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

VOLUME 3

Implementing a Registration and Market Authorization Scheme

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
CPP	Certificate of Pharmaceutical Product
CRS	Caribbean Regulatory System
CT	Clinical Trials' Oversight
EML	Model List of Essential Medicines
GBT	Global Benchmarking Tool
GMP	Good Manufacturing Practices
GReP	Good Reliance Practices
GRevP	Good Review Practices
GRP	Good Regulatory Practices
ICH	International Council on Harmonization
IMDF	International Medical Devices Forum
INN	International Non-Proprietary Name
MA	Registration and Marketing Authorization
ML	Maturity Level
MoH	Ministry of Health
NRA	National Regulatory Authority
PAHO	Pan American Health Organization
PIC/s	Pharmaceutical Inspection Cooperation/Scheme
SF	Substandard or Falsified
SOP	Standard Operating Procedure
VL	Vigilance
WLA	WHO-Listed Authority
WHO	World Health Organization

Introduction and Background

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 It should also identify the circumstances under which a marketing authorization already granted may be withdrawn, suspended, or revoked.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 authorization.

The decision on how to develop and implement the required capacity for granting market authorizations in a small market state must be based on its local context, particularly in consideration of whether local manufacturing exist or whether the medical products used are strictly imported. The development and implementation of a medicines regulatory oversight framework in small market states need to consider existing health care processes in place to avoid leading to significant disruptions that could put the entire population at increased risks. Knowledge and tracking of products that are being manufactured in or imported into the country is a pre-requisite to the establishment of a registration and market authorization scheme.

The development of a long-term stepwise process to establish the system responsible for issuing a registration and marketing authorization is strongly encouraged. This document outlines a suggested step-wise approach, but this will need to be tailored to address the specific context of the country, in consideration of the nature and type of any local manufacturer, the types of products that are considered essential and whether the state has no or minimal system currently in place or is looking to strengthen an existing registration and market authorization system.

The Stepwise Approach

STEP 1

Inventory the products being used

The first step towards the actual establishment of a registration and market authorization system is to complete an inventory of all medical products that are currently being used in the state, whether imported or domestically manufactured. This is sometimes referred to as a **notification system**. It is an information gathering process, with no judgement being made on whether the product is needed or meets any types of marketing requirements.

A notification system will require the National Regulatory Authority (NRA) or Ministry of Health to inform each facility known to be purchasing and importing medical products (pharmacies, hospitals, distributors, wholesalers and retailers public, or private) of the need for them to reply, by a specified date, providing information on all medical products they are purchasing. Standard information about each product, such as the international non-proprietary name (INN), trade name if any, manufacturer(s), country of origin and importer, dosage form, and how the product is packaged and supplied is obtained and entered into a register.

Examples of standard information form

Trade Name/INN*	Manufacturer (company name)	Country of Origin	Importer name/ address	Strength/ Concentration	Route of administration and Dosage	Packaging/ Pack size	Storage Conditions

Most products imported should have a Certificate of Pharmaceutical Product (CPP) document as a shipping document and which could be used as a reference to populate a national database. The CPP provides verified data on a medicine's approval status and manufacturing standards. For more information, please see Model certificate of a pharmaceutical product.

Voluntary compliance is preferable and should be pursued as a first step in obtaining the information, but in the likely event that not all facilities reply during the timeframe provided, legal means to compel compliance should be used if available, such as policies or regulations. The inventory of existing legislation conducted as described in Volume 2 of this Toolkit will help identify any law that can be used to compel a domestic facility to provide information to the authority when requested.

An electronic database or digitized system will be necessary to establish, update and maintain this registry. Preferably, this registry can be published as an online database or list that will allow eventual access from outside the NRA, by health care professionals and members of the public, through an NRA website.

STEP 2

Establishing a List of Essential Medicines

Essential medicines are those that satisfy the priority health care needs of a population. They are selected with due regard to disease prevalence and public health relevance, evidence of efficacy and safety and comparative cost-effectiveness. They are intended to be always available in functioning health systems, in appropriate dosage forms, of assured quality and at prices individuals and health systems can afford. The selection of a limited number of medicines as essential, taking into consideration national disease burden and clinical need, can lead to improved access through streamlined procurement and distribution of quality-assured products, support more rational or appropriate prescribing and use, and lower costs for both health care systems and for patients.

The WHO Model List of Essential Medicines (EML)(13) is a register of minimum medicines needs for every health-care system. It serves as an evidence-based guide for products for rational selection and prescribing. The medicines in the list should be always available in the health system for all people. The idea behind the list is that the use of a limited number of well-known and cost-effective medicines would lead to improved long-term medicine supply, lower costs, better health care and more equitable and sustainable access to products. First published in 1977, the WHO EML is revised every 2 years by a committee of experts from around the world in fields such as medicine, pharmacology, policy, regulation, and health organizations. The WHO EML list is not meant to replace domestic lists or formularies, but to inform and guide selection and purchasing decisions in the context of national health agendas. Differences between the WHO EML and domestic medicines lists are expected, given the diversity of countries' health challenges and resources.

The procedure to create and revise the EML has changed substantially over time. In response to concerns about the original methodology to update the list, an approach based on more objective and systematic assessment of the evidence was adopted, which included the careful appraisal of efficacy, safety,

cost-effectiveness, and public-health relevance. Applications for inclusions, changes or deletions to the list can now be prepared by external institutions, but such requests must be evidence-based and must explain why a specific drug meets the criteria for inclusion in the list. Factors such as disease prevalence, scientific evidence and comparative cost-effectiveness are also considered. Each of these factors contributes with a different weight to the decision process, depending on which kind of medicine is under evaluation for which condition.

The WHO EML was established with the goal of making the included therapies widely available and affordable, but with time the selection of medicines for inclusion has also become increasingly complicated by the escalating prices of new drugs entering the market. Regardless, it remains a voluntary guideline for national formularies. In that regard, health authorities in small states are encouraged to consider the possibility of modifying and adapting it to their own purposes. PAHO can provide technical guidance for this purpose.

While the EML is an important approach on priority medicines with public health relevance, a health care system may require broader and specialized lists in addition to the EML to support public procurement decisions, clinical practice and insurance coverage. A National Formulary, for instance, can be an alternative if an extended approach to the EML is needed. Some countries prefer to use a VEN list (Vital, Essential, Necessary) such as in Jamaica.
Also refer to medlist.paho.org/search/

STEP 3

Establishing a list of provisionally authorized medicines

Once the inventory described in Step 2 is finalized, and provided that the required legal framework is in place or under development, the development and implementation of a new registration and market authorization scheme by the NRA can start. The first step should be the production of a list of provisionally authorized medicines and their suppliers. This list should be developed based on the initial inventory of medical products being used in the state, excluding any products where justification exists that they should not be provisionally authorized (e.g., products with questionable, missing, or contradictory information in the inventory; products that were received as gifts or donation; expired or soon to be medicines, etc.). The list should be made public and include the qualification that it remains in effect only until decisions on market authorization can be made under the pending registration and market authorization system. Any product not on the list of provisionally authorized medicines would only be added at the request of the importer and with sufficient justification.

There should always be a provision or procedure for allowing access to a non-authorized medicine in a special or emergency, such as a situation of a rare disease, or where existing therapies have failed.

STEP 4

Transitioning products to a Registered and Market Authorized status

From the list of provisionally authorized medicines, the NRA needs to establish and implement a process to determine which products should be "grandfathered" (given an automatic market authorization based on need, history from time already on market and market authorization status in other countries with trusted NRAs) as authorized medicines when the system is in place.

The initial steps of the process to define which products from the provisionally authorized list should be grandfathered, could include:

1. Establishing criteria of eligibility of products for grandfathering. Considering resource limitations and small market state needs, selecting products in the state's essential list of medicines, if available, or in the WHO Model EML, appears as a logical key criterion to consider for the grandfathering prioritization.

2. Defining the conditions to apply to the grandfathering of eligible products. In the absence of well-established procedures of product regulatory assessment for marketing purposes, small market states need to find acceptable elements from the review of relevant information or use reliance from recommendations made by others after the assessment of these eligible products. If available, relying on positive recommendations for authorization issued by a regional regulatory body, such as CRS, or a trusted regional NRA should be strongly considered for grandfathering. It would be prudent to consult the WHO Alerts to verify that there are no ongoing alerts or recalls for suspected Substandard or Falsified (SF) products related to potentially eligible products.

3. Eligible products with no related-regional regulatory body recommendation, will need to follow an alternative procedure with some extra steps. For those products, the grandfathering decision could be based on reliance and verification. The following procedure could be proposed:

    - Products that are WHO prequalified, or that have been authorized by a trusted regulatory authority (e.g., WHO listed authorities, U.S. Food and Drug Administration, Health Canada, European Medicines Agency, or a PAHO National Regulatory Authority of Regional Reference could also be considered for grandfathering authorization, but after formal confirmation by the manufacturer and verification by the NRA, that the product in the local market is the same as the one approved by the trusted authorities.

    - Products approved by a trusted regulatory authority, but with no formal verification and confirmation by the manufacturer, should be considered for authorization, only after additional product assessment by the local NRA.

4. Once the grandfathering determination is completed, notify the manufacturers and importers of those newly grandfathered authorized products. They should be informed that these products are being transitioned to the new registered/market authorized system under development, and that additional regulatory obligations could follow post-market.

5. Develop and implement procedures to conduct regulatory reviews of all those products that were not authorized via the grandfathering approach.

STEP 5

Defining Pathways for Registering New Products

Following the transition phase and the grandfathering of previously imported products, small market states must move toward establishing a formal registration and market authorization (MA) process for all new products entering the national market. The implementation of this process can follow three different pathways, depending on the regulatory capacity and resources available to the country (Table 2). These are:

- Reliance on a reference NRA – for products authorized by trusted authorities such as WHO-Listed Authorities (WLAs), the U.S. Food and Drug Administration, or the European Medicines Agency (EMA); or the PAHO National Regulatory Authorities of Regional Reference.

- GMP certification only – for products not authorized by a reference NRA, but manufactured at a site certified by a PIC/S member authority;

- Full national review – for products

In the context of small states, Pathway 1 is strongly recommended as the preferred and most resource-efficient approach. This pathway aligns with WHO Good Reliance Practices (GReP) and allows countries to benefit from assessments already conducted by trusted regulators. The example of the Caribbean Regulatory System (CRS) illustrates how such a reliance-based approach can be operationalized effectively in the region. The remainder of this section focuses primarily on how to implement Pathway 1, while also acknowledging the conditions under which Pathways 2 or 3 may be necessary.

TABLE 2

Potential Pathways for registering new products

Pathway	Criteria	Type of Review Needed	Regulatory Action	Risk Level
1.Approved by a Reference NRA	Product is authorized by a trusted/reference NRA (e.g. CRS, NRA of regional reference, WLA) AND sameness is verified	Minimal or no additional review (verification only)	**Register via reliance** - accept or abridge the local process	Low
2. Manufacturing Site Certified by PIC/S Member NRA	Product is not registered by a reference NRA, but manufacturing site is GMP certified by PIC/S member	Partial review verify GMP, assess limited queality documentation	**Conditional registration** based on GMP + limited data	Medium
3. Neither authorized nor PIC/S-certified	Product is not authorized by a trusted NRA AND manufacturing site is not GMP-certified by a recognized authority	Full national review of quality, safety, efficacy dossier	**Full registration required-** full dossier assessment needed	High

In addition, ad hoc procedures may be created to accommodate special cases while respecting the quality reference criteria of the three main pathways. Examples of such procedures include:

- Importation of products procured via PAHO Strategic or Revolving Fund.
- Emergencies.
- Donations as stated in WHO Guidelines for Medicines Donations: There should be no double standard in quality. If the quality of an item is unacceptable in the donor country, it is also unacceptable as a donation. The NRA's role is to verify that this requirement is met (in addition to the main criteria mentioned above: reliance or GMP verification).
- Special access schemes. Applications concerning import permits for products that are not authorized for marketing. Precondition: a regulation and guidelines are in place providing details for making use of this pathway.

STEP 6

Operationalizing the Pathways

Pathway 1-Reliance-Based Registration

The most efficient and resource-conscious method for small states to register new products is to rely on the decisions of trusted regulatory authorities, often referred to as reference NRAs. Under this approach, products that have already been authorized by a reference NRA—provided they are identical in essential characteristics—may be registered locally through a verification process, avoiding duplicative assessments. This model is strongly encouraged by WHO and aligns with the principles of Good Reliance Practices (GReP) and the WHO Global Benchmarking Tool (GBT).

Countries must formally define which NRAs they consider "trusted" for the purposes of reliance. According to WHO recommendations, these may include:

- NRAs that are part of the WHO-Listed Authorities (WLA) framework (once established), or those evaluated as maturity level 3 or 4 under the WHO GBT.
- Authorities that conduct transparent, science-based product assessments and regularly publish regulatory decisions or assessment reports in accessible formats.
- Members of international regulatory networks, such as PIC/S, ICH, or IMDRF.
- NRAs that are formally recognized within regional systems, such as the Caribbean Regulatory System (CRS), or PAHO's National Regulatory Authorities of Regional Reference.

It is recommended that countries develop an internal policy or standard operating procedure (SOP) to clearly identify their reference authorities and define how reliance decisions will be applied.

An application for registration and marketing authorization based on verification should include, at minimum:

- A certificate of GMP compliance from a trusted, reference regulatory authority
- Verification of the authorization status of the product by one or more trusted regulatory authorities via a market authorization letter or certificate issued by the authorizing NRA.
- A verification of sameness (as defined in the WHO Good Reliance Practices document) This is an essential step for any reliance approach, checking that the product has "identical essential characteristics" as the one authorized by the trusted, reference authority or provision of Certificate of Pharmaceutical Product issued by the exporting country under the WHO Certification Scheme
- A copy of the product labelling, necessary for patient education and information and to reduce the possibility of counterfeit or falsified versions of the product being distributed.
- A signed statement from a representative of the manufacturer certifying that the information submitted is correct and certifying agreement to have the product registered and marketed in the country.
- Contact names and addresses of the manufacturer and any agents working on the manufacturer's behalf.

A simple way to implement a registration and market authorization process based on reliance is to recognize recommendations of the regional regulatory bodies such as CRS or one or more trusted, foreign NRAs. For example, for Caribbean Community and Common Market (CARICOM) countries, any new product that has received a positive recommendation from the CRS could be recognized as authorized, and the manufacturer notified of such. The review process of CRS has already verified the information supporting the safety, efficacy and quality of the product, and its suitability for marketing in the Caribbean region. Furthermore, the manufacturer has also indicated, via filing to CRS, its agreement to be authorized by Caribbean countries and presumably manufacturers would have no objection to their product being authorized for marketing in other small, non-Caribbean states in the PAHO region.

Operationalizing other Pathways

For products not recommended by a reference authority but manufactured at sites certified by a PIC/S Member NRA, these should only be authorized at the request of the interested party wishing to import it and subject to the same criteria as the decision-making on grandfathering, including a verification review of its global regulatory status with trusted authorities or its WHO pre-qualification status and verification that the product imported will be the same as distributed globally. The importers should be responsible for obtaining the information from the manufacturer to support its authorization.

Products not meeting the Pathway 1 or 2 criteria will require a full assessment of quality, safety and efficacy information prior to the issuance of a registration and marketing authorization.

As previously mentioned, there are other, simple forms of marketing authorization that can be used by small states, but they are limited in the amount of regulatory oversight they provide. A list of countries from which drugs can be imported, or the publication of a list of products deemed authorized by virtue of their global regulatory authorization status can serve as rudimentary market authorization processes, but they provide no mechanism of verifying that the product being imported is of the same quality as what is available elsewhere and provide no mechanism to monitor and trace what is on the market. However, these methods may be useful as part of the transition process towards implementing a more complete market authorization process and should be considered by small states.

The development of a checklist of requirements for a Registration and Market Authorization application is recommended and can be used by both the NRA and the party submitting the application.

Special situations, emergencies and pandemic preparedness

Certain circumstances can lead to a need to register products in an accelerated fashion or allowing for a bypassing of normal regulatory requirements. These circumstances can include but are not limited to shortages of essential medicines, natural disasters, disease outbreaks and pandemics. In emergency situations, it is advised to adopt a risk-based approach that considers the severity and magnitude of the emergency when evaluating products in conjunction with various regulatory pathways.

To respond to emergency situations, it is imperative that an NRA's enabling legislation provides the authority for a deviation from the regulatory requirements that would apply in a non-emergency situations. The WHO GBT describes the necessary indicators to be met to ensure an NRA's capabilities to respond to emergencies. These are:

- Are there legal provisions to cover circumstances under which the routine market authorization procedures may not be followed in an emergency (e.g. Is there an Emergency Use Authorization procedure or equivalent)? (GBT indicator MA1.06, ML1)

- Are there legal provisions or regulations that define regulatory requirements and procedures to approve the use of donations of medical products? (GBT indicator MA1.07, ML1)

- Are there legal provisions or regulations related to circumstances in which routine clinical trials regulations may not be followed in an emergency? (GBT indicator CT1.05, ML2).

- Are there legal provisions and regulations that allow the NRA to require manufacturers and/or market authorization holders to conduct specific studies on product safety and effectiveness under specific conditions (e.g. public health emergencies)? (GBT indicator VL1.04, ML2).

In addition to legal provisions, NRAs are advised to have guidelines and SOPs defining the criteria to be applied to considering that a situation constitutes an emergency with respect to the supply of medical products, and what procedures are used administratively as alternatives to standard procedures. While it is impossible to foretell every type of emergency that could arise, set criteria and procedures for the use of emergency provisions will help prevent misuse of these alternate pathways.

Conducting Scientific Assessments

While non-producing states can use reliance and recognition as the basis of their registration and market authorization system, the presence of locally produced products places an additional and different level of burden and responsibility on the domestic NRA. Thus, in accordance with the GBT, the NRA of a country with local production will need to establish regulatory capacity in the main functions of a regulatory system for medical products and the use of reliance may not be sufficient when considering the need to issue a registration and marketing authorization for a locally produced product. NRAs will need to possess the resources and processes necessary to conduct science-based assessments of locally produced products as well as products not produced locally which have not been approved by a trusted reference authority. Small states pursuing local production of medical products should refer to the companion document Roadmap for Strengthening Regulatory Systems for the Oversight of Local Production of Medical Products.

Expertise required to assess an application for registration and market authorization

An NRA needing to conduct product reviews will need appropriate teams of experts capable of assessing the quality, safety, and efficacy of medical products for registration and market authorization. They may also have a responsibility for the review and authorization of applications to conduct clinical trials and investigative studies of products if these are conducted within their jurisdiction. A review team may need to be capable of determining:

- Whether it is reasonably safe to conduct a clinical study of a product in humans and will the design of a proposed study provide the data necessary to show safety and efficacy.
- Whether the methods, techniques, tests, and material used in the manufacturing of the product are adequate to ensure the safety of the product.
- Whether the product is safe and effective in its proposed use and do the benefits of the product outweigh the risks and are the risks appropriately managed.
- Whether there is sufficient data to support the stability of the product in relation to the storage conditions available and appropriate in the state.
- Is the proposed labeling appropriate and if not, what should it contain.

Depending on the type of product being reviewed, review teams may consist of the following members. **It is recognized that resource constraints will influence the extent to which a comprehensive team such as the one described below can be established. The membership described below should be viewed as an ideal and is presented to provide guidance to NRAs in establishing their own teams, to the extent possible considering available resources.**

Project Manager

To coordinate the activities of the review team throughout the review process.

Bioethicists

To examine the ethics of clinical trials and their design if they are conducted in the state.

Clinical Specialists

These specialists review all clinical studies. They are responsible for:

- Evaluating and advising on clinical trial protocol designs, endpoints, and analysis of data from clinical studies for product approval.

Pharmacology/Toxicology Specialist

These specialists review all nonclinical (animal) studies to assess, if applicable:

- The pharmacological action of the product and any potential toxic effects of the products as related to its intended use and any real or potential reproductive and /or fetal effects.

Statistician

These specialists review the statistical analysis plan and conduct or review the statistical analyses of safety and efficacy data provide conclusions on the credibility of the safety and efficacy data.

Chemists/Biologists/Microbiologists

These specialists evaluate the quality of the product by evaluating and assessing the: components, manufacturing, and controls and other related information.

The WHO **Guideline Good Review Practices: Guidelines for National and Regional Regulatory Authorities** provides guidance on the implementation and maintenance of GRevP within an NRA. It defines GRevP as "documented best practices for any aspect related to the process, format, content, and management of a medical product review. The objective of GRevP is to help achieve timeliness, predictability, consistency, transparency, clarity, efficiency, and high quality in both the content and management of reviews. This is done through the development of tools such as standard operating procedures (SOPs) and templates and reviewer training and learning activities. GRevP are part of continuous improvement activities for an NRA, and all aspects of GRevPs should be continuously evaluated and updated".

Post Registration and Marketing

A decision to issue a registration and marketing authorization for a medical product will necessitate the creation of a document, indicating that the product has been authorized. It is also prudent to issue a registration number for the product, which can be used in correspondence with the manufacturer or importer and used as a tool to track the market status of the product. In many countries, there are regulations requiring the registration number to be displayed on the label of the product within the state, but for small states is may not be possible to have products labelled with special, unique requirements. See Volume 4 of this Toolkit, Establishing a Vigilance and Market Surveillance and Control System for additional information.

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