Toolkit for the Establishment of a Medical Products Regulatory System in Small States

VOLUME 1

Introduction and Foundations

In partnership with Canada

PAHO Pan American Health Organization

World Health Organization Americas Region

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Abbreviations and Acronyms

CARICOM	Caribbean Community and Common Market
CARPHA	Caribbean Public Health Agency
CIP	Coalition of Interested Parties
CRS	Caribbean Regulatory System
GBT	Global Benchmarking Tool
GMP	Good Manufacturing Practices
GReP	Good Reliance Practices
GRP	Good Regulatory Practices
HR	Human Resources
IDP	Institutional Development Plan
ML	Maturity Level
NRA	National Regulatory Authority
NRAr	National Regulatory Authority of Regional Reference
PAHO	Pan American Health Organization
PIC/S	Pharmaceutical Inspection Cooperation/Scheme
WHA	World Health Assembly
WHO	World Health Organization

Introduction and Background

National Regulatory Authorities (NRAs) play a crucial role in ensuring that medical products used in their jurisdiction are safe, effective, and consistently of quality, whether produced domestically or imported. Access to affordable, quality medicines and medical devices and their rational use is an essential component for effective disease management, and for addressing public health emergencies, particularly infectious disease outbreaks.

Medical products regulation aims to ensure access to products of required quality, safety, and efficacy, and to prevent the entry of substandard, falsified, and other products that are harmful to the population. It requires enforcement of stringent standards for the full product lifecycle, including the development, production, testing, supply, use and disposal of medicines, to mitigate risks and deal with problems in a timely and effective manner while appropriately sanctioning non-compliance. Regulation requires the conduct of a range of regulatory activities over the course of a product's life cycle including premarket evaluation, inspection and licensing of facilities, regulation of labelling and promotional activities, and post-market surveillance following approval.

The importance of effective regulatory systems was recognized by the Sixty-Seventh World Health 193 Assembly (WHA) in endorsing Resolution WHA 67.20 Regulatory system strengthening for medical products and the Pan American Health Organization (PAHO) Resolution CD50.R9, Strengthening National Regulatory Authorities for Medicines and Biologicals. These Resolutions note: (i) that effective regulatory systems are an essential component of health system strengthening and contribute to better public health outcomes, (ii) that inefficient regulatory systems can be a barrier to access to safe, effective, and quality medical products, and (iii) that there is a need for regional approaches for supporting countries to develop their capacities. Subsequently the 30th Pan American Sanitary Conference, 74th Session of the Regional Committee of the World Health Organization (WHO) for the Americas endorsed the CSP30/11 Policty to Strengthen National Regulatory Systems for Medicines and Other Health Technologies, which promotes the strengthening of regulatory systems to ensure consistent, transparent processes based on regulatory science.

NRAs of PAHO Member States face increasing challenges in ensuring that their populations have ongoing, expeditious access to required medical products, particularly medicines, vaccines, and other biologic medicines, and medical devices. Compounding these challenges is the fact that many small market states currently lack a functional regulatory system for medical products and have no registration and market authorization processes for medical products being used in their countries.

Objective of this Toolkit

The objective of this Toolkit is to provide governments of small market states with an overview of tools and steps to be used and followed in the creation or strengthening of a national regulatory system for medical products, with a particular focus on the establishment of a product registration and marketing authorization system. This Toolkit emphasizes the principles of Good Regulatory Practices (GRP), Good Reliance Practices (GReP), and the importance of the use of regionalization and reliance for small market states seeking to establish or strengthen their regulatory systems. Personnel of the Ministries of Health of small market states are encouraged to refer to this toolkit when considering establishing a national regulatory system for medical products, or when endeavoring to strengthen and enhance the capacity of an existing regulatory system.

How to use this Toolkit

PAHO has developed this comprehensive Toolkit to provide guidance on the establishment of a regulatory system for medical products based on the practices and principles of reliance and the WHO Global Benchmarking Tool (GBT). The Toolkit is intended to provide general recommendations and observations for broad guidance. It can be adapted by a state based on its specific needs, which PAHO recommends be incorporated through an internal review of the state's regulatory capacity and the desired level of advancement.

This Toolkit is organized in six (6) volumes:

VOLUME 1 Describes the general principles, foundations and models of an effective national regulatory system.

VOLUME 2 Describes steps to take to establish a strong legal framework for the regulation of medical products.

VOLUME 3 Describes how to establish a Registration and Market Authorization Scheme

VOLUME 4 Describes how to establish vigilance and market surveillance and control programs

VOLUME 5 Describes how to establish an establishment licensing and inspection program.

VOLUME 6 Describes Communication and Outreach or National Regulatory Authorities.

While the recommendations in this Toolkit can apply to any small state wishing to develop or strengthen regulatory oversight of medical products, it is intended primarily for small states relying on imported products, and without local production.

• 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 Essential Regulatory Functions and the Global Benchmarking Tool

To help support countries in strengthening their regulatory capacity for medical products, WHO has developed the Global Benchmarking Tool (GBT). The GBT serves as the global standard for assessing a state's (or an agency's) capacity for regulating medical products. The tool and benchmarking methodology enable NRAs to identify areas of strength as well as areas for improvement within a regulatory system. The use of the GBT can facilitate the formulation of an institutional development plan (IDP) to build upon strengths and address identified gaps, prioritize investment needs and to help monitor progress.

The GBT defines the main functions of a regulatory system for medical products as:

- Registration and Marketing Authorization
- Regulatory Inspection
- Licensing Establishments (e.g., manufacturers, importers, distributors, retailers)
- Vigilance
- Market surveillance and control
- Clinical trial oversight
- Laboratory testing

Some additional functions apply only to certain medical products. These less common functions include:

- NRA lot release for vaccines, plasma-derived medicinal products, and blood-related in-vitro diagnostics.
- Approval of blood and blood components, including plasma for fractionation (product and/or process approval); and
- Regulatory oversight of blood products associated substances and medical devices including in vitro diagnostics

The WHO GBT uses 268 sub-indicators to measure capacity across an overarching framework (national regulatory system), and the regulatory functions. (Fig. 1). The system is scored using the sub-indicators, in terms of maturity level, ranging from 1 to 4 (Table 1). The levels correlate to no formal approach (level 1); reactive approach (level 2); stable, well-functioning system (level 3) and continual improvement emphasized (level 4).

FIGURE 1

WHO Global Benchmarking Tool (GTB)

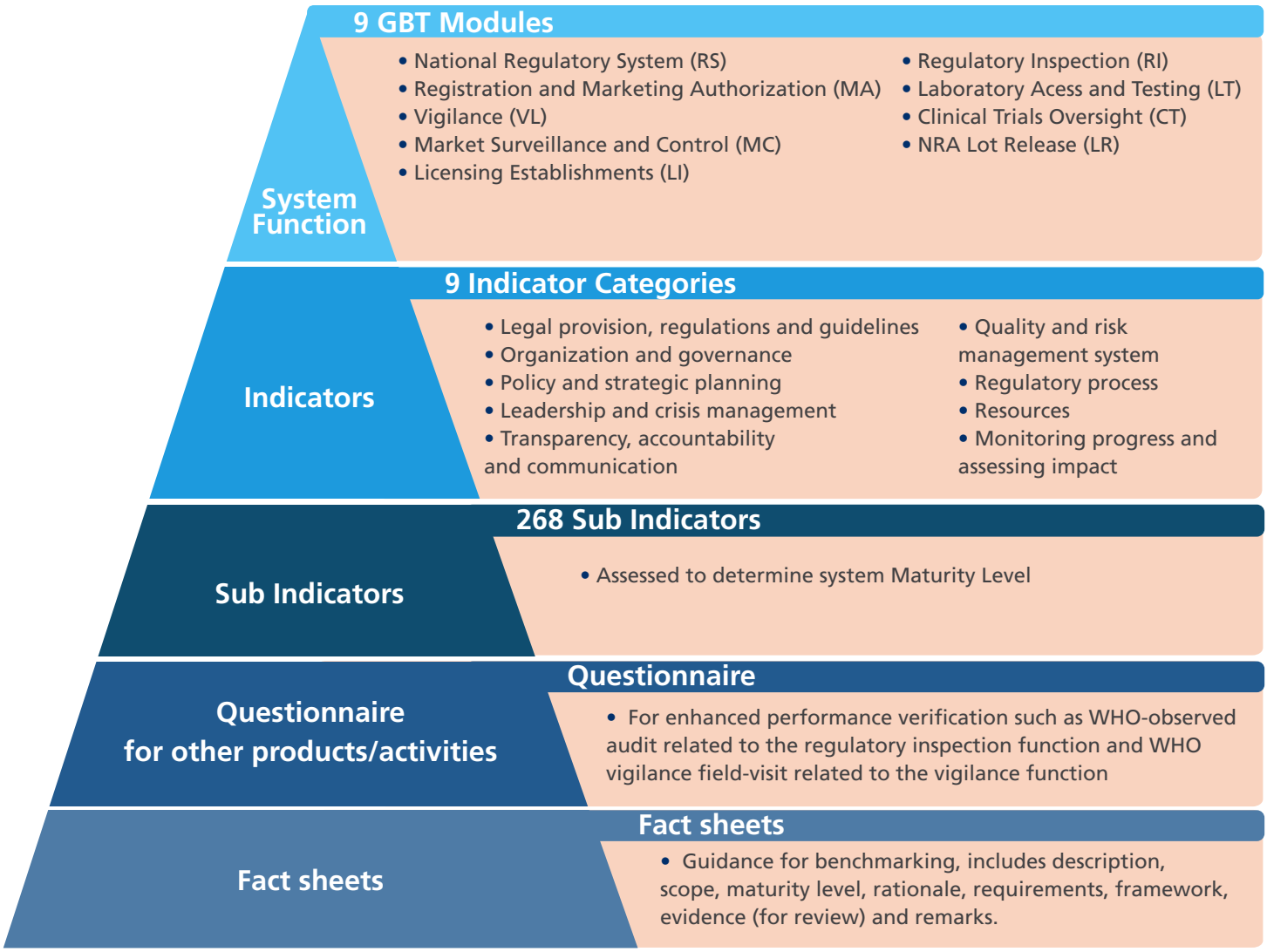


TABLE 1

Scoring Categories for the sub-indicators of the GBT

NOT AVAILABLE (NA)	No data is provided. It is an option that can exist only prior to the self-benchmarking.
NOT IMPLEMENTED (NI)	No evidence is provided to demonstrate any degree of implementation og the sub-indicator
ONGOING IMPLEMENTATION (OI)	Some actions/steps/activities are taken towards the implementation of the concerned sub-indicator; the sub-indicator is not yet implemented in full
PARTIALLY IMPLEMENTED (PI)	Some actions/activities are showing the full implementation of the sub-indicator; however, such full implementation is recent or relatively new with little cumulative data for consistent implementation. Supporting documented evidence is expected to be provided to show the recent full implementation of the concerned sub-indicator.
IMPLEMENTED (I)	Some actions/steps/activities demostrate the consistent and full implementation of the sub-indicator over a period. Supporting evidence is expected to be provided that demonstrates the full, consistent implementation of the sub-indicator.
NOT APPLICABLE	The relevant sub-indicator does not apply and should be supported with a justification explaining how the sub-indicator's exclusion does not pose any adverse or unwanted effects on the relevant regulatory function. It could be an option for some (but never all) sub-indicators.

The GBT is supported by a computerized platform to facilitate benchmarking, including the calculation of maturity levels. The computerized GBT (cGBT) is available, upon request, to Member States and organizations working with WHO under the Coalition of Interested Partners (CIP).

For more detailed information on the core functions of a regulatory system and guidance on how to evaluate and strengthen these capacities, countries are encouraged to consult the WHO GBT for evaluation of national regulatory systems. The official GBT publication can be accessed at: https://www.who.int/publications/i/item/9789240087637.

Applying the GBT to a Small State

A small state/market may not be able to devote many resources and significant funding to the regulatory system. One way to address these challenges is for a small state to build a regulatory system with a narrow scope, focused on a subset of the WHO recommended functions, tailoring the approach to the needs of their country and the available resources. Small states wishing to establish a regulatory system for medical products should initially focus their work on the following three essential functions of a Regulatory System identified in the WHO GBT:

1. **Registration and marketing authorization**, also sometimes referred to as licensing or approval, is the function that allows a regulatory system to act a gatekeeper for the entry of products for use in patient care within a jurisdiction and for monitoring what is available on the market. A registration and marketing authorization process considers the safety, quality, and efficacy of each product before it enters the market. It should also identify the circumstances under which a marketing authorization already granted may be withdrawn, suspended, or revoked. A registration and market authorization process requires a scientific regulatory review of a product dossier that has been submitted by a manufacturer, containing sufficient data to support the safety, efficacy, and quality of the product, along with proposed labelling, pharmacovigilance, and risk management strategies. However, not all scientific reviews need to be conducted by the NRA issuing the registration/market authorization.

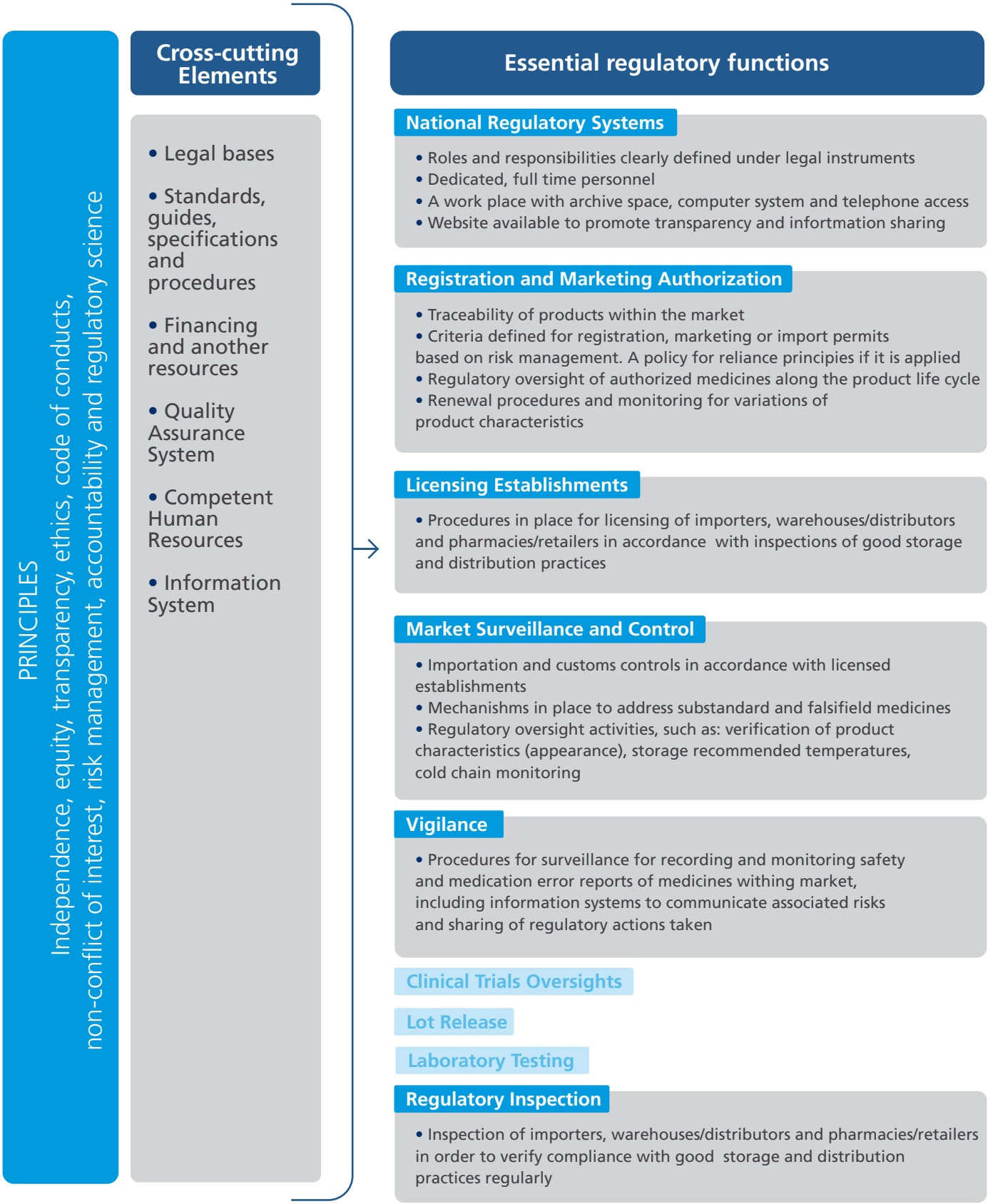
2. **Licensing of establishments and inspections.** While the licensing of establishments and regulatory inspection functions are separate activities under the GBT, they are linked as regulatory inspection can be a critical factor in the issuance and renewal of establishment licences. Generally, most medicines used in a small market state are imported products, the control of the importation activities including point of entries is critical, hence the licensing of importers and distributors is important. Small market states should put in place systems for licensing of establishments that import, store, and distribute medicines, particularly those involved in the supply chain such as distributors and retailers. Ideally, this form of regulation will include inspections of establishments, and the practices involved in the procurement, storage, and distribution of medical products. Regular inspections of licensed establishments using standardized inspection protocols and checklists, will provide evidence of ongoing compliance with the regulations, including assuring that only registered products are being procured. Adequate inspection capacity will also be needed for risk management, allowing reports of regulatory non-compliance to be investigated and actioned. This will result in a regulated supply chain, covering registration and market authorization, procurement, importation, storage, and distribution of medical products.

3 **Vigilance and market surveillance and control** are the activities and the science relating to the detection, assessment, understanding and prevention of adverse events, adverse reactions or other product-related problems. It aims to contribute to patient care by supporting safe, rational, and appropriate use of medicines. Adverse event and adverse reaction reporting is a key component of a vigilance system. Small market states can develop a system for spontaneous adverse event reporting by stakeholders but must have personnel assigned to receive, investigate, and analyse these reports so that they added value in supporting the detection of problems with products in use in their jurisdiction. To request and receive reports that are not analysed due to a lack of trained personnel, negates the value of the reports, may create mistrust between the NRA and the public, and may put a level of heightened liability on the NRA should a safety issue arise that had been reported to them but was not acted upon. Surveillance can be enhanced by participation in a regional pharmacovigilance programme. Similarly, while laboratory testing is also integral part of the post-market surveillance programmes, especially when addressing cases of suspected falsified or substandard medicines, a testing strategy should be risk-based and can be outsourced or shared with other trusted jurisdictions, since establishing domestic laboratory testing is a complicated and expensive process. Small market states should have a well-established process to access laboratory facilities when needed via formal agreements with other regulatory authorities or regional bodies operating accredited testing laboratories

These essential functions are carried out under the legal foundation of a National Regulatory System (Figure 2)

FIGURE 2

Essential Regulatory Functions recommended for a Small State/Market



Source: Pan American Health Organization and Medicines and other Health Technology Unit/HSS. (9)

Conducting a Self-Benchmarking

The formal WHO benchmarking process includes, a self-benchmarking in which an NRA performs an assessment of its own functions against the set of GBT sub-indicators and finally a formal benchmarking by WHO, in which a team of independent experts assesses an NRA's maturity level against the GBT indicators and sub-indicators. The self-benchmarking will help the NRA identify strengths and weaknesses in the various regulatory functions. For example,

- It will aid in the clear identification of legislative amendments and regulations necessary to implement effective registration and market authorization, market surveillance and control, pharmacovigilance, and licensing of establishments and inspections functions.
- It will determine whether the current organizational structure and level of resources within the NRA are sufficient to perform the essential functions.
- The exercise will also help identify additional documents, such as guidelines and procedures that are necessary.
- It will aid in the design of a workplan or Institutional Development Plan (IDP), which will provide each state with a tailored approach for strengthening its regulatory system.

The self-benchmarking process can also offer an opportunity for frank reflection and discussion, allowing for both recognition of successes and shortcomings, and the creation of clear objectives for the future. The documentation of a self-benchmarking against the WHO GBT sub-indicators can also be a valuable tool to justify the need for increased resources for an NRA. Furthermore, the self-benchmarking process is meant to be repeated so that progress can be tracked and documented. Periodic, pre-scheduled self-benchmarkings can contribute to the implementation of a quality management system for an NRA, in which the organization takes pride of ownership in the standards that have been reached and maintained.

As a first step of the self-benchmarking exercise, a target for the desired maturity level (eg. ML 1, 2, 3 or 4) should be established. For each sub-indicator evaluated in the self-benchmarking, scores for implementation (implemented, partially implemented, ongoing implementation and not implemented) should be recorded (Table 1).

Using the information obtained from the self-benchmarking process, an IDP should be developed, reflecting the identified strengths and weaknesses in capacity. The IDP should set realistic goals, priorities and define the actions, timelines and responsibilities needed to progress to a level of system maturity.

The self-benchmarking process will involve the following steps:

Obtaining commitment and buy-in

It is important that that senior staff explain the purpose and importance of the self-benchmarking and encourage staff to participate in and give their valuable time to the exercise.

Allocating time and resources

Allocating enough time and resources for the self-benchmarking process is critical.

Training of designated personnel

In the use of the GBT and the self-benchmarking process

Ensuring adequate representation

It is important to collect insight from all levels of the organization.

Planning in detail

Careful sequencing of the required steps such as document reviews and interviews in a work plan.

Managing information

Take detailed notes and assemble the documents that provide evidence of meeting any of the sub indicators as well as information regarding the conduct of the self-benchmarking itself.

Following up

Provide a detailed report, with copies or links to supporting documents.

The WHO Manual for Benchmarking of the National Regulatory System of Medical Products and Formulation of Institutional Development Plans (6)provides the required guidance on the benchmarking of regulatory systems for medical products, and the development of IDPs to address areas for improvement.

For small states, it may be challenging to assess all 268 sub-indicators. Hence small market states may choose to focus on the subindicators associated with the essential regulatory functions.

Models of Regulatory Efficiency

Considering the limited regulatory capacity that may be available to the NRAs of small states, efficiencies can be gained by using the decisions of well-established regulatory authorities as the basis for functions such as the registration and market authorization process. This is known as reliance.

Reliance occurs when an NRA uses information and/or evaluations performed by a different institution to reach its own decisions. Both PAHO and WHO support reliance among regulators as a tool to make the best use of available resources and expertise. In 2021 WHO published **Good Reliance Practices (GReP)(4)**. If adopted properly, GreP allows NRAs to leverage the output and expertise of other NRAs, when possible and appropriate, allowing them to concentrate efforts and resources on value-added regulatory activities that cannot be undertaken by other authorities, such as pharmacovigilance and oversight of distribution across the supply chain and local manufacturing. The practice of regulatory reliance is encouraged by PAHO and PANDRH, which identifies five principles for practicing reliance: **sovereignty, transparency, consistency, legal basis, and competency.**

One of the most common applications of reliance is the registration and market authorization of a product where one NRA uses the results of another's assessment report to help decide on the approval of a particular product. The relying NRA remains responsible and accountable for decisions taken, even when it relies on the decisions and information of others.

Recognition falls under the umbrella of reliance, but is a specific form, and occurs when an NRA adopts the decision of another NRA. Mutual recognition agreements to accept the results of domestic Good Manufacturing Practices (GMP)(7) inspections of drug manufacturers is a common form of reliance used by regulators. Recognition should be based on evidence that the regulatory requirements of the reference NRA are sufficient to meet the regulatory requirements of the relying NRA. Recognition may be unilateral, bilateral, or multilateral, and is usually the subject of a policy or legal agreement.

Another important form of reliance is **work-sharing**, whereby the NRAs of two or more jurisdictions divide and/or share activities to accomplish a specific regulatory task. Common examples of work-sharing include joint assessment of applications for marketing authorisation, joint GMP inspections, joint evaluation of risk management plans, and joint development of standards and technical documents. Work-sharing requires the exchange of information within the context of each party's legal framework and is subject to information-sharing and confidentiality agreements between the work-sharing parties.

Reliance, recognition, and work-sharing can be used in a variety of ways to facilitate decision-making, but central to each of these methods is the concept of a trusted NRA, serving as a reference authority. Reliance, recognition, and work-sharing are important considerations in this regard, and these can be expanded upon further with **regionalization**, a reliance approach in which a group of countries or regional organizations combine their resources in regulatory activities using common policies and procedures and committing to share information. Regionalization increases the market size available to a manufacturer,

standardizes the regulatory requirements, and enables small states working together to achieve an appropriate oversight of products that would not be possible if they were working alone. Regional networks can also provide a "single window" entry point for manufacturers to gain regulatory authorization for several countries in a region.

One prominent example of regionalization is the Caribbean Regulatory System (CRS). The CRS is the result of an initiative of the Caribbean Community and Common Market (CARICOM) and is managed as a regulatory unit within CARICOM's regional public health body, the Caribbean Public Health Agency (CARPHA), with support from PAHO, WHO, the PAHO designated NRAR and the Bill and Melinda Gates Foundation. Through the CRS, manufacturers can apply for market entry among CARPHA Member States providing a combined market of over 18 million people. Using a streamlined review process based on reliance, the CRS provides faster access to this market for manufacturers while reducing the resources needed to review medicines for market authorization. The CRS' review also identifies potential safety issues that may require ongoing additional or enhanced monitoring.

The CRS requires the filing of a submission containing an attestation that the product is the same as in reference authority country, a copy of the reference NRA's marketing authorization; a summary of product characteristics, labelling, GMP compliance certificates for the manufacturing sites from a reference authority, batch certificates of analysis, finished product specifications, proof of therapeutic effect and safety, or bioequivalence, stability studies, periodic safety update reports (in some cases), and quality information summaries. The CRS' review is targeted for completion within 60 days. The Member States are then responsible for issuing marketing authorizations, within a recommended 60 days of communication of the CRS decision.

The CRS also manages the VigiCarib network for sub-regional pharmacovigilance, and reports medicines-related adverse reactions and substandard and falsified products to the member states and global monitoring systems.

Other practices, such as **fast-track reviews** of products for urgent public health needs, and **information sharing** amongst NRAs for market surveillance and control and pharmacovigilance purposes are important efficiency promotors for small state NRAs (Table 2).

TABLE 2

Key Approaches to Enhance Regulatory Efficiencies in Small States/Markets

Efficiency	Description and benefits
Regionalization	It occurs when countries or organizations with similar characteristics collaborate to accomplish regulatory functions. In the regulation of medical products, this can result in a single portal of entry that increases market size, reduces fragmentation of standards, and enables countries to conduct regulatory functions collectively or through individual members performing functions on behalf of others.
Reliance (including recognition)	The act whereby the NRA in one jurisdiction may consider and give significant weight to assessments performed by another regulatory authority or trusted institution or to any other authoritative information, in reaching its own decision. The relying authority remains independent, responsible, and accountable for the decisions taken, even when it relies on the decisions, assessments, and information of others. Recognition, a form of reliance, is the acceptance of the regulatory decision of another regulator or trusted institution. Recognition should be based on evidence that the regulatory requirements of the reference regulatory authority are sufficient to meet the regulatory requirements of the relying authority. Recognition may be unilateral or mutual and may, in the latter case, be the subject of a mutual recognition agreement.
Fast-track/ accelerated reviews	Many NRAs employ mechanisms to speed the processing of products deemed of high public health value. These can occur with a reprioritization of resources and focus or can be the result of shortened reliance-based processes. Product safety, efficacy or manufacturing quality standards should not be compromised.
Work sharing	A process, usually within the context of reliance, by which NRAs collaborate on regulatory activities such as assessing applications for marketing authorization, joint work in post marketing surveillance of therapeutic product safety, among others. Benefits include conserving staff and time resources and pooling scientific and regulatory expertise.
Information sharing	A process whereby information on a variety of regulatory activities is shared either publicly or confidentially. It can be particularly helpful to share postmarked surveillance information among countries that have common products in their markets.
Digitization	Digitizing systems using commonly available software can provide benefits ranging from easier searching and organization of records to decreased need for physical storage space. Allows for digital submissions that can attract off-site and foreign manufacturers. Use of a public website for the NRA on the Ministry of Health webpage can be an inexpensive way to dramatically improve transparency and accountability, such as through publishing lists of approved products, licensed importers, and enforcement actions.

Source : Preston, C., et al. Addressing the challenges of regulatory systems strengthening in small states. BMJ Glob Health 2020 Mar 2;5(2): e 001912. doi: 10.1136/bmjgh-2019-001912. ecollection 2020.

Developing a Human Resources Plan

Human resources (HR) planning is the process of identifying current and future human resources needs and determining as to how the existing human resource capacity of the organization can be utilized to fulfill these requirements. It involves securing the right people for each role, building a suitable work environment, and developing the capacity to ensure the organization's ability to meet the needs of the present day and the future. Human resources planning is more than just the hiring of people. It includes looking at innovative ways to maximize the resources available and promote efficiencies in work processes.

Most HR planning processes will involve the following four broad steps:

1. Assessing the current HR situation

Assessment of the current human resource availability in an organization is the key first step in HR Planning. It includes examining the current human resources of the organization in terms of numbers, skills, talents, competencies, qualifications, experience, age, tenures, performance ratings, designations, grades, compensations, benefits, etc.

Factors to consider when assessing the impact of staffing on regulatory oversight is the ratio between technical and administrative staff, their level of education, and the proportion of permanent versus temporary or contract workers. In general, too many administrative staff may come at the expense of scientific work, and too many.

temporary staff can harm continuity of mission and purpose and pose a threat to control of conflicts of interest. Because regulatory oversight is complex, it requires hands-on training, coaching, and time, in addition to the usual professional qualifications. Therefore, low retention and high staff turnover are generally considered to hinder regulatory performance, consistency, and predictability.

2. Determining future HR needs

Analysis of the future workforce requirements of the organization is the second step in HR Planning. The results of the assessment of the current HR situation will provide some valuable information regarding future HR needs, by identifying foreseeable future vacancies due to retirements, promotions, or likely departures from the organization. A determination of future needs must also consider the desired state of the organization, in terms of the activities not currently performed but which the organization plans to implement. This analysis needs to consider not only the number of staff needed for each function, but also the qualifications necessary for any hires.

3. Create an HR needs forecast

The next step is to match the current HR supply with the future HR needs and determine what is needed. Again, it is essential to know the longer-term objectives of the organization so that the demand forecast is aligned to those objectives. For small market states wishing to establish a national regulatory system that meets the essential criteria, resources will be needed for:

- The drafting of legislation, regulations.
- The implementation of procedures, as well as the ongoing costs for the maintenance of the registration and market authorization
- Post-market surveillance/pharmacovigilance programmes
- Conducting licensing and inspection activities
- Administrative, legal and information technology support.

Small states must plan to have at minimum one full time resource person dedicated to the pharmacovigilance and market surveillance and control activities plus capacity to backfill this position urgently on a temporary or permanent basis, as needed. This is particularly important to ensure that these activities, which are of equal priority, are conducted in a way that facilitates the identification and the assessment of safety signals expeditiously, allowing appropriate and timely actions to be taken.

4. Develop a "Sourcing Strategy"

After reviewing the HR needs forecast, develop and implement a plan to obtain the necessary resources. The strategy should include options not only for the creation of positions and hiring of new staff, but reallocation and training of existing staff to meet the organization's objectives.

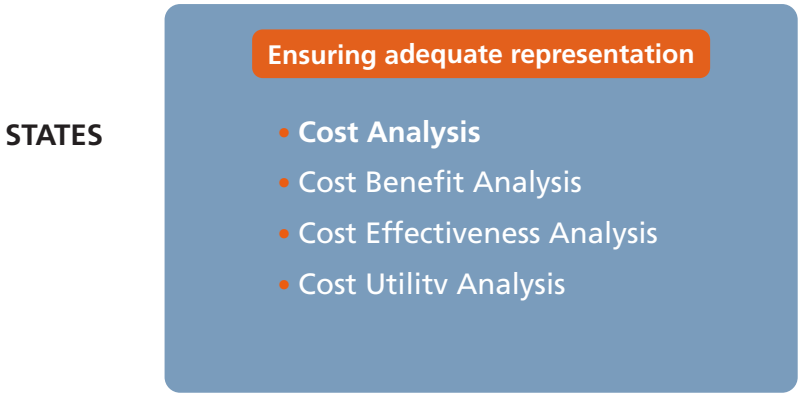
To implement a sourcing strategy, the necessary budget and finances must be obtained. This will necessitate a cost analysis, to accompany the HR Plan. A cost analysis will also aid in determining what fees, if any, should be charged for various regulatory activities and the development of a fee structure.

Conducting a Cost Analysis

To implement a national regulatory system which can perform the essential functions, it is imperative to know what resources are needed and what financial support will be necessary to put those resources in place. A cost analysis is a type of economic evaluation that focuses on the costs of implementing a program without regard to the ultimate outcome. A cost analysis is an important first step before engaging in other types of economic evaluation to determine the suitability or feasibility of a potential project (Figure 3). However, it is recognized that the limited budget that may be available in many small states will affect the scope of the activities that can be conducted.

FIGURE 3

Types of Economic Evaluation



States should conduct a cost analysis, to determine the costs and resources necessary to implement a national regulatory system for medical products. This cost analysis should include the cost of resources needed in the short term, for the drafting of legislation, regulations, and the implementation of procedures, as well as the ongoing costs for the maintenance of the registration and market authorization, vigilance and market surveillance programmes and licensing and inspection programmes. A concrete analysis of the costs involved can help secure the resources necessary and convince senior government officials that the benefits will outweigh the costs in the longer term.

The cost analysis will need to estimate the costs involved in developing, implementing, and maintaining:

A A registration and market authorization system

Market authorization for imported products can be based on reliance, taking on the decisions made by the CRS and other well-established NRAs. The use of reliance can preserve the valuable human and financial resources in small states, increase commercial incentives for industry to operate in these markets and ultimately accelerate access to priority medicines for patients. Resources will be needed to monitor regulatory decisions, verify that the product is identical to that which has been approved by the other authority, issue a country-specific registration and market authorization, and maintain databases of the authorized products and their labels.

For locally manufactured products, resources will be needed for a science-based assessment of the product's safety, efficacy and quality to support the issuance of a registration and market authorization. It is important that the domestic regulatory can conduct this function, necessitating the availability of resources to fulfill this function.

Even with the use of reliance, it is important to take a risk-based approach to the registration and market authorization process, particularly the quantity of information about a product that must be submitted. For very low risk products, for example, a simple verification of the product's marketing status in a reference country may be sufficient, with little supporting documentation required.

B Licensing and inspection systems

In states that rely on imported products, licensing of importers, distributors and retailers is of importance. Having local manufacturers introduces a high level of complexity to a small state's regulatory strategy, because licensing and inspection of manufacturing facilities requires the implementation of more complex regulatory functions. As a result, small market states should decide if local manufacturing provides enough value to the health system to merit the establishment of a comprehensive regulatory system.

Small states should not prioritize the conduct of GMP inspections of foreign manufacturing establishments, as the resource needs for foreign inspections are heavy. Verifying the GMP compliance status of foreign manufacturing sites is one of the most common uses of reliance. Many NRAs globally, including established reference NRAs, share and rely on GMP inspection reports of the national NRA of a foreign manufacturer, or another established NRA, particularly one which is a member of the Pharmaceutical Inspection Co-operation Scheme (PIC/S)(8). Many countries have Memoranda of Understanding allowing for the sharing of inspection reports, or Mutual Recognition Agreements allowing them to accept the inspection results of another NRA.

C Pharmacovigilance and market control and surveillance systems

Post market surveillance is a function that needs to be performed locally. However, efficiencies can be gained via the use of regional networks for sharing information on products and reliance on regional laboratories for product testing.

Small market states should have a mechanism for spontaneous adverse reaction reporting by stakeholders, preferably one that captures also reports of substandard and falsified products. Resources will be needed for the development of standard reporting forms, and guidance, although these resources can be minimized by using those produced by other jurisdictions as a model. It is imperative that there be human resources assigned to receiving, investigating, and analysing these reports, to guarantee that the country readily detects and responds to problematic products on their markets.

The cost analysis should also include estimates for implementing digital systems for regulatory processes, using available software. Digitization can serve to streamline processes and the searching and organization of records while significantly reducing the need for physical storage space.

Some parameters requiring consideration in the conduct of a cost analysis are shown in Table 3.

TABLE 3

Elements of a Cost Analysis

Resources Required	Specific Function or Purpose
Personnel (salaries and benefits)	• Drafting of legislation and regulations • Ongoing legal support • Registration and Marketing Authorization • Monitoring, inspection and pharmacovigilance • Enforcement
Physical Space and Infraestructure	• Office space • Computers, software, and office equipment • Vehicles for inspectors, enforcement
Technical support	• Data compilation • Information dissemination and communication • Website maintenance
Financial and Administration	• Domestic travel for inspectors • Employee training • Stalkeholder information sessions

Summary

Completion of these foundational activities will help governments and NRAs set the stage to develop or advance a national regulatory system for medical products. The Toolkit is intended to provide general recommendations and observations for broad guidance. It can be adapted by a state based on its specific needs, which PAHO recommends be incorporated through an internal review of the state's regulatory capacity and the desired level of advancement.

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