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

VOLUME 4

Establishing a Vigilance and Market Surveillance and Control System

In partnership with Canada

PAHO

Pan American Health Organization

World Health Organization

Americas Region

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Abbreviations and Acronyms

ADR	Adverse Drug Reaction
CARICOM	Caribbean Community and Common Market
CARPHA	Caribbean Public Health Agency
CIOMS	Council for International Organizations of Medical Sciences
CRS	Caribbean Regulatory System
GBT	Global Benchmarking Tool
GSDP	Good Storage and Distribution Practices
GMP	Good Manufacturing Practices
GReP	Good Reliance Practices
GRP	Good Regulatory Practices
ICH	International Council on Harmonization
ICSR	Individual Case Safety Report
IDP	Institutional Development Plan
LMIC	Low to medium income countries
MoH	Ministry of Health
MQCSD	Medicines Quality Control and Surveillance Department
NRA	National Regulatory Authority
PAHO	Pan American Health Organization
PANDRH	Pan American Network for Drug Regulatory Harmonization
PIC/S	Pharmaceutical Inspection Cooperation/Scheme
PIDM	Programme for International Drug Monitoring
PV	Pharmacovigilance
WHO	World Health Organization

Introduction and Background

Small states need to prioritize and allocate resources to develop and maintain a system to conduct the minimal regulatory functions that cannot be undertaken by other authorities. Vigilance and Market Surveillance and Control are essential regulatory functions that must be conducted locally.

Pharmacovigilance (PV) is currently defined as the "science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other possible drug-related problems". It aims at preventing drug-related adverse effects to ensure patient safety and promote the rational use of drugs. It must be regarded as an essential public health activity in the state's health system.

In general, the functions of a well-established PV system include:

- **Detection and Assessment of Adverse Drug Reactions (ADRs)** and other medicine-related problems. This includes identifying new, previously unknown adverse effects or changes in the frequency of known ADRs, promoting and encouraging ADR reporting, evaluating the causality, seriousness, classification and frequency of ADRs to determine the risk associated with a product, and implementing strategies to prevent and minimize the risk of ADRs, It also includes collaboration and harmonization with existing ADR collection activities within the country (e.g., national disease control programs, Ministry of Health etc.) as well as international cohorts monitoring ADRs in defined patients or populations.

- **Signal identification, assessment and management i.e.**, of information on previously unknown or poorly characterized adverse events in relation to the use of a medicine, or a combination of medicines.

- **Performing risk assessment and options for risk management.**

- **Identification of quality problems in medicines**, which may result in ADRs.

- **Communication with stakeholders** on aspects related to product safety, including dispelling unfounded rumors of toxicity attributed to medicines and/or vaccines among other misinformation. Disseminating timely and relevant safety information to patients, health care professionals and regulatory authorities, particularly during emergencies.

- **Developing and maintaining drug utilization information.**

- **Identification of issues associated with unregulated prescribing and dispensing of medicines.**

To ensure that small states can implement, and conduct required PV activities, they will need:

- To ideally have at least one full-time employee is named and is fully funded and mandated to conduct PV activities.
- To prioritize the acquisition and use of the Vigiflow platform for reporting ADRs
- To support their national PV staff, identifying and implementing useful national PV structures, and procedures to join and maintain active participation at the WHO PIDM.
- To design a national form to report suspected ADR.
- To provide guidance, promote, and implement the use of the national ADR form.
- To develop procedures to collect, manage, and use the information gathered from domestic ADR reports, ensuring that results from analyses of the ADR information collected are used to support the safe and rational use of medicines.
- To coordinate actions with other countries and to report to the Uppsala Monitoring Centre.
- To establish a national ADR or PV advisory committee able to provide technical assistance for further analyses, if needed. A multidisciplinary committee is encouraged, as members are expected to support diverse tasks including case investigation and ADR causality assessment, risk-benefit assessment, risk management, and, where necessary, crisis management including crisis communication.
- To define clear communication strategies for routine communication and crisis communication.

Although a new PV centre can start operating relatively quickly, the development of the broader PV system is a process that requires time, vision, dedication, expertise, information systems, a database, literature resources, and financing for continuity. Thus, governmental support is needed for national PV coordination, and the related regional and international undertakings. The location of a new PV centre may depend on the organisation and development of the healthcare system in the country and other local issues.

In every region, small states should consider and try to take advantage of country proximity and similarities, to help each other and to develop together a more robust and efficient sub-regional PV systems. By following well-aligned standard forms and procedures, each country could independently implement its own national centre and contribute within the broader regional PV system. A coordinating centre within the sub-regional PV system could function in close communication with the WHO PIDM at the Uppsala Monitoring Centre, for the ADR reporting and monitoring activities. If desired, that centre could also serve as coordinator for joint PV activities to respond to tasks that are part

of the individual national regulatory authorities' responsibilities. In fact, activities like reviewing periodic safety update reports, conducting targeted benefit-risk assessments, or evaluating and monitoring risk management plans, which need to be conducted as part of regulatory duties on medicine safety during the lifecycle of the product, could be easier accomplished if countries in the region share essential medicines lists and resources and work together.

Given local development and recent experience from joint regulatory work activities in the Latin American region, the sub-regional pharmacovigilance system in the Caribbean, VigiCarib, could be further enhanced with active participation of member states, and the use of the CRS as the PV coordinating centre. For that, the WHO Guidelines for the setting up of a PV Centre will be particularly helpful Safety Monitoring of Medicinal Products. Guidelines for setting up and running a Pharmacovigilance Centre. Uppsala Monitoring Centre (the UMC), WHO Collaborating Centre for International Drug Monitoring (2000).

The national ADR reporting form plays a critical role and is a key component of the national PV system. Since it is primarily used to monitor and enable the exchange of ADR information with local and external stakeholders, small market states should consider and take advantage of available international resources and standards when designing their form, particularly those developed by the WHO PIDM. To be effective, a reporting form needs to be available in the local language(s), have the required fields for reporting, including for vaccines, and have features relating it to the responsible authority (e.g. a logo, and the address and contact details of the issuing institution). Reporting needs to be made as convenient as possible. If other methods are available, they may be preferred by some health professionals, but full confidentiality needs to be respected. (e.g., Examples and good practice in designing an ADR reporting form. UMC WHO (2014).

Promoting Spontaneous Adverse Drug Reaction Reporting

Spontaneous reporting of suspected ADR is the most used method of surveillance throughout the world. Despite well-known limitations related to risks of reporting bias, underreporting, and lack of information on actual product use, spontaneous reporting has played and continues to play a major role in the identification of safety signals throughout the marketed lifetime of medicines in general. The development of an ADR reporting culture using a newly designed national ADR form, requires time and a regular communication with relevant stakeholders. It is important to develop a positive attitude towards PV among healthcare professionals and the public so that ADR reports are submitted routinely and become valued, well-accepted and understood.

ADR reporting is commonly perceived as a voluntary activity for the public and healthcare professionals, while mandatory for market authorization holders. However, if desired, consideration can be given to a longer-term transition to make reporting by hospitals mandatory via regulation. Regardless, it is important to highlight that small states need to focus their PV efforts into the collection, management and evaluation of their own domestic ADR reported information small states can easily become overwhelmed by trying to manage and assess ADR information from other jurisdictions. However, they should be aware of major new drug safety developments worldwide, and hence there should be a procedure in place for evaluating information from both manufacturers and other countries on serious adverse events, rather than relying only on local information. Reliance principles can be applied to any risk-management decisions.

Strategies to stimulate domestic ADR reporting include:

- Easy access or prepaid mail reporting forms, and availability of other means of reporting (e.g., electronic, phone, etc.).
- Acknowledging the receipt of ADR reports by personal letter, email, text messages, or phone calls.
- Providing feedback to reporters in the form of articles in journals, ADR bulletins, newsletters, targeted communications, etc.
- Active participation in pre- and postgraduate education and scientific meetings
- Collaboration with local drug and therapeutics or PV committees.

- Collaboration with public health programmes and national immunization programmes.
- Collaboration with professional and patients' associations.
- Integration of PV in the (further) development of clinical pharmacy and clinical pharmacology in a country.

The development of procedures to manage and to allow effective use of the increasing amounts of ADR information must be acknowledged and accounted for. Although reporting can be easy to manage manually at the beginning of the implementation, the system will need carefully planning and the development of efficient electronic procedures later. Such procedures will enable an organized transition and response to the higher demands of a well-established pharmacovigilance system that meets the required Maturity Level requirements of the GBT. In this regard, the WHO Guidelines for the setting up of a PV Centre will once again be particularly helpful. Detailed instructions on how to organise data for submission to the WHO database are obtainable from the Uppsala Monitoring Centre. The following two general documents complement and support well long-term broad PV activities: WHO Aide Memoire for a National Strategy for safe drugs and their appropriate use and WHO pharmacovigilance indicators: a practical manual for the assessment of pharmacovigilance systems.

Countries in the WHO PIDM acquire both the obligations and the benefits of membership. WHO PIDM member states benefit from the continued mining of drug safety information submitted to the WHO global database for ADR reports known as VigiBase, which is screened on a regular basis for signs of any medicine- induced problems that have yet to be identified worldwide, an activity commonly known as signal detection. As stated earlier, small states need to prioritize and develop their own procedures to evaluate and act on domestic and foreign medicine safety matters and ADR reported information, that may include issues related to product quality.

An important task of a newly established national PV Centre is the identification of safety signals, i.e., raising hypothesis based on information of new or known side effect that may be caused by a product which is typically generated from more than a single report of the suspected side effect. A signal by itself is not evidence of a direct causal relationship between a side effect and a medicine, but together with data and arguments, it justifies the need for further assessment. Thus, the PV Centre in small market states will need to develop strategies to assess domestic information aiming at both detecting and assessing signals, and if needed, to communicate and manage the associated risk.

Effective communications play a key role in the development and implementation of the system and need to be carefully fostered. They are essential to establish the well needed alliances and collaboration among stakeholders. Recent experience from the Covid-19 pandemics has demonstrated that communications become particularly critical in front of perceived major medicine safety issues, when important information needs to be communicated to either shed light on potential risks, manage and minimize newly detected risks, or to handle a crisis.

The development of an effective national PV system is a journey that requires careful planning, long-term resources, work commitment, and government support. The system should be sustained by adequate level of regulations and use of international standards. However, the actual shape and type of procedures to be developed and implemented depend very much on the individual country's situation. Although it is difficult to suggest the implementation of a particular procedure, small states are strongly

encouraged to consult the many reports and discussions prepared by the CIOMS, which are publicly available on their website (See text box), as well as self-paced e-learning courses, on the website of the Uppsala Monitoring Centre. Although based on the EU legislation, general and advanced topics in PV are also worth consulting in EMA's dedicated websites for Good Pharmacovigilance Practices, and Pharmacovigilance Training Materials

Useful PV resources

An introduction to pharmacovigilance. P Waller & M Harrison-Woolrych. 2nd edition. Chichester, West Sussex, UK; Hoboken, NJ: John Wiley & Sons Inc. (2017)

CIOMS Practical Aspects of Signal Detection in Pharmacovigilance
CIOMS Current Challenges in Pharmacovigilance
CIOMS Evidence Synthesis and Meta-Analysis
CIOMS Practical Approaches to Risk Minimizations for Medicinal Products
Expecting the worst UMC WHO Collaborating Centre
Responding to Drug Safety Issues
P C Waller & E H Lee. Pharmacoepidemiology and Drug Safety, 8: 535±552 (1999)

Accessing Laboratory Testing

Laboratory testing plays an important role in assuring product quality and detecting substandard and falsified (SF) medicines. Laboratory testing needs to be conceived as just one element of a comprehensive strategy on post marketing monitoring. The main purpose of testing is to contribute to confirm that the strategy achieves its objectives. In addition, there is a need to ensure that laboratory work has solid grounds, broad scope of work, and formal recognition (e.g. ISO 17025 accreditation).

Data generated from laboratory testing are used to inform regulatory actions and public health interventions associated with SF products. Laboratory personnel of a national pharmaceutical quality control laboratory are responsible for the investigation and quality control analysis of medical products under their responsibility. They need to use appropriate methods and equipment to be able to generate the technical reports required to support regulatory actions. If possible and given the high cost and level of technical expertise required to conduct such tests, small market states should avoid trying to train or hire highly specialized staff or develop their own laboratory capacities. Instead, they should rely on or work with well-established, accredited laboratory testing facilities in neighboring jurisdictions.

For post-market quality testing of medicines, small states are encouraged to join established programmes in the region such as the Medicines Quality Control and Surveillance Department (MQCSD) of the Caribbean Public Health Agency (CARPHA). However, the decision to conduct laboratory testing of marketed medicines should be risk-based and conducted only after careful assessment of the need to test. Although the CARPHA MQCSD laboratories provide a valuable service, all testing laboratories have limited capacity, especially the ones that serve entire regions. Thus, states need to develop additional means of detection of SF products and streamline product quality-related procedures.

Since VigiCarib has been established as a voluntary regional system for CARICOM states to report suspected adverse drug reactions and SF products to the CRS, and to the WHO PIDM and the WHO Global Surveillance and Monitoring System (GSMS), the determination of the need for laboratory testing in the region, should also consider the monitoring activities and the information shared in the VigiCarib network.

What is risk-based product testing?

A risk-based approach to quality testing means sampling and testing in cases where there is a known or likely safety, effectiveness, or quality issue with a product. A risk-based approach helps ensure efficient use of resources to address products of concern for public health such as substandard and falsified medical products.

The level of risk associated with a product will be based on many factors including the nature of the product, the complaint or suspected problem, and the context in which the product is used in a jurisdiction. Some factors that may be used to determine the level of risk associated with a product issue include:

- Medicines frequently used or in demand by large populations or public health programmes
- Newly marketed medicines, including innovator products with less characterized safety profiles
- Products with quality issues reported to other regulatory authorities
- Products with reports of substandard issues or falsification within the WHO GSMS or PAHO regional network for SF products
- Medicines imported from unregulated and/or poorly regulated markets
- Medicines with dangerous risk profiles, such as narrow therapeutic indices or complex manufacturing processes.

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