authorities. Since this pathway forgoes doing a full marketing authorization review, the process is shorter and thus accelerated.

Case Study: WHO Collaborative Procedure between WHO and National Regulatory System in Assessment and Accelerated National Registration of Prequalified Pharmaceutical Products and Vaccines ^a

WHO has an important reliance initiative, informally called the “Collaborative Procedure.” In it, regulatory systems have access to confidential WHO information from their prequalification of medicines and vaccines programs, such as inspection and other assessment reports, to facilitate accelerated marketing authorizations in-country.

WHO stipulates that governments can participate in the Collaborative Procedure if they agree to make a decision on whether to grant marketing authorization to the product within 90 days. The program is limited to what WHO prequalifies, which are HIV, tuberculosis, malaria, and reproductive health medicines, and vaccines, but WHO may offer an expanded grouping of medicines in the future. Very few countries in the Americas participate in this program.

^a WHO Collaborative Procedure: <https://extranet.who.int/prequal/>

11 Pan American Health Organization. *Regulatory Reliance Principles: Concept note and recommendations*. Ninth Conference of the Pan American Network for Drug Regulatory Harmonization (PANDRH). (San Salvador, 24 to 26 October, 2018). Washington, D.C.: PAHO; 2019. Available from: <https://iris.paho.org/xmlui/handle/123456789/51549>

12 U.S. Food and Drug Administration: <https://www.fda.gov/forpatients/approvals/fast/default.htm>

Work-Sharing

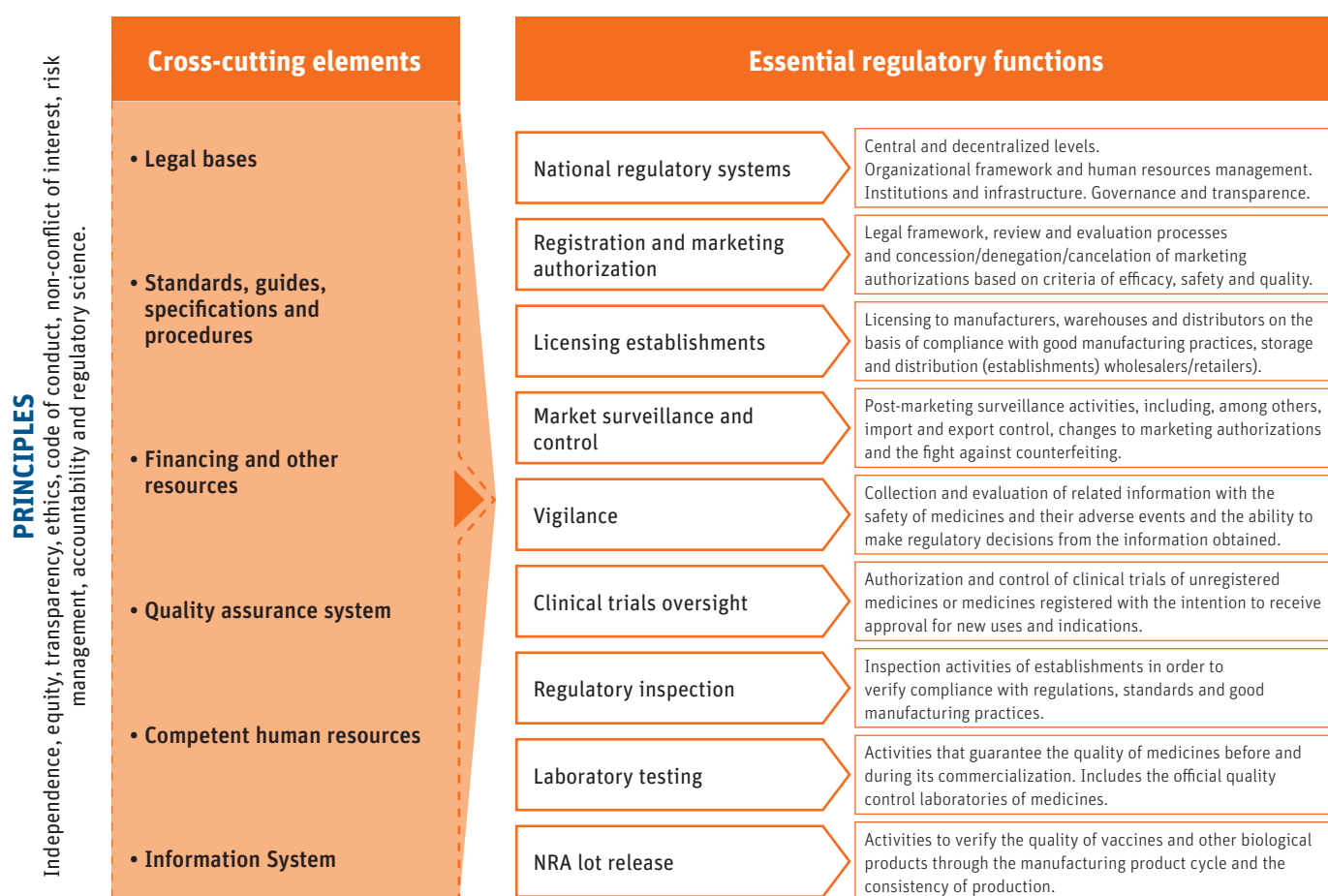
The WHO definition of “work-sharing” is a process by which regulatory systems collaborate on regulatory activities. It entails exchange of information consistent with the provisions of existing agreements for reliance and compliant with each institution’s legislative framework.

Opportunities for work-sharing can include assessing applications for marketing authorization, joint work in post market surveillance of therapeutic product safety, etc.

APPROACHES TO STRENGTHENING REGULATORY FUNCTIONS IN SMALL STATES/MARKETS

The principles, cross-cutting elements, and recommended functions that a comprehensive regulatory system should strive for are summarized in Figure 3. These recommendations reflect WHO guidance and the functions assessed when evaluating regulatory capacities using internationally recognized benchmarking tools. It is a “roadmap” or “true north” for attaining a comprehensive regulatory system.

Figure 3. Regulatory system principles, cross-cutting elements, and recommended functions

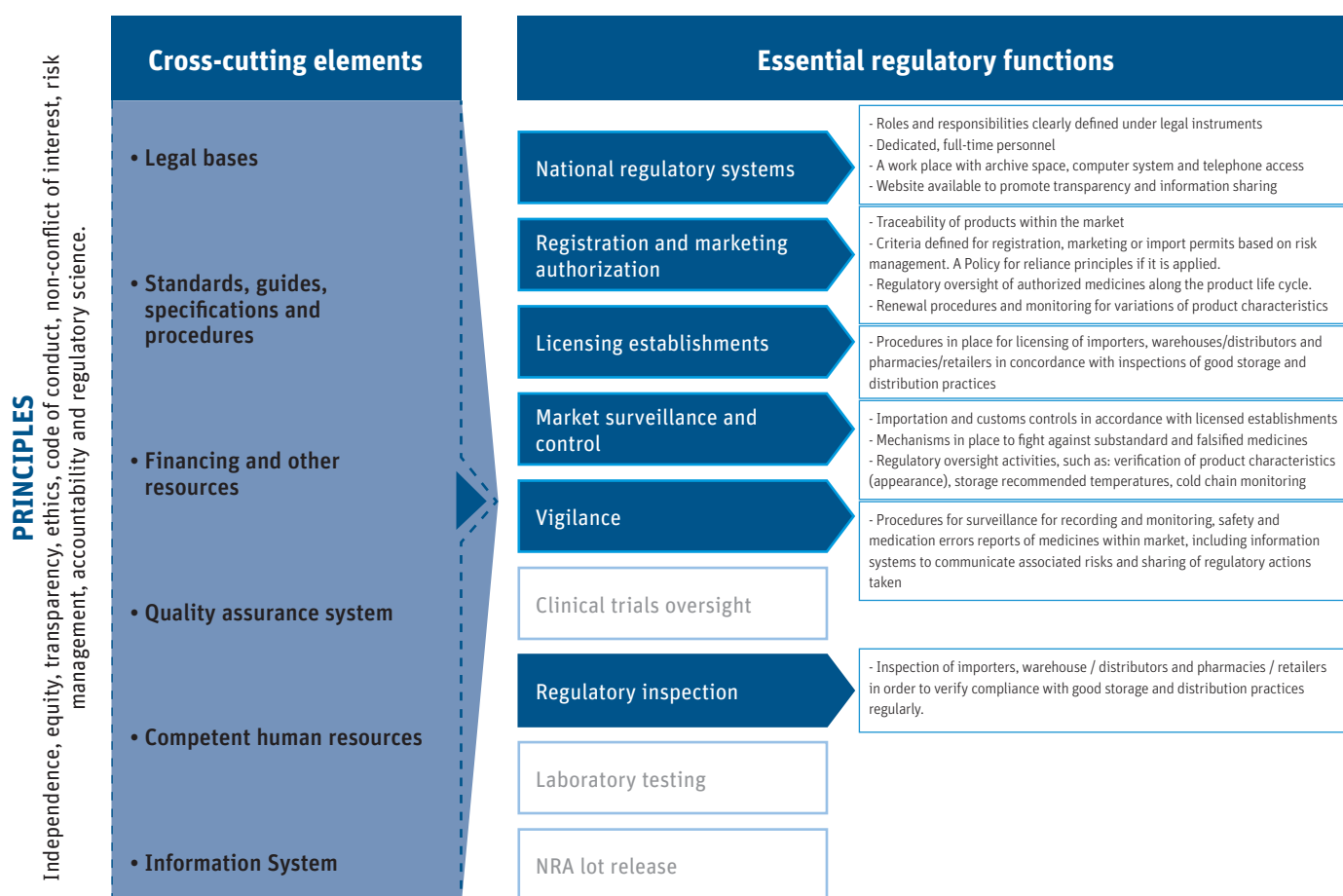


Source: Pan American Health Organization. Conceptos, estrategias y herramientas para una política farmacéutica nacional en las Américas. Washington, DC: PAHO; 2016. p. 47 [modified].

Essential Functions

In small states with limited resources, there is a need for prioritization of regulatory functions because it may not be possible to conduct all; moreover, depending on the national health system and industrial needs, it may be unnecessary. PAHO therefore recommends that small states develop national regulatory systems with a narrower scope of certain “essential functions.” States can perform these functions either on their own or through a system of reliance. Figure 4 depicts the essential functions recommended for smaller states along with a description of some of the key activities that must be done for each function.

Figure 4. Essential regulatory functions



Source: Pan American Health Organization, Medicines and other Health Technology Unit/HSS. Conceptos estrategias y herramientas para una política farmacéutica nacional en las Américas. Washington, DC: OPS, 2016, p.47 ISBN 978-92-75-31887-4 (Modified)

Principles, Cross-Cutting, and Regulatory System Functions

Any regulatory system, regardless of its size or context, should be guided by a series of basic principles. Regulatory systems should be independent, strive for equity and transparency, follow clear ethical conduct, remain accountable, and be guided by regulatory science.

In addition, regulatory systems of any type or size should have a number of cross-cutting elements adapted to their specific context, including having a legal basis; standards, guides, specifications, and procedures; financing and other resources; a quality assurance system; competent human resources; and information systems.

Market Entry/Marketing Authorization

Marketing authorization is critical for many regulatory functions, but at a minimum it is the function that allows a health system to act as a gatekeeper for market entry of products and for having information on what is legally present within the system. However, a number of small states in the Americas do not conduct marketing authorization. Rather, they embed quality control in their procurement systems, and prequalify manufacturers to supply public tenders. The risk is that manufacturers can make good and bad products, and it is important to have processes in place to distinguish between them. This means having regulatory systems that consider the safety, quality, and efficacy of each product seeking marketing authorization. Marketing authorization should be separate from procurement to insulate from conflict of interests, for example, due to pressures to select products based on price.

There are key factors to consider when implementing a marketing authorization system. There should be a legal/regulatory framework that has a product evaluation process, as well as set standards for how they will be evaluated according to safety, quality, efficacy, and principles of risk management. The system should enable traceability of authorized products throughout the supply chain. If a product is evaluated favorably, the regulatory system should issue a public authorization and maintain a public list of authorized products. Another issue is the degree to which reliance can be used.

Small states can leverage the marketing authorization evaluation of both innovative and generic products done by trusted authorities as an important efficiency. Marketing authorization is resource intensive and using trusted authorities that have already done the work and which oversee the products in their own markets can provide a high level of assurance for products allowed into small markets.

A good practice in reliance is to develop procedures for verification that can check whether the medicines approved by the trusted authority are the same as what is intended to be sold in the local market, and WHO has begun to issue guidance on this.¹³ It is also important to keep in mind that in the beginning phases of

¹³ Collaborative procedure in the assessment and accelerated national registration of pharmaceutical products and vaccines approved by stringent regulatory authorities. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations, fifty-second report. Geneva: World Health Organization; 2018 (WHO Technical Report Series, No. 1010). Annex 11. Available from: <https://apps.who.int/medicinedocs/documents/s23456en/s23456en.pdf>

implementation of regulatory systems, small states must strike a careful balance between regulation and access/availability of medicines but should increase regulatory standards over time so all medicines on the market are quality assured.

There are other important points to keep in mind in conducting the marketing authorization function. It is critical to set clear accountability goals with industry, including around how the process will work, and how long it will take. Processes with little feedback, or that take an unjustifiable amount of time, discourage legitimate companies and deny access to products for patients. Small states should examine their requirements to pinpoint areas that take unusually long amounts of time and streamline them. This includes incorporating efficiencies, such as asking for “electronic samples” (including mockups of artwork, labeling, as well as photos of the product in market-ready packaging). This is instead of requesting physical samples or requiring pre-registration testing. Physical samples take up space and are costly to provide (i.e., in time, shipping, etc.). If ever needed, they are often expired and cannot be used for testing. Further, it is not advisable to require pre-registration testing. Rather, quality should be built into the process through good manufacturing practice (GMP) and testing should only be required if risk necessitates. Electronic artwork and photos can be compared to any of the same products on the market. If there are deviations, there are grounds for designating the product unregistered or falsified. Samples can always be requested if there is a post market surveillance issue.

Import

WHO recommends that only products with marketing authorizations should be allowed to enter the country, and the importer should be duly licensed to undertake the activity through the licensing of establishment function.¹⁴ Private or public procurement should only occur when legal importation and valid marketing authorization exists for a given supplier and product, respectively.

Non-manufacturing countries rely on importation as the sole means to cover their medicines needs. Thus, regulating import of medicines should be top priority for small states. The process should be a first step for establishing a marketing authorization where required. Reliance on trusted authorities can help decide which products should be readily trusted to enter the health system.

14 Guidelines on import procedures for pharmaceutical products. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations, thirty-fourth report. Geneva: World Health Organization; 1996 (WHO Technical Report Series, No. 863). Annex 12. Available from: <https://apps.who.int/medicinedocs/documents/s21962en/s21962en.pdf>

Market Surveillance and Control and Vigilance

Market surveillance and control and vigilance (also known as post market surveillance and pharmacovigilance) may be the most critical function small states should perform on their own. These activities entail import and export control in accordance with licensed establishments, surveillance of quality in the supply chain, and the collection, evaluation, and regulatory response to adverse events related to the safety of medicines. These cannot be done exclusively by reliance because the products on the market, and how they are tolerated by citizens, are unique to the national health system and thus, a local responsibility. Market surveillance and control and vigilance can be done at a basic level inexpensively through developing a reporting system, creating a database to collect reports, designating a focal point to conduct these duties, implementing protocols for determining whether to take regulatory actions, and putting in place processes for routine and crisis communication of findings.¹⁵

Sharing post market surveillance information is critical because manufacturing and distribution are global, and a problem in one jurisdiction can also be a problem in another, especially in regional markets with similar economic and linguistic profiles. It is therefore a responsibility of post market surveillance officers to alert local, regional, and global colleagues. There are various tools that can be leveraged to share and store this information, including PAHO networks for substandard and falsified medicines and pharmacovigilance, and VigiCarib,¹⁶ which is a regional reporting mechanism in the Caribbean Community (CARICOM) block of countries through the Caribbean Regulatory System (CRS).

¹⁵ WHO minimal pharmacovigilance functions. Available from: <http://apps.who.int/medicinedocs/documents/s19107en/s19107en.pdf>

¹⁶ VigiCarib: <http://carpha.org/What-We-Do/Programmes-and-Projects/CRS/VigiCarib>

Case Study: Caribbean Regulatory System ^B

The CRS is a regionalization model that applies efficiency concepts to strengthen regulation in small states. It mitigates small state regulator capacity challenges by introducing reliance, work-sharing, and modernized evaluation criteria. It enhances small state market incentives by pooling markets, offering one market entry standard, and increasing accountability via faster timelines and more transparency.

It is situated in the CARICOM and managed by CARICOM's regional public health agency, the Caribbean Public Health Agency (CARPHA), in technical cooperation with PAHO/WHO. It is founded on certain building blocks, including a pharmaceutical policy that promotes regionalization (overseen by a group of Member State experts on pharmaceutical policy and regulation called TECHPHARM), a regional drug testing laboratory, and ministerial endorsements that established a small regulatory unit in CARPHA.

Specifically, it helps Member States with certain essential functions: marketing authorization, market surveillance and control, and vigilance. It uses reliance on the marketing authorization decisions of PAHO NRAR, the European Union, and WHO Prequalification, and verifies that the product is the same. It then makes the submitted information available to Member States, and recommends qualified products for marketing authorization (all published on the CRS website).

The system is voluntary, but CARICOM states are requested to process the recommendation for decision within 60 calendar days. Such a process should engender confidence because the medicine has been reviewed and authorized by a PAHO trusted authority, and then verified by the CRS to be the same medicine.

Since implementation in April 2016, an increasing number of small states are using the CRS but some are still not fully participating, or they have not eliminated additional barriers after CRS recommendation.

One part of the CRS vision is to recommend quality versions of all products on the WHO Essential Medicines List. Another part is to help the region develop stronger systems and protocols for responding to dangerous products on the market.

^B Caribbean Regulatory System: <http://carpha.org/what-we-do/laboratory-services-and-networks/crs>

WHO offers programs for reporting substandard and falsified products and adverse events, including the WHO Global Surveillance and Monitoring System (GSMS),¹⁷ and the WHO Programme for International Drug Monitoring (PIDM).¹⁸

Licensing of Establishments and Inspections

Small states should put in place systems for licensing of establishments. This includes the conduct of inspections of premises and their practices involved in the storage and distribution of products. Doing so creates a comprehensively regulated supply chain, from marketing authorization and procurement, to importation, storage, and distribution.

The last part of a product's journey (e.g., whether stored in a warehouse at an appropriate temperature, done in accordance with good distribution practices, maintaining cold chain) can be one of the most important areas of vulnerability for medicines along the supply chain.

Context-Specific Regulatory Functions

Whether to implement the broader set of regulatory functions (Figure 3) should be considered based on local context. Small states should ask themselves the following:

- Is there local manufacturing?
- Are there local clinical trials?
- When is a laboratory needed?
- Is vaccine lot release required?

17 WHO Global Surveillance and Monitoring System: <https://www.who.int/medicines/regulation/ssffc/surveillance/en/>

18 WHO Programme for International Drug Monitoring: https://www.who.int/medicines/areas/quality_safety/safety_efficacy/National_PV_Centres_Map/en/

Is There Local Manufacturing?

Having local manufacturers in the market introduces a high level of complexity to a small state's regulatory strategy because licensing and oversight of manufacturing facilities requires the development of a comprehensive regulatory system, such as the one described in Figure 3.

At the very least, it is necessary to conduct inspections of local manufacturers. This should be done to ensure that local manufacturers are producing products according to good manufacturing practice (GMP) standards.

Another factor to consider is that regulation of local manufacturing should follow the same procedures as imported products so as not to create different sets of standards. Small states should decide if local manufacturing provides sufficient value to the health system to merit the establishment of a comprehensive regulatory system that can ensure quality of medicines.

Are There Local Clinical Trials for Product Development and Approval?

Many small markets lack regulatory control over the conduct of clinical trials for product development and approval in their markets. Unscrupulous investigators sometimes take advantage of limited requirements. At the same time, conducting clinical trials in the local setting may be extremely helpful to the health priorities of the country.

WHO advises a few key principles, including that the regulator have provisions to permit the importation of unregistered medicines for clinical trials, provided it is for treatment of a condition with high local prevalence. Another principle is that trials should take place if given formal clearance by the regulator, including validation that the trials will be conducted according to good clinical practices.

When Is a Laboratory Needed?

Laboratory testing is integral to strong post market surveillance programs, but having a laboratory is not necessary in every individual small state. They are very expensive to operate and require large investments in human resources and equipment to evaluate product characteristics and guarantee reproducibility of the results obtained.

New ideas on quality control testing are important to consider, including the concept “the product is the

process,” which means that GMP verification and its accomplishment is more relevant than quality control of finished products. Further, there is much that can be done without a laboratory, including implementing simple testing such as physical appearance compared with approved characteristics prior to, or when, the product is in the market and/or checking whether products have valid legal documentation such as import license and/or marketing authorization.

Having access to a laboratory as part of post market surveillance is possible in small states by applying reliance principles, using either WHO prequalified laboratories or existing official quality control laboratory networks.

Is Vaccine Lot Release Required?

WHO does not recommend implementation of this function if there is not local production. However, several countries in the region have implemented an abbreviated/abridged process to control the import permit of vaccines, verify product characteristics, and improve communication with immunization programs. This can be done by verifying the documents that accompany international recommended shipping documents, including summary protocol of manufacturing and control, and lot release granted by the respective national regulatory authority (NRA) in a foreign country (the latter is another form of reliance practice).

PANDRH RECOMMENDATIONS

Concerning regulatory system models for small states/markets with limited resources, the Ninth Conference of the Pan American Network for Drug Harmonization has recommended Member States: (a) to strengthen regulatory systems in small states with limited resources according to frameworks in this concept paper, as well as CD50.R9 and WHA 67.20; (b) to encourage NRAs to support regulatory system strengthening in small states with limited resources according to CD50.R9; (c) to request PAHO to develop tool kits for small states/markets with limited resources to implement essential functions for regulation of medicines and other health technologies; and (d) to call on global health and development stakeholders and industry to support regulatory system strengthening in small states/markets with limited resources.

PAHO

PANDRH Pan American Network for Drug Regulatory Harmonization



Pan American
Health
Organization



World Health
Organization
REGIONAL OFFICE FOR THE
Americas