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

VOLUME 5

Developing and Implementing an Establishment Licensing and Regulatory Inspection Programme

In partnership with Canada

PAHO Pan American Health Organization

World Health Organization Americas Region

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Abbreviations and Acronyms

GBT Global Benchmarking Tool

GSDP Good Storage and Distribution Practices

GMP Good Manufacturing Practices

MoH Ministry of Health

NRA National Regulatory Authority

PAHO Pan American Health Organization

PIC/S Pharmaceutical Inspection Cooperation/Scheme

WHO World Health Organization

Introduction and Background

National Regulatory Authorities (NRAs) of small market states must ensure that the importation, storage, and distribution of medical products is conducted in compliance with the highest standards. The licensing and inspection of facilities involved in the manufacturing, importing, distribution and storage of medical products is a vital component of medical products regulation. Hence an establishment licensing and inspection program is an essential activity of a functional national regulatory system.

Licensing and inspection are separate but interacting activities. While the NRA would normally be responsible for the issuance of licences, regulatory inspections can be performed by the NRA itself or can rely/recognize the inspection by another NRA, or by an independent third party. Both inspection and licensing are necessary activities to ensure that products are manufactured and distributed in accordance with Good Manufacturing Practices (GMP) and Good Storage and Distribution Practices (GSDP).

The NRA should be responsible for coordinating the licensing and inspection activities with a program that is based on legal provisions, regulations and guidelines which ensure that establishments throughout the supply chain are adherent to GMP and GSDP and that the NRA has the legal power to issue, suspend or revoke licenses.

As an essential regulatory function, small states seeking to set up an inspection and licensing system should refer to the WHO GBT for guidance which outlines the indicators that should be met to have a functional licensing and inspection program in place. Small states are likely to have little or no local manufacturing, meaning that the licensing and inspection process will be focused on importing and distribution establishments, including hospitals and pharmacies.

Licensing Establishments

The licensing process will require an application on the part of the establishment importing or distributing products. Many jurisdictions in the Americas, such as Belize, have developed and published license application forms which can be used as a model. The licensing procedure will also require the creation of a document that forms the actual license, containing the name and address of the facility, the activities the establishment is licensed to perform, the products handled, and the duration of the license (the period before a renewal of the license is required). The NRA should regularly post a listing of the licensed facilities on their website, preferably in a searchable database.

General elements of an application for a licence to manufacturer, import or distribute medical products

- Name and address of facility
- Nature of facility and activity
- Type of licence (new, amended, renewed)
- Type of product and detailed attached list with manufacturer and origin
- Designated contact officials
- Signed certification
- Accompanying documentation to support quality of medical products

An NRA will need to develop criteria and conditions for the period a license is valid before requiring renewal, as well as for amending a license. These criteria and conditions should be clearly communicated in regulations and guidance. Many jurisdictions issue licenses requiring renewal after one, two or five years, but the determination of the appropriate period for duration of a license must be made by each NRA in consideration of its resources and the nature of the manufacturing, importing and distributing activities in the jurisdiction. For example, to issue licenses requiring renewal every year is extremely resource intensive and may place an unnecessary burden on both the facility and the NRA. Similarly, the requirement to amend a license must be restricted to situations involving the addition of a new activity or product, or other changes of significance.

When a national regulatory system is first being established, consideration should be given to a "grandfathering" of any establishments identified as already importing, distributing, or retailing products and identified under the Notification System described in Volume 3 unless there is known cause not to issue a license. This is important in order not to interrupt the supply of necessary products to the country. Any new establishment wishing to begin manufacturing, importing, distributing, or retailing medical products would need to apply for a license, and possibly be subject to an inspection before a license is issued and the activity can begin.

An up-to-date list or database of all licensed facilities should be published and publicly available.

Inspections

An inspection function is vital to securing the quality, safety and efficacy of medical products used by the population in a state. However, even for well-resourced NRAs, the function must be justified and risk-based since it is a very resource-intense activity. Inspection activities must be prioritized based on risk and balanced against the resources available. NRAs of small states should not undertake inspections of foreign manufacturing facilities but instead should use reliance on trusted NRAs and public databases, such as EudraGMDP and WHO prequalification databases to verify compliance with GMPs of foreign manufacturers. The focus of inspections must be on the domestic establishments importing and distributing medical products.

When establishing a regulatory system, it is imperative not to interrupt the supply of medical products. Therefore, it will not be possible to prohibit any establishment currently importing or distributing until they have been inspected and then licensed, unless there is cause to do so because of safety concerns. As described under licensing above, establishments performing these activities should be licensed under a "grandfathering" provision until the regulatory system is established. A post-licensing schedule of inspections should then be developed with the highest risk establishment inspected first.

An inspection system involves more than on-site inspections or visits. One element of a risk-based inspection program is desk audits or assessments, where information about the establishment's layout, safety provisions, procedures and activities are submitted to the NRA for review. Desk audits can be a valuable tool to be used in lieu of an on-site inspection or to decide whether to perform a further inspection. Another approach is the use of third parties to conduct inspections. For example, the inspection function for a hospital that is importing or distributing medical products could be performed on behalf of the NRA, by a body responsible for accreditation of the hospital, if legal frameworks allow.

However, a full inspection may be required for establishments that:

- are newly established or operational.
- have introduced new products with storage issues, or has made significant modifications or changes in key personnel, premises, equipment, etc.
- have a history of non-compliance with GSDP or other good practices or
- have not been inspected during the last 3–5 years.

Inspector qualification and training is an essential component of an inspection program. For the inspection of importers and distributors, people with a pharmacy or chemistry background will be required. A training program should ensure knowledge of WHO Technical Report Series, no. 1025 Annex 7 Good storage and distribution practices for medical products and include an apprenticeship by accompanying experienced inspectors on site visits, perhaps in another country via a regional or international collaboration effort.

An inspection can begin with a request to the establishment for information about its facility and operations related to medical products and a desk review of these documents. Copies of self-inspection or internal audit reports can be valuable sources of information and help in the planning for the actual inspection. At a site visit inspectors can use a checklist, developed from the GSDP guidelines to ensure that all areas of operations have been investigated. Checklists are also very valuable tools for the training of inspectors. Inspections can be announced (i.e., a date is confirmed in advance with the establishment) or unannounced. Announced inspections are often used for routine inspections to support license issuance or renewal, and unannounced when inspecting because of a complaint or specific concern about an establishment.

Inspector Training

PAHO offers a training course Inspection of medical products distributors against WHO Good Storage and Distribution Practices on its Virtual Campus for Public Health. This training provides personnel in NRAs with the skills to conduct GSDP inspections of wholesalers and distributors. The course is based on WHO standards and covers all medical products. Specific attention is given to the management of vaccines in the supply chain.

WHO has published numerous guidelines and technical reports to aid NRA inspectors and establishments importing, storing, and distributing medical products

It is important to view inspections not just as a search for deficiencies and irregularities but as an opportunity to provide an establishment with positive suggestions for improvement and to assist in reaching and adhering to GSDP.

Transparency is an important factor in a functional inspection program. Inspection-related information including inspection reports should be publicly available on the NRA website and establishments should be encouraged to authorize the sharing of inspection reports among NRAs.

Establish a Risk-based Approach to Product Life-Cycle Management

It is essential that products, once issued a registration and market authorization, continue to be monitored for safety, effectiveness, and quality via a pharmacovigilance system. However, no regulator, regardless of its size and state of development, has the resources to conduct detailed surveillance on every product and take regulatory action on every issue that may arise. The limited resources of an NRA in a small state, combined with the large number of medical products likely to be in use, emphasize the need for small market states to have a risk-based approach to the monitoring of products across their life cycle, using reliance as a mechanism to enhance monitoring. Product life-cycle management involves more than just adverse reaction monitoring. Product quality must also be addressed, to protect the public from the potential harm from falsified or substandard products. Laboratory testing is integral to post market surveillance programs and small states will need a process to access laboratory facilities using a risk-based testing strategy.

A risk-based system for life-cycle management for a small market state should use information gathered from local adverse event report assessments, information from a regional pharmacovigilance system, inspection, and product sampling for suspected falsified or substandard products followed by laboratory testing, as key activities contributing to the life cycle management of medical products. Risk-based approaches should be used to determine the types of medicines that will be closely followed from a surveillance perspective, sampled, the sampling locations, the sample size, and the appropriate analytical test to perform.

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