Safety of Medicinal Products in the Philippines: Assessment of the Pharmacovigilance System and its Performance

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About Food and Drug Administration (FDA) Philippines

The Food and Drug Administration of the Philippines's mission is to ensure safety, efficacy, purity, and quality of products regulated through effective implementation of the national regulatory framework consistent with international best practices.

About SIAPS

The goal of the USAID-funded Systems for Improved Access to Pharmaceuticals and Services (SIAPS) Program implemented by Management Sciences for Health is to assure the availability of quality pharmaceutical products and effective pharmaceutical services to achieve the desired health outcomes. Toward this end, the SIAPS result areas include improving governance, building capacity for pharmaceutical management and services, addressing information needed for decision-making in the pharmaceutical sector, strengthening financing strategies and mechanisms to improve access to medicines, and increasing quality pharmaceutical services.

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Key Words

Pharmacovigilance, adverse drug reaction, adverse event, post marketing surveillance, medicine safety, Philippines, Food and Drug Administration

CONTENTS

ACRONYMS AND ABBREVIATIONS

ADE	adverse drug event
ADR	adverse drug reaction
AERS	Adverse Event Reporting System
AO	administrative order
ART	antiretroviral therapy
CHD	Center for Health Development (Regional Health Office)
CRO	clinical research organization
DOH	Department of Health
DTC	Drug and Therapeutics Committee
EMA	European Medicines Agency
EO	Executive Order
EU	European Union
FDA	Food and Drug Administration - Philippines
FDAAA	Food and Drug Administration Amendments Act
GAVI	GAVI Alliance, formerly Global Alliance for Vaccines and Immunization
GMP	Good Manufacturing Practices
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
IPAT	indicator-based pharmacovigilance assessment tool
MAH	marketing authorization holder
MGC	multinational generics companies
MSH	Management Sciences for Health
NADRAC	National Adverse Drug Reaction Advisory Committee
NCPAM	National Center for Pharmaceutical Access and Management
NMP	National Medicines Policy
NRA	National Regulatory Authority
NTD	neglected tropical disease
PHP	public health program
PMI	President's Malaria Initiative
PQM	Promoting the Quality of Medicines [USAID]
PRs	Principle recipients
PRAC	Pharmacovigilance Risk Assessment Committee
PSUR	periodic safety update report
PV	pharmacovigilance
RMP	risk management plan
SAE	serious adverse event
SOP	standard operating procedure
SPS	Strengthening Pharmaceutical Services [USAID]
SIAPS	Systems for Improved Access to Pharmaceuticals and Services [USAID]
SRA	stringent regulatory authority
TB	tuberculosis
UMC	Uppsala Monitoring Centre [WHO]
USAID	US Agency for International Development
USD	US dollars
US FDA	US Food and Drug Administration
VAERS	Vaccine Adverse Event Reporting System
WHO	World Health Organization

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EXECUTIVE SUMMARY

The Food and Drug Administration (FDA) Philippines, with support from the US Agency for International Development (USAID)-funded Systems for Improved Access to Pharmaceuticals and Services (SIAPS) Program conducted an assessment of the Philippines' pharmacovigilance (PV) system and its components. They are (1) governance, policy, law, and regulation; (2) systems, structures, and stakeholder coordination; (3) signal generation and data management; (4) risk assessment and evaluation; and (5) risk management and communication, using the Indicator-based Pharmacovigilance Assessment Tool.

Selected Assessment Results

Governance, Policy, Law, and Regulation

The FDA of the–Philippines ensures the safety, efficacy, and quality of regulated products through effective implementation of the national regulatory framework, recognizes its responsibility to lead, govern and strengthen the pharmacovigilance (PV) systems in the country. Basic governance and legislative instruments are in place providing legal mandate to FDA to develop and implement an in-country pharmacovigilance system. The assessment showed that policy documents including the National Policy and Program on Pharmacovigilance (AO 2011-0009) are in place. However, legislation governing the implementation of pharmacovigilance is outdated and requires revision. Several other regulations surrounding medicine safety existed for medicine registration and marketing, patents, quality, access, and price regulations.

Systems, Structures, and Stakeholder Coordination

The FDA National Center for Pharmacovigilance, situated within the Product Services Division, has the primary responsibility and central authority to implement PV activities and coordinate the improvement of the organizational structures, processes, and instruments for efficient functioning of the system. With collaboration from the Uppsala Monitoring Centre (UMC), the unit has been set up to l train FDA staff to monitor the implementation of PV in the Philippines. The findings of the assessment found that FDA has the structures and systems to implement PV throughout service delivery, industry, and civil society organizations.

The study showed the absence of a national medicine safety committee, which supports FDA in the analysis and actions of reported adverse events. The study also noted a weakness in coordination of the national pharmacovigilance system among various stakeholders.

Signal Generation and Data Management

The assessment found that the adverse event reporting (ADR) form is accessible through the FDA Philippines website, and is available in 70% of the health facilities and 55% of the pharmacies visited. Some facilities with no internet connection could not access the ADR form in the FDA website. The form includes fields for reporting suspected product quality issues, therapeutic failure, and medication errors. The ADR forms are inadequately available and underutilized by service providers, industry, and consumers.

In 2011, the FDA pharmacovigilance unit received 3,351 ADR completed forms. According to WHO Programme for International Drug Monitoring recommendation, the National Pharmacovigilance Center should submit over 200 expected ADR reports per million population.* At the time of the assesment, the expected reports per 94.9 million population should be at least 18,970. The study found that fear of reprisal from law suits seem to contribute to health workers reluctance to report and is likely contributing to underreporting of adverse drug reactions (ADRs). Poor reporting on therapeutic failure and medication errors were noted in the assessment.

There were inadequate activities implemented to support the documentation and management of drug exposure and outcome data. More activities to generate signals about safety and effectiveness of medicines should be developed.

Risk Assessment and Evaluation

Efforts at risk assessment and evaluation are limited. Adverse event data were poorly assessed and analyzed for the establishment of causality. Of the 3,351 ADR reports in 2011, only a third (32%) was assessed for causality. This has implications in the ability to generate and evaluate risk signals of public health importance.

Risk Management and Communication

The risk management and communication component targets efforts to mitigate the risk of medicine use. Insufficient responses from DOH, FDA, consumers, medical device companies, and public health programs (PHPs) with regards to the medicine safety issues were identified.

The assessment shows that medication safety was inadequately addressed in PHPs, medical device companies, and clinical research organizations. Though there exist safety advisories, bulletins, newsletters, and ads in newspaper and media regarding pharmaceutical safety exist, these are not well disseminated and have little impact as few people were aware of these communication efforts.

*World Health Organization Pharmacovigilance Reporting Trends: http://who-umc.org/DynPage.aspx?id=108476&mn1=7347&mn2=7252&mn3=7322&mn4=7558

INTRODUCTION

Pharmacovigilance (PV) began in the early 1950s following the incident of congenital limb deformities in offspring of women worldwide who were exposed to thalidomide during pregnancy. This medical tragedy was a wake-up call to authorities and the general public that safety must come first to ensure that untoward effects of medical products are monitored, communicated, and averted.

The Philippine national drug regulatory agency was called Food and Drug Administration (FDA) through the Republic Act 3720 until 1982 when Executive Order (EO) No.581 changed the name to the Bureau of Food and Drug (BFAD). The R.A. 3720, particularly Chapter II, was amended by Section 3 of the EO No.175 requiring the national drug regulatory agency among other things to adopt measures: (1) to ensure pure and safe supply of foods and cosmetics; pure, safe, efficacious and good quality drugs and devices; and (2) to adopt measures to ensure the rational use of drugs,devices and cosmetics, such as, but not limited to, banning, recalling or withdrawing from the market drugs and devices which are not registered, unsafe, inefficacious or of doubtful therapeutic value, the adoption of an official National Drug Formulary, and the use of generic names in the labeling of drugs .[1]

The national ADR database was established in 1995 and, as of 2012, includes nearly 10,000 reports.

In 1994, the National Adverse Drug Reaction Advisory Committee (NADRAC) was created to ensure safety of drug products and other therapeutic agents through nationwide post-marketing monitoring of adverse drug reactions (ADR).[2] Through the work of this committee, the Philippines joined the World Health Organization (WHO) Collaborating Centre for Drug Monitoring, Uppsala Sweden in February 1995.

NADRAC started the Adverse Drug Reaction Monitoring Project involving two private and one government tertiary hospitals in monitoring and evaluating adverse drug reactions (ADRs). In 1997, ADR monitoring was institutionalized by the composition of an ADR unit in BFAD with over 50 participating hospitals. NADRAC became an advisory group to BFAD for drug safety and post marketing surveillance with significant contribution such as the creation of ADR database, managing nationwide system of monitoring medication safety, promoting rational drug procurement and detection of problems in the quality of medicines in the market. The last recorded meeting of NADRAC was in December 1997 and the committee was subsequently replaced by the National Pharmacovigilance Advisory Committee (NPVAC).

In 2011, FDA issued A.O. 2011-0009 known as the National Policy and Program on Pharmacovigilance. This administrative order (AO) aims to strengthen the detection, assessment, understanding and prevention of adverse effects or any other possible drug related problems and has the specific objectives to establish and implement the national pharmacovigilance program that shall describe a strategic framework for the implementation of pharmacovigilance policies. This policy also sets the direction for the Food and Drug

[1] Food and Drugs Administration Philippines. EO 175 Amendment of Food, Drug, and Cosmetic Act. Available from http://www.fda.gov.ph/republic%20acts/eo%20175.pdf
[2] http://www.fda.gov.ph/NADRAC/About%20us.htm

Administration (FDA) and the DOH offices, attached agencies, local government units, and other partners in the implementation of the national pharmacovigilance program.[3]

Summary tables of the Philippines pharmaceutical profile and pharmacovigilance profile can be seen in annex B.

Assessment Objectives

The U.S. Agency for International Development (USAID)-funded Systems for Improved Access to Pharmaceuticals and Services Program (SIAPS) Program, through an interagency agreement with the US Food and Drugs Administration (US FDA), supported the Food and Drug Administration- Philippines to conduct an assessment of PV systems and capacity in the Philippines in 2012 across a range of stakeholders. This assessment is part of a regional PV systems and capacity assessment conducted in five Asian countries including Bangladesh, Cambodia, Nepal, the Philippines, and Thailand.

The objectives of this study were to:

- Assess and analyze systems performance for PV and post-market surveillance
- Identify successful, and replicable experiences to further enhance medicines safety and quality systems
- Map out how donor agencies and local/regional/global health efforts are contributing to PV
- Recommend options for enhancing PV and post-market surveillance systems capacity and performance

[3] DOH, Republic of Philippines. Administrative Order 2011-0009. National Policy and Program on Pharmacovigilance. Available from http://www.fda.gov.ph/AO/ao2011-0009%20Pharmacovigilance.pdf

ASSESSMENT FINDINGS, ANALYSIS, RESULTS, AND RECOMMENDATIONS

Introduction

The indicator-based assessment reflects the level of PV capability achieved in the country based on the comprehensive review of its PV system and its performance in the country. Several stakeholders and various respondents were invited to take part in the process of this assessment which is locally led by the FDA.

In gathering data, respondents were selected to represent the national regulatory authority, PHPs, health facilities, private pharmacies, health professionals, consumer groups, universities/training institutions, and pharmaceutical industries. The idea of various respondent groups is to link findings from the national level to what actually occurs at the lower levels with the facilities, pharmacies, and industries, which includes the pharmaceutical companies, medical device companies, and clinical research organizations (figure 1). These respondents were then grouped according to:

- National level—FDA central and regional, and National Center for Pharmaceutical Access and Management (NCPAM)
- Service provider level—PHPs, health facilities, and pharmacies
- Pharmaceutical industry—pharmaceutical companies, medical device companies and clinical research organizations
- Civil society organizations—academia, professional associations, and consumer groups

A background of this assessment is available in annex A.

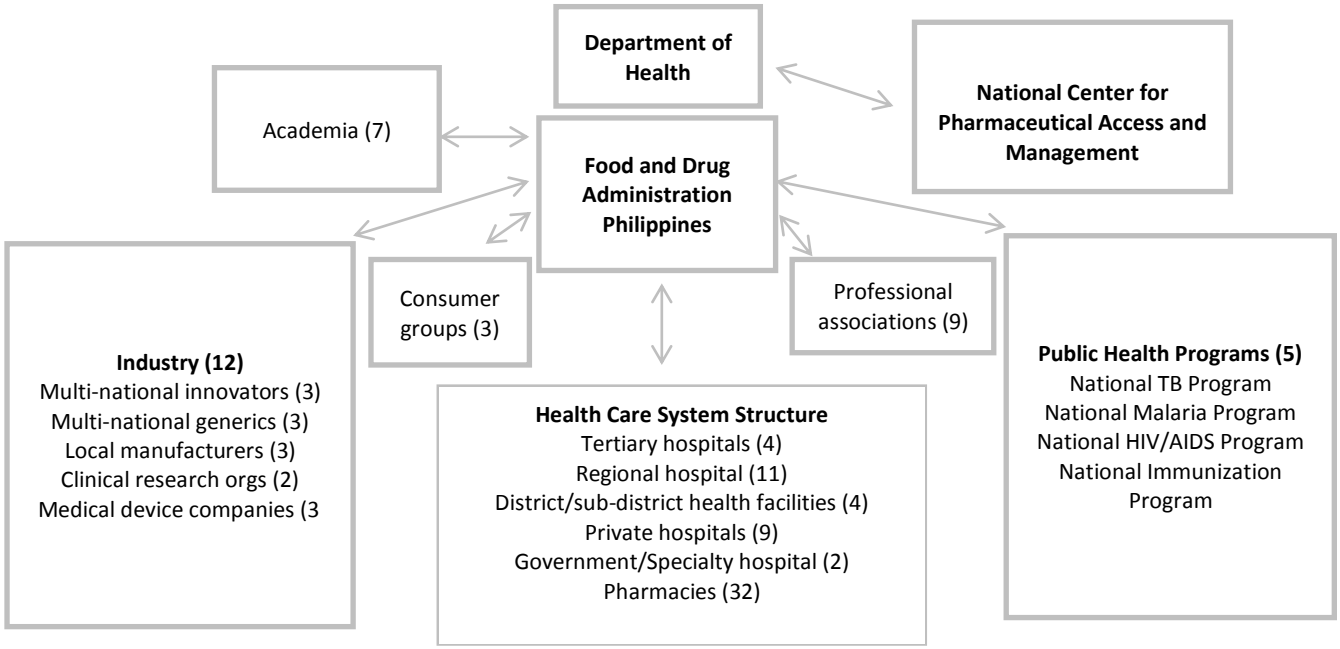


Figure 1. Sampling framework

PHARMACOVIGILANCE AT THE NATIONAL LEVEL

Governance and Policy, Law, and Regulation

Existence of supportive governance systems within national regulatory authorities is key to ensuring institutional capacity to support product regulation, safeguard public health, and promote pharmaceutical sector trade and economic growth. As illustrated in tables 1 and 2, the FDA has a regulatory framework of pharmaceutical regulations, rules, and laws in place to govern and ensure patient and medicines safety nationally, including governance structures addressing accountability, transparency, and legislative enforcement; and a clear mission, vision, and mandate.

Table 1. Governance at the National Level

Indicator	Score	Status
Regulatory rramework	Yes	N/A
Regulatory registers	Yes	N/A
Governance structures mandated and in practice	Yes	N/A

Table 2. Policy, Law, and Regulations at the National Level

Indicator	Score	Status
PV or Medicines Safety in National Policy	Yes	*AO 2011-0009, National Policy and Program on PV 2011*
PV or Medicines Safety in National Legislation	Yes	N/A
MAH[a] Mandated by Law to Report Serious ADRs to NRA	Yes	N/A
MAH Mandated by Law to Conduct PMS[b] per Stringent Regulatory Authority Standards	Yes	N/A
Legal Provision for Product Quality Assurance	Yes	N/A
Legal Provision for Promotion and Advertisement	Yes	N/A

a Marketing authorization holder
b Post-marketing surveillance

Laws and regulations provide the legal foundation for conducting medicines safety in a country, with regulations guiding the implementation of the law. According to WHO, national medicines policies should contain several elements relating to medicine safety including requirements for establishing PV systems and developing legislation and regulations for monitoring of medicine safety.[4] Additionally, national medicines policies should include provisions related to product quality assurance and control of promotion and advertising. An approved national policy on PV or medicines safety is the guiding document that provides the authority and mandate to monitor medicine safety and take appropriate regulatory actions. Further, PV guidelines provide operational direction and standards for implementing activities such as spontaneous reporting of ADRs, active surveillance,

[4] WHO. 2004. Pharmacovigilance: Ensuring the safe use of medicines. WHO Policy Perspectives on Medicines 9. http://apps.who.int/medicinedocs/pdf/s6164e/s6164e.pdf.

provision of drug information, and delineation and coordination of stakeholder roles and responsibilities.

Findings and Implications

The assessment confirmed that regulatory registers for licensed pharmaceutical premises, licensed pharmaceutical personnel, and registered medicines all exist. As of June 2012, 32,069 medicines and 301 manufacturers are registered with FDA.[5] All 98 medicines included in the latest Philippine National Drug Formulary (PNDF) are registered with the FDA. The essential medicine list and PNDF list are maintained by the National Formulary Committee.

In the Philippines, the Foods, Drugs and Devices, and Cosmetics Act, Republic Act 3720 of 1963 (as amended by Executive Order 175 of 1987) serves as the national medicines policy and provides clear guidance on ensuring the safety and purity of products marketed to the public to protect the health of the people and instill awareness of medicines safety and quality. This law established the creation of the national medicines regulatory agency under the DOH, which in 2009 was renamed the Food and Drug Administration of the Philippines. Several other regulations were submitted surrounding the governance of pharmaceuticals: registration and marketing, patent (Intellectual Property Code), quality assurance (Special Law on Counterfeit Drugs), access and price regulation (Generics Act, Price Act, Universally Accessible Cheaper and Quality Medicines Act, Consumer Act), pharmacy practice (Pharmacy Law), and PV.

NCPAM is a unit within the DOH that ensures a policy environment conducive to universal access to quality essential medicines. NCPAM drafted the Philippines Medicines Policy AO 2010 and related manual based on the DOH "SARAH" principles of (1) safety, efficacy, and quality; (2) availability and affordability; (3) rational medicine use; (4) accountability and transparency; and (5) health systems support. Legal provision for the management of clinical trials is also included in the policy.

The National Policy and Program on Pharmacovigilance 2011, AO 2011-0009, provides for establishing and operating the PV unit of FDA, the National Pharmacovigilance Center. It lists the mandatory guidelines for reporting ADRs and adverse effects (AEs) from clinical trials to post-marketing of pharmaceuticals. Legal provisions also exist for product quality assurance including quality control (BC 5s 1997) and product quality post-marketing surveillance activities (BC 5s 1997). Challenges exist with full implementation and enforcement of PV policies and regulations to ensure compliance with the reporting of adverse events and conduct of other activities. Such challenges include undeveloped PV centers at regional offices and insufficient support from the central office. Implementing rules and regulations of the national PV policy that should set the details of the proper implementation of the AO such as in data collection and management, signal detection, risk assessment, decision making, communication, and development and maintenance of the standard operating procedures (SOPs) does not exist.

Adaptation and implementation of the pharmaceutical inspection cooperation scheme guides for the good manufacturing practices (GMP) for medicinal products are in place though GMP

[5] FDA Philippines, June 2012

inspection and issuance of certificate are encouraged but are not mandatory. Mandatory current GMP, Good Distribution Practices (GDP), and Good Storage Practices (GSP) are in the process of being implemented.

Service providers reported fear of harassment and lawsuits or other legal measures, and perceived lack of legal recourse as the primary reason for choosing not to report ADRs, treatment failure, and medication errors. Our analysis failed to identify legal provisions to address this concern. The National Policy and Program on Pharmacovigilance 2011, AO 2011-0009, requires health workers to report AEs and states that a culture of blame-free reporting will be encouraged. However, neither the policy nor legislations provide protection for the reporters from litigation nor do they provide safeguard from presumed culpability. Service providers also raised concerns of confidentiality when reporting.

A Medicine Regulatory Assessment of the FDA is being conducted by the World Health Organization. Due to its recent introduction, implementation of AO 2011-0009 has not yet been assessed.

Several donor organizations and technical agencies extend assistance to FDA to fulfill its functions. Included are assistance and support from the World Health Organization, Food and Agriculture Organization of the United Nations, European Commission, US FDA, Korea Food and Drug Administration, Australian Agency for International Development, USAID through SIAPS program and United States Pharmacopeia Promoting the Quality of Medicines program, European Union, United Nations Children's Fund (UNICEF), and World Bank.[6]

Recommendations

- The DOH, FDA, and other entities should fully implement the national PV policy AO 2011-0009 as stipulated.

- The FDA should create a national guideline on PV and draft related standard operating procedures that provide operational guidance for the National Pharmacovigilance Center and stakeholders with medicines safety monitoring and reporting responsibilities.

- The FDA should introduce mandatory compliance with good practices, particularly Good Clinical Practice (GCP), GMP, GDP, Good Pharmacovigilance Practice (GVP), and Good Pharmacy Practice (GPP) for pharmaceutical products.

- The NCPAM should provide assistance to the National Pharmacovigilance Center for review and implementation of current PV policies, in collaboration with the FDA.

- The DOH and FDA should conduct an analysis of legislation and pursue legislative reforms that will promote an environment where service providers feel safe to report ADRs, treatment failure, and medication errors. This should enhance reporting by addressing the reported consequence of harassments and lawsuits in reporting.

[6] WHO. Philippines Country Profile, 2011

Systems, Structures, and Stakeholder Coordination

A comprehensive PV and medicine safety program requires the development of sustainable, functional systems and structures with appropriate resources and technical expertise, and clearly defined roles and responsibilities. . These components facilitate the effective use of staff, skills, and tools to perform critical functions of signal generation and data management, risk assessment and evaluation, and risk management and communication. Effective stakeholder coordination and linkages between a country's national PV program and PHPs ensure that no gaps exist in-country and that there is communication and opportunities for leveraging resources occurs. WHO describes a minimally functional PV system as including a national PV center with dedicated staff, spontaneous reporting system, ADR database, national advisory committee, and communication strategy for routine and emergency events.[7]

Findings and Indicators

The Philippines National Pharmacovigilance Center operates with a clearly defined and documented mandate, structure, and function. It was formed in 1995 as the ADR Monitoring Program with assistance from AusAID through the National Drug Policy Program, and is organized as seen in figure 2.

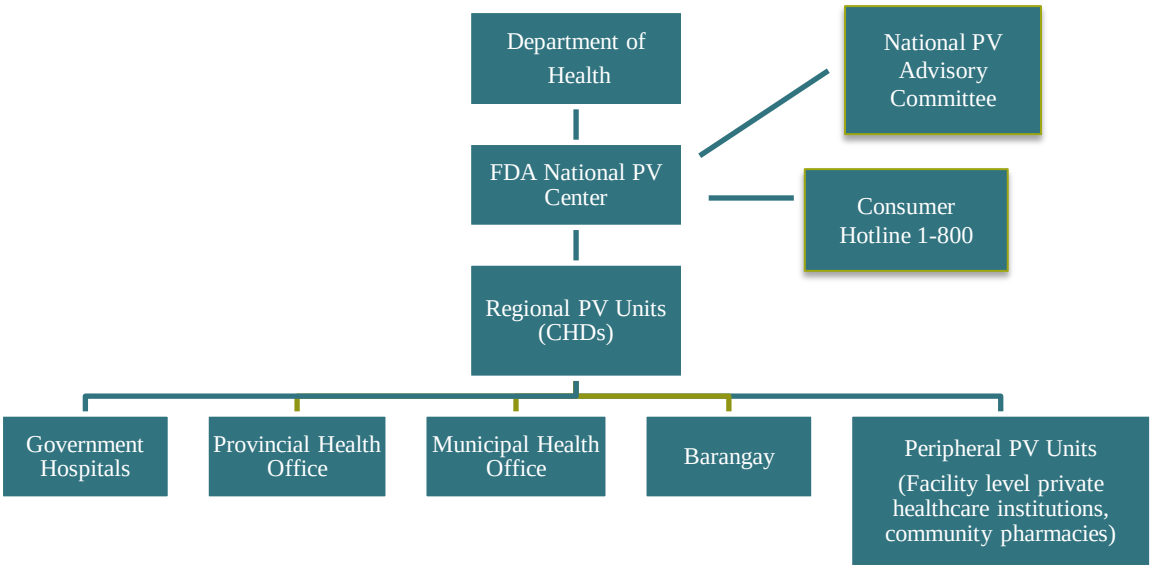


Figure 2. The National Pharmacovigilance Program organizational chart[8]

A designated doctor is assigned to the National Pharmacovigilance Center with a contracted pharmacist as support, though the required human resources for the National Pharmacovigilance Center and management support from FDA were not fully reviewed as part of this assessment. The National PV Center and PV activities within the FDA do not have an annual budget allocation although communication technologies are in place to allow for medicines safety reporting and information sharing. The FDA website (www.fda.gov.ph) provides PV information including medical product advisories and safety alerts. A consumer

[7] WHO, 2010, *Minimum Requirements for a functional Pharmacovigilance System*, Geneva: WHO.
[8] AO No. 2011- 0009, Annex 1

hotline is featured prominently on the website to encourage reporting of substandard and counterfeit medicines.

No national medicine safety advisory committee exists to provide technical advice and support on medicines safety to the FDA. The NADRAC served this function beginning in 1994 but was dissolved in 2007, though discussions are underway within FDA to revive the committee. During its existence, NADRAC served as the consultative body in reviewing and analyzing ADR reports. Without NADRAC, there were difficulties in decision-making, guidelines development, and review and management of clinical trials for medicine safety and quality assurance. The Philippines joined the WHO Uppsala Monitoring Center International Drug Monitoring Program in 1995 and continues to actively collaborate.

The quality control laboratory network within FDA is functional and is currently being strengthened and expanded. As per Republic Act 9711 of 2009, chapter 14, section 35, the FDA is mandated to set up at least one state-of-the-art testing laboratory on each regional island of the country: Luzon, Visayas, and Mindanao. The main laboratory at the central office will lead the network, including supporting product research and evaluation, standards development, assays, supervision, oversight, and audit of bioequivalence and bioavailability tests. The FDA became ISO 17025 certified as of July 1, 2012, by Department of Trade and Industry— Philippine Accreditation Office per the general requirements for the competence of testing and calibration laboratories. However, noted in the assessment is the absence of a national quality control committee or any other committee with the responsibility to provide technical advice to FDA. Standard operating procedures are in place for quality assurance control including inspections and product quality surveys and surveillance. Standard operating procedures for PV activities are limited to the reporting of suspected adverse drug reaction. Pharmacovigilance SOPs should include data collection and management, signal detection, risk assessment, decision making, communication, and development and maintenance of the SOPs.

A quality management system is approved by FDA for implementing the PV system and quality assurance system. At the time of assessment, inspectors have conducted 41,030 PV audits. The assessment noted that the FDA quality management system is still insufficient for performing PV and quality assurance activities.

FDA has conducted 246 pre-service PV trainings for health care professionals, as of the time of the assessment, though deficiencies in both pre- and in-service training within health facilities and academia were noted. A strategy for fostering collaboration among stakeholders such as with marketing authorization holders, service providers, medical professional societies and other civil society groups is in place, as mentioned in AO 2011-0009. This coordination strategy is targeted down to only the secondary health care level, whereas, local government units are yet to be engaged. Although there had been a website to conduct stakeholder coordination for the PV system in the past, it is no longer functional. A strategy of collaboration was defined in the AO, however, the assessment noted inadequate coordination with stakeholders at all levels from central to regional offices, service providers, PHPs, etc., shown in Table 3. Most health facilities (18 out of 21) surveyed do not have a functional drug and therapeutic committee in place to address medicine safety and PV issues.

Table 3. System, Structure, and Stakeholder Coordination at the National Level

Indicator	Score	Status
PV center or unit	Yes	N/A
PV center or unit has clear mandate, structure, roles, relation	Yes	N/A
Quality control lab (or unit) with clear mandate, structure, and functions	Yes	N/A
PV information service	Yes	N/A
Staff for PV (>1)	Yes	N/A
Budget for PV	No	In 2009, budget allocation was made for staff training on PV and reproduction of audio-visual materials.
National PV Guideline	No	National PV policy serves in place of national PV guideline
National SOPs for PV and QC	Yes	N/A
Medicines Safety Advisory Committee	No	Dissolved in 2007, National PV Policy calls for reinstatement
Quality Control Advisory Committee	No	The National Clinical Trials Advisory Committee was dissolved in 2007.
Core communication technologies for PV	Yes	N/A
Core PV reference material in PV Unit	Yes	N/A
Core PV topics in pre-service training curricula (<70%)	Yes	N/A
Healthcare workers trained on PV	Yes	N/A
PV Stakeholder Coordination Mechanism	Yes	N/A
WHO Programme for International Drug Monitoring	Yes	N/A
Quality Management System PV and QA	Yes	N/A

Recommendations

- The National PV Center and other units in FDA are encouraged to increase coordination of their efforts within the central and at the regional levels.

- The National PV Center should develop and disseminate a checklist of roles and responsibilities for each key stakeholder in PV activities.

- The National PV Center should expand its technical collaboration, including training and operational research, with universities, research institutions, and medical professional associations.

- The FDA should revive the medication safety advisory committee and related expert committees, per the AO 2011-0009 National Policy and Program on Pharmacovigilance.

- The National PV Center should expand PV training to all FDA department units and regional FDA offices. The center should review or generate training modules and manuals, and consider establishing a pool of trained trainers.

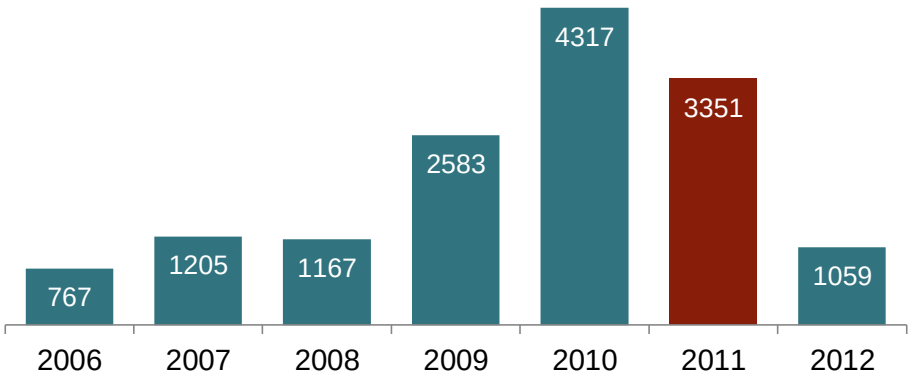
Signal Generation and Data Management

The PV processes involve signal detection, signal evaluation, and risk management. WHO defines a signal as "reported information on a possible causal relationship between an adverse event and a drug, the relationship being unknown or incompletely documented previously."[9] A safety signal is defined as "information that arises from one or multiple sources (including observations and experiments), which suggests a new potentially causal association, or a new aspect of a known association, between an intervention and an event or set of related events, either adverse or beneficial, which would command regulatory, societal or clinical attention, and is judged to be of sufficient likelihood to justify verifiable, and when necessary, remedial actions."[10] PV includes monitoring for therapeutic ineffectiveness, medication errors, and product quality.[11] Ineffectiveness is a reportable event in PV.[12]

Signal generation and data management addresses the mechanisms through which medicine safety issues or "signals" are detected and how that data is managed by the receiving regulatory agency.

Findings and Implications

The National PV Center of the Philippines received 3,351 suspected adverse event reports in 2011 (figure 3). Identification of ADRs was noted in some government (district, or sub-district) health care facilities in the Philippines, although there is a high level of fear of lawsuits from reporting ADRs and is probably contributing to their underreporting of. Reporting of therapeutic ineffectiveness and medication errors were low.



**Represents partial data from January to August 2012*

Figure 3. Number of individual case safety reports received by National PV Center (2006- 2012)

[9] The Uppsala Monitoring Centre, WHO. 2000. *Safety Monitoring of Medicinal Products: Guidelines for Setting Up and Running a Pharmacovigilance Center.* http://apps.who.int/medicinedocs/en/d/Jh2934e/
[10] Hauben, M. and J. Aronson. 2009. "Defining 'Signal' and its Subtypes in Pharmacovigilance Based on a Systematic Review of Previous Definitions." *Drug Safety* 32 (2): 99–110.
[11] Strengthening Pharmaceutical Systems (SPS). 2009. *Supporting Pharmacovigilance in Developing Countries: The Systems Perspective.* Submitted to the US Agency for International Development by the SPS Program. Arlington, VA: Management Sciences for Health.
[12] Meyboom, R.H.B., M. Lindquist, A-K Flygare, C. Biriell, and I. R. Edwards. 2000. "The Value of Reporting Therapeutic Ineffectiveness as an Adverse Drug Reaction." *Drug Safety* 23(2): 95–99.

The FDA has a national ADR form, which was developed in consultation with technical institutions, and is available on its website. Reports may be submitted in paper or electronically to FDA, but are typically submitted by post or delivered in person. Data is stored in a computerized database within the FDA—this database currently contains 13,390 ADR reports submitted between 2006 and 2011 (figure 6). FDA submits reports regularly to WHO Uppsala Monitoring Center since 1995. In 2010, FDA has started using the VigiFlow reporting system, a standardized Uppsala Monitoring Center reporting tool that is International Conference on Harmonization (ICH) E2B compatible and uses WHO antiretroviral therapy standardized terminology for coding reactions and indications.

The ADR form also includes fields to report on product quality, medication errors, and treatment failures. Unfortunately, such data are rarely reported to the National PV Center. During the assessments respondents expressed concern that the national ADR form is tedious to complete, has small fonts and has insufficient space to include comments. In addition, some surveyed health facilities did not have enough forms.

FDA, in partnership with WHO, has designed the *Bantay Gamot form, where* consumers are encouraged to submit hard copies oronline reports to FDA of any medicine complaints, along with other information such as: sources of medicines, and details and management of ADR/adverse drug events (ADEs). The forms were made available at all FDA licensed drugstores as part of FDA's public campaign to fight against counterfeit medicines. The related *Pekeng Gamot Salot, Nakakamatay!* campaign promotes collaboration among stakeholders. A review of these information services and campaigns is needed to determine their success and effectiveness.

Assessment results in figure 4 indicate that a signal generation and data management system are in place in the Philippines; however, there are still challenges in the coordination and use of information among stakeholders. Some stakeholders report regularly, particularly those that are mandated to do so; but the assessment revealed that responses from other health institutions are low.

Table 4. Signal Generation and Data Management at the National Level

Indicator	Score	Status
National PV Data Collation System	Yes	N/A
Consumer Reporting Form	Yes	N/A
Suspected ADR Reporting Form	Yes	N/A
Product Quality Reporting Form (or subset of)	Yes	Subset of ADR form
Medication Error Reporting Form (or subset of)	Yes	Subset of ADR form
Treatment Failure Reporting Form (or subset of)	Yes	Subset of ADR form

Recommendations

- The National PV Center should present its recommendations on the current and available individual case safety reports (ICSRs) s and the actions taken to improve safety.

- The National PV Center should consider simplifying the suspected adverse event reporting form and introducing separate forms for product quality issues, medication errors, and treatment failures.

- The National PV Center should take measures to ensure confidentiality with regards to identity of the reporter and content of the report; the FDA should advocate for the legal protection of reporters.

- The DOH and FDA should provide immediate technical and financial support to National PV Center for data entry, management, and analysis of ADR reports, including assigning causality assessments.

- The National PV Center should work in conjunction with PHPs and clinical research organizations to ensure that safety events detected are reported to the National PV Center.

Risk Assessment and Evaluation

When a signal—particularly a potential signal that has significant public health importance—arises from one or more sources, it should be further investigated. Signals can be generated when suspected ADRs are reported. Risk assessment and evaluation involves confirming a signal's validity, searching the appropriate literature and databases, gathering expert opinions, making decisions, and then taking appropriate actions to minimize the risks.[13] A spontaneous report can generate a qualitative signal that provides new and important data, if the quality, completeness, and case causality are sufficient. In contrast, a quantitative signal may be detected only when an increase in frequency of its occurrence is observed from epidemiological studies, clinical trials, or active surveillance.[14]

Active surveillance includes a wide range of approaches to detect and evaluate risks, such as cohort event monitoring, registries, sentinel sites cohort studies, epidemiological studies (case control study, cohort study, cross sectional study), and phase 4 clinical trials.[15] The combination of the periodic review of the nature, severity, and specificity of AEs through passive surveillance and evaluation of significant safety signals through active surveillance are fundamental to build a comprehensive and systematic PV and medicine safety system. Active surveillance is particularly valuable for PHPs, such as HIV and AIDS, tuberculosis (TB), immunization, and malaria control programs, as it can provide useful information for evaluating new medicines and making evidence-based decisions involving revision of standard treatment guidelines. Active surveillance has a role for new chemical entities or those products with high risk of causing adverse events when initially introduced into the market. This is to support the regulatory assurance of medicines safety. For programs, it is critical to be able to derive information to guide programmatic decisions on the safety and therapeutic benefits of regimens that are being implemented in the public sector.

[13] Cobert, B. L. and P. Biron. 2002. *Pharmacovigilance from A to Z: Adverse Drug Event Surveillance.* Massacheusets: Blackwell Science.
[14] Meyboom, R.H., A.C. Eqberts, I.R. Edwards, et al. 1997. "Principles of Signal Detection in Pharmacovigilance." *Drug Safety* 16(6):355–65.
[15] European Medicines Agency. 2006. *Pharmacovigilance Planning: Note for Guidance on Planning Pharmacovigilance Activities* (CPMP/ICH/5716/03). Available at http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500002818.pdf

Findings and Implications

The size of the problem of medicines and patient safety is not known. Although the FDA received 3,351 suspected ADR reports in 2011, only a third (32% [1,063]) were assessed for causality using standardized measures such as the WHO categories of causality or the Naranjo causality scale. This means that although many stakeholders are aware of the national ADR form and some spontaneous medicines safety signals are being generated, ICSRs generated from ADR reports are not being adequately evaluated once received to understand the medicine safety implications and inform necessarily regulatory action.

Significant deficiencies currently exist in risk assessment and evaluation activities within the FDA and the National PV Center (table 5). Product quality surveys were neither planned nor conducted by the FDA in 2011, although it was reported that approximately 2–3 site inspections were frequently conducted per day.. Additionally, medication error, medicine utilization, or active surveillance activities were not conducted by the FDA in 2011, though academic institutions conducted medication error and medicine utilization studies.

Table 5. Risk Assessment and Evaluation at the National Level

Indicator	Score	Status
Spontaneous reporting > 100 per million population per year	No	3351 reports received in 2011 vs. 94.9 million population
ICSRs with causality assessed > 50%	No	Causality assessed for 32% of reports
Product quality survey planned and conducted	No	N/A
Medication errors studied	No	N/A
Medication utilization studies	No	N/A
Active surveillance activities	No	N/A

The absence of active surveillance activities in the Philippines for a selected high risk list of medicines is one of the most significant challenges of the national PV system in performing its duty to protect patient safety and medical product quality.

Recommendations

- The National PV Center should work in conjunction with the PHPs and academia to detect and document any evidence that significant problems are occurring but not being acknowledged publicly.

- Based on the above recommendation the National PV Center should consider establishing an active surveillance to address safety concerns in the use of high priority medicines particularly in vulnerable populations, such as infants, children, and pregnant women.

- Support the FDA and National PV Center to increase the number of assessed reports (even with underreporting, only 32% of received reports are assessed for causality in 2011)

- The National PV Center should collaborate with academia and research institutions to conduct active surveillance activities, and studies on medication errors, and utilization.

- FDA should monitor institutions and stakeholders, including pharmaceutical companies and health institutions, to determine if they are complying with the reporting of ADRs.

Risk Management and Communication

Risk management involves identifying, characterizing, preventing, or minimizing risks related to a medicine or a medicinal product. Assessing the effectiveness of risk minimization interventions and updating them as needed is an essential component of risk management, as is communicating those risks to patients and health care providers. Risks can be assessed through routine PV activities or, when a specific risk is detected, through enhanced PV activities.

Findings and Implications

Information from respondents and reviewed documents indicate that FDA conducted a number of medicine safety risk management and communication activities. See table 6. The FDA reported receiving 4,298 medicine safety information requests in 2011 and addressed 97.4% of these requests. Medicine safety advisories are also regulatory published on the FDA website.

The DOH Procurement Division/ Central Office Bids and Awards Committee Secretariat use WHO prequalification in medicine procurement decisions, primarily for vaccines. With other medicine products including generics, procurement decisions are made via a bidding process and awarded to the lowest cost bidder.

The FDA also tested 97.4% of 4,298 medical products, although no data was available on the number of products that failed quality assurance testing. In 2011, there were 64 medicines identified during inspections which are unregistered in the country, representing less than 3% of total registered medicines.

The plan for mitigation of high risk medicines is available but not well developed. High risk medicines have warnings on their labels and packaging. These medicines undergo evidence review for their safety profiles, cost-effectiveness, etc. New safety information is sent to health care professionals and patients via the Legal Division of FDA. According to FDA, safety signals and significant safety issues are promptly communicated to the public within one day. In 2011, there were more than 10 activities on community education conducted by FDA. Safety alerts are sent to NCPAM to develop actions and distribute information to inform clinical management, guideline revisions, and regulatory decisions. In 2011, FDA took several regulatory actions, including changing 636 package inserts, recalling one drug product, and suspending 50 marketing authorizations. FDA recommended 293 risk management activities such as post-marketing surveillance in 2011. Risk mitigation actions were taken against high-risk medicines including rosiglitazone tablets, which were withdrawn from the market in the Philippines, and pioglitazone tablets, for which warning signals were issued and the manufacturer was informed of associated risks.

Table 6. Risk Management and Communication at the National Level

Indicator	Score	Status
Medicine safety information requests addressed	Yes	More than 4,000
Medicine safety bulletin planned	No	No bulletin published advisories published on website
Prequalification schemes used in medicine procurement decisions	Yes	N/A
Unregistered medicines in pharmaceutical market (<3%)	Yes	N/A
Medicines sampled and analyzed for product quality (>95%)	Yes	N/A
Risk mitigation plans for high-risk medicines	Yes	N/A
Medicine safety issues identified from external sources and acted on	No	
Time from ADR signal generation to communication to hcws and public <3 weeks	Yes	N/A
Public or community education activities	Yes	N/A
Medicine safety action taken (other than ADR reporting)	Yes	N/A

Recommendations

FDA should work in conjunction with other stakeholders to develop and distribute safety communications and publications, such as regularly planned and published medicines safety bulletins that are available on the website and distributed electronically.

The Philippines PV Situation at the National Level

Figure 4 represents performance of Philippine's PV system at the national level as demonstrated by assessment findings. Higher scores are depicted by points further from the center of the diagram, on a scale of 0 to 100 for each of the five components.

The figure shows that the Philippines FDA is doing well at central level in the areas of policy and regulation and in signal generation and data management (100), while scoring slightly less (80) on systems and structures and coordination and Risk Management and communications. The weakest area shown is in risk assessment and evaluation.

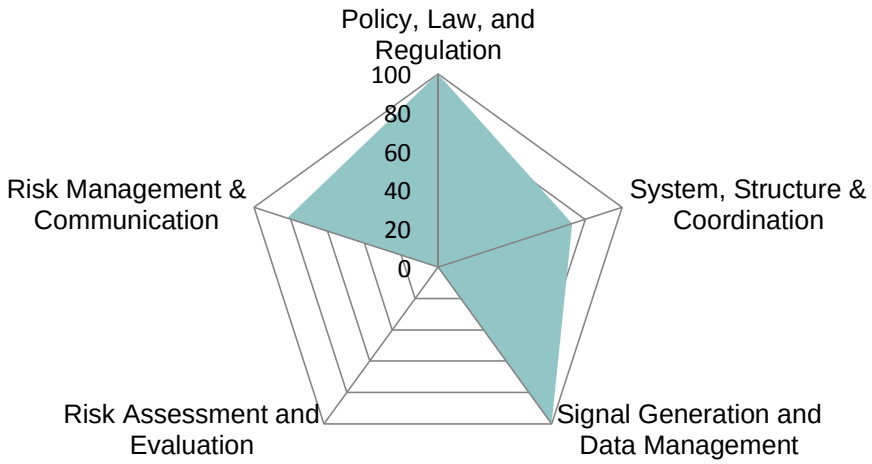


Figure 4. PV profile at national level

PHARMACOVIGILANCE AT THE SERVICE PROVIDER LEVEL— PUBLIC HEALTH PROGRAMS, HEALTH FACILITIES, AND PHARMACIES

This study interviewed representatives and collected data from service providers including PHPs, health facilities, and pharmacies, to map out the extent to which these service providers are involved in PV with the central level. The role of such groups is important because of the direct patient contact. The WHO recommendation on integrating PV into PHPs advises that the model should draw on the strengths of the PV and PHPs to avoid duplication. The model should emphasize sharing human resources and expanding knowledge on effectiveness/risk, collaboration, effective communication, integration, training, and capacity building.[16]

This assessment interviewed health staff from two levels: central, and peripheral. At DOH central, staff of several national public health programs such as HIV and AIDS, malaria, TB, and immunization were selected. Additionally, peripheral health staff from health facilities, and pharmacies from different levels (i.e. regional, provincial, municipal, or city)were sampled (see list of sites assessed in annex A, table 16).

Policy, Law, and Regulation

Findings and Implications

Table 7 show that key respondents from the national PHPs all knew and were aware of the FDA PV and medication safety system. Programs depend on FDA for the governance, policy, laws and regulation promulgation of PV activities including the monitoring and ensuring safety of medicines. The Philippines is one of the few countries that chose to have public health program managers appointed to the PV advisory committee. The investigator of this assessment did not have the opportunity to meet the members of this committee.

Public health programs included in the assessment receive funding from foreign assistance institutions such as UNICEF and Global Fund to Fight AIDS, Tuberculosis and Malaria. Medicines procured with donor funds are subject to strict quality control and assurance procedures such as WHO prequalification schemes. Meanwhile, in procurement with Philippines government funds, the PHPs rely on the quality control policies and governance of FDA. All PHPs have PV policies in place and all except for one have also included policies on quality control.

Ninety percent of nine pharmacies sampled reported awareness of the national policy on PV and 85% knew about the legal provisions in reporting and monitoring of adverse reactions. Most pharmacies sampled were branch pharmacies of major pharmacy chains. Typically, ADRs are reported by the branch office through the regulatory affairs office in the chain's main office, which in turn reports to the FDA. When asked about their awareness of laws and regulations for monitoring of adverse events, several pharmacies expressed familiarity with the "Bantay Gamot" patient and consumer reporting project of FDA and WHO.

[16] WHO. 2006. *The Safety of Medicines in Public Health Programmes.* Geneva: WHO.

Questions related to national policies, laws, and regulations were found not to be relevant at this level and were not included in health facility questionnaires.

Table 7. Policy, Law, and Regulation Component within PHPs

	HIV/AIDS	Malaria	TB	Immunization
PV or medicines safety policy	●	●	●	●
Quality control policy	●	●	●	–

The dot (•) signifies the presence of that system/structure in each program. The dash (–)signifies absence of structure in each program.

Recommendations

- The FDA should consider amending the current legislation on PV to include relevant provisions that address the role of PHPs in monitoring safety among their respective patient populations.

- PHPs and other service provider institutions should have PV procedures incorporated and customized in their respective national health guidelines.

Systems, Structures, and Stakeholder Coordination

Findings and Implications

Public health programs rely on the FDA's systems and structures to implement PV activities, including the use of the quality control laboratory, medicine information service, and the budget to implement activities. PHPs do not have a focal PV person to ensure medicine safety and rely on the regional or hospital-based medicine safety advisory committees. The advisory committees do not meet regularly and few have guidelines for making decisions.

In 2011, the National PV Center conducted trainings for health care workers from the HIV and AIDS, and Immunization programs on PV and medicine safety. Health workers from other programs such as TB were not trained.

Staff interviewed in three of the four PHPs were aware of national efforts to coordinate PV stakeholders as seen in table 8 . Both the TB, and Immunization programs are aware that they are responsible for monitoring procured medicines, and are responsible for proper distribution of medicines and reporting of utilization and adverse reactions.

Pharmacies reported some awareness of the national PV policy, in spite of lack of detailed guidelines for implementation of the policy. Only 40% of the pharmacies sampled were aware that there is a PV unit within FDA. Some pharmacies rely on receipt of medicine safety information from product manufacturers and report ADRs to the product manufacturers instead of the FDA. All pharmacies reported awareness of their roles in the national PV system, particularly in informing patients of medicine safety information and ensuring there are available prescriptions before dispensing.

Most health facilities sampled have a PV unit responsible for medicines safety within their facilities, most commonly through the Drug Therapeutics Committee or a team within the

pharmacy department. At least one dedicated staff member and core communication technologies for reporting medicine safety information is in place in most facilities. Of the 23 health facilities sampled, only two reported that they did not have a medicines safety unit and five reported no clear mandate or structure for the unit. Two-thirds of health facilities reported that they have medicine safety information services, while one-third had core reference materials for PV on hand. Only 22% of health facilities conducted training on PV for any staff members with little feedback after the sessions.

Table 8. System, Structure, and Stakeholder Coordination—PHPs

Existence of System/Structure and Coordination	HIV and AIDS	Malaria	TB	Immunization
PV center or unit	●	●	●	●
PV center/unit with clear mandate, structure, function	●	●	●	●
PV information service	●	●	●	●
Staff for PV	●	●	●	●
Budget for PV	–	–	–	–
Up-to-date national guideline for PV	●	●	●	●
SOPs	–	–	–	–
Medicine safety advisory committee	–	–	–	–
Core communication technologies for PV	●	●	●	●
Core PV reference materials in PV Center	●	●	–	●
Health care workers trained on PV and medicine safety	●	●	–	●
PV stakeholder coordination mechanism	–	●	●	●

The dot (•) signifies the presence of that system/structure in each program. The dash (–) signifies the absence of structure in each program.

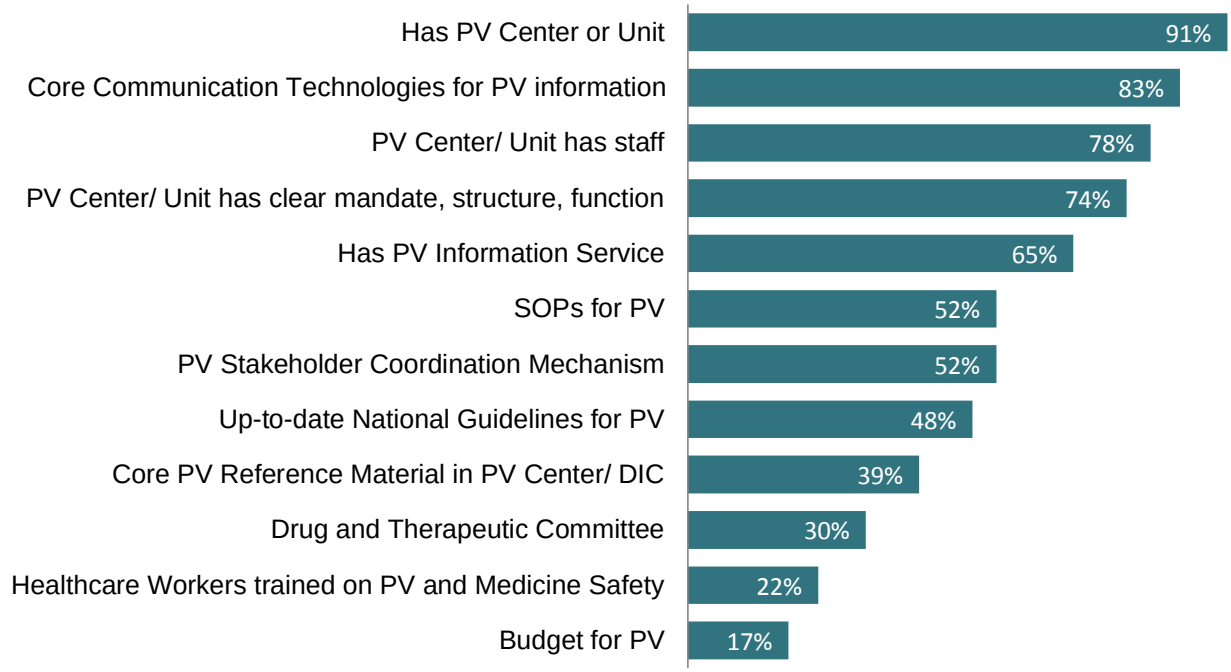


Figure 5. Percentage of respondents with system, structure, and stakeholder coordination within selected health facilities

Recommendations

- Public health programs are strongly encouraged to coordinate all PV activities with the FDA.

- FDA should promote and advocate to all service delivery stakeholders the need and importance of reporting ADRs, treatment failures, and medicine errors.

- Service providers need to strengthen their collaboration with FDA, not only for communication of PV issues but including quality control testing of pharmaceuticals.

Signal Generation and Data Management

The importance of reporting ADEs, medication errors, and treatment failures cannot be overemphasized. It is only through adequate reporting that all stakeholders have the necessary information to enable each other to make appropriate decisions regarding their health.

Findings and Implications

All PHPs reported existence of a product quality reporting form and a suspected ADR form. No PHPs reported existence of a medication error or treatment failure reporting form or subset of another form (i.e. ADR form), despite the fact that the national ADR form includes such data fields. See table 9. In addition, the assessment found that the PHPs do not have databases for the collation and management of PV data they collect and send to FDA.

Table 9. Signal Generation and Data Management–PHPs

Existence of Signal Generation and Data Management	HIV/AIDS	Malaria	TB	Immunization
PV data collation system from country sources	–	–	–	–
Suspected ADR reporting form	●	●	●	●
Product quality reporting form (or subset)	●	●	●	●
Medication error reporting form (or subset)	–	–	–	–
Treatment failure reporting form (or subset)	–	–	–	–

The dot (•)signifies the presence of that system/structure in each program. The dash (–) signifies absence of specific structure in each program.

Only 48% of the pharmacies assessed had consumer reporting forms available in the pharmacy. About 70% have ADR reporting forms; 32% reported having a product quality reporting form and 30% reported having a medication error reporting form or subset of the ADR form. Most of the pharmacies without these forms assumed that patients and consumers communicate ADRs and medication errors to their physicians or to the product manufacturers for any product quality issues.

In figure 6, 70% of the health facilities have existing suspected ADR forms, Less than half of the health facilities do not maintain a database regarding PV reports and do not report any PV data to FDA. One reason noted for deterred reporting is that facilities consider this data confidential and fear legal backlash including lawsuits and harassment by the product manufacturers. For those who report, submission to FDA is either online or through postal mail.

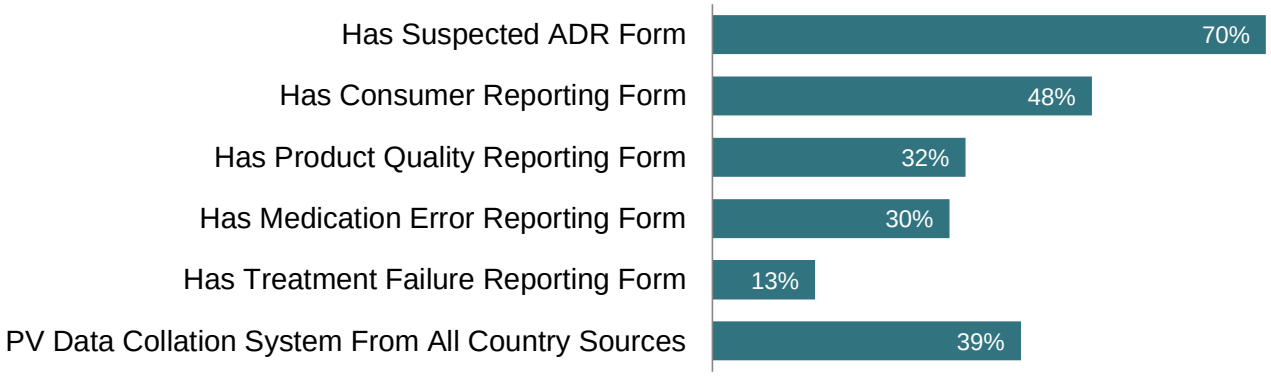


Figure 6. Percentage of respondent with signal generation and data management within selected health facilities

Recommendations

- Service providers should be encouraged to submit ADR reports to FDA, and seek to build their capacity to manage internal data and conduct internal analysis. FDA should collaborate with service providers to develop strategies for improving reporting.

- Service providers should have a functional database for PV.

- Data collation from one system must be improved by having an organized and integrated mechanism of reporting from each public health program and health facilities and pharmacies. Having an organized and integrated reporting mechanism would facilitate the collection of data and help prevent redundancy of function with regards to data analysis and dissemination of information.

Risk Assessment and Evaluation

Findings and Implications

Table 10 and figure 7 showed that methods for generating safety signals were not present in most of the sampled PHPs, and health facilities. No PHPs reported ADRs in the last year to FDA. This presents an opportunity for strengthening the national PV system through data sharing and collaboration between PHPs and the National PV Center. Due to high reliance on FDA, PHPs have not conducted their own surveys on product quality, medication errors, medicine utilization and active surveillance. None of the pharmacies reported receipt of any spontaneous reports from patients and consumers for ADRs, product quality, and medication errors. PHPs and health facilities rely on FDA for quality control laboratory testing. Generally, facilities do not carry out studies about medication errors, medication utilization,

or have an active surveillance activity. Only a few facilities conducted specific internal studies such as antimicrobial usage versus resistance, missed medicine doses, medicine orders not carried out, and active surveillance for patients using intravenous therapy.

Table 10. Risk Assessment and Evaluation—PHPs

Existence of Risk Assessment and Evaluation	HIV and AIDS	Malaria	TB	Immunization
Spontaneous reporting	–	–	–	–
Product quality survey and inspections Planned and conducted	–	–	–	–
Medication errors studied	–	–	–	–
Medicine utilization studies	–	–	–	–
Active surveillance activities	–	–	–	–
Patients in PHP with documented ADRs >1%	–	–	–	–

The dot (•) signifies the presence of that system/structure in each program. The dash (-) signifies absence of specific structure in each program.

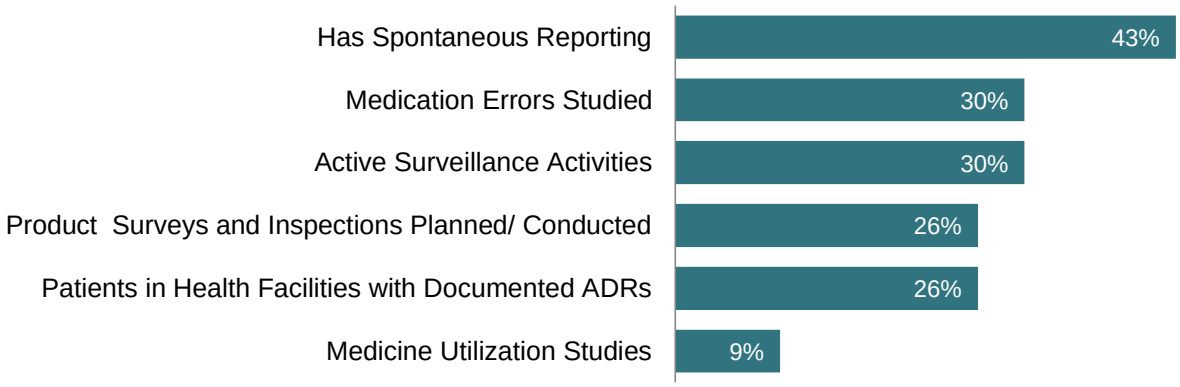


Figure 7. Percentage of respondents with risk assessment and evaluation within selected health facilities

Table 10 and figure 7 above show that PHPs are weak in risk assessment and evaluation. There is reliance on FDA for the risk assessment and evaluation component for all indicators.

Recommendations

- Service providers need to seek technical support to build internal PV structures and system to collect, analyze, and report PV issues to FDA.
- Service providers should consider strategies to encourage and promote reporting.
- Service providers should be trained to categorize ADR reports according to severity, type of suspected medicines, or any unexpected drug reactions.

- The National PV Center should develop a system of information management and other support activities for reporting ADRs.

- PHPs should collaborate with the NPVC and other stakeholders to study priority safety issues arising from the use of medicines in their programs. These studies can best be conducted through the setup of properly designed prospective active surveillance systems.

Risk Management and Communication

Findings and Implications

In the Philippines, PHPs purchasing medicines with donor funds are required by donor policy to use WHO prequalification schemes when making medicine procurement decisions. The government-funded local procurement goes through FDA quality testing upon delivery to DOH. The national malaria program was the only PHP to report submitting product for quality testing, as seen in table 11. Three programs answered that they have a strategy to mitigate the use of high-risk medicines and two of the three programs have started implementing this strategy. Three programs answered that safety signals and significant safety issues are promptly communicated to health workers and the public. The estimated lead time for communication to reach concerned entities takes one week from the time of identification of the problem.

Table 11. Risk Management and Communication—PHPs

Existence of Risk Management and communication system	HIV/AIDS	Malaria	TB	Immunization
Medicine safety information requests addressed	–	–	–	–
Medicine safety bulletins	–	–	–	–
Prequalification schemes used in procurement decisions	•	•	•	•
Medicines sampled and analyzed for product quality	–	•	–	–
Risk mitigation plans for high-risk medicines	–	•	•	–
Medicine safety issues identified from external sources and acted on	–	–	–	–
Time from ADR signal generation to communication to health care workers and public <3 weeks	•	–	•	•
Public or community education activities	•	•	•	•
Medicine safety action taken other than ADR reporting	–	•	–	–

The dot (•) signifies the presence of that system/structure in each program. The dash (–) signifies absence of specific structure in each program.

Among the pharmacies sampled as to medicines information and safety requests, only two received information requests from consumers in the last year. Of these, only one was forwarded to National PV Center. Forty-five percent of pharmacies reported receiving any medicine safety bulletins and most of these came from pharmaceutical manufacturers.

Although this was not verified, all pharmacies surveyed, reported that all medicines available in their pharmacy are FDA registered and that they only order and purchase medicines from legitimate and registered suppliers. Pharmacies update themselves through pharmaceutical references literature, journals, in-house training, notification from head offices, and manufacturers' product seminars and awareness activities. Information and updates about label changes, changes in treatment guidelines, or withdrawn licenses are communicated to pharmacists from manufacturers and the main office of the government pharmacy branch. Pharmacists in these settings claimed that they provide education and information to patients and consumers who inquire, but none reported of carrying out outreach community activities on medicine safety.

Most facilities answered that they have access to safety advisories though very few mentioned the advisories posted on FDA website. This leads the investigating team to assume that health facilities do not have access or the time to check on FDA advisories posted on the website. Very few health facilities follow WHO prequalification schemes in their procurement decision making. Some were found not to follow the national hospital formulary. Although a small number of facilities submitted products for quality analysis, based on the data collected, those who did, found products that failed QA testing. Most health facilities do not have risk mitigation plans in place. Almost none of the facilities sampled conducted training or patient education programs relating to medicine safety, nor did they report taking medicine safety action related to risk management or communication figure 8.

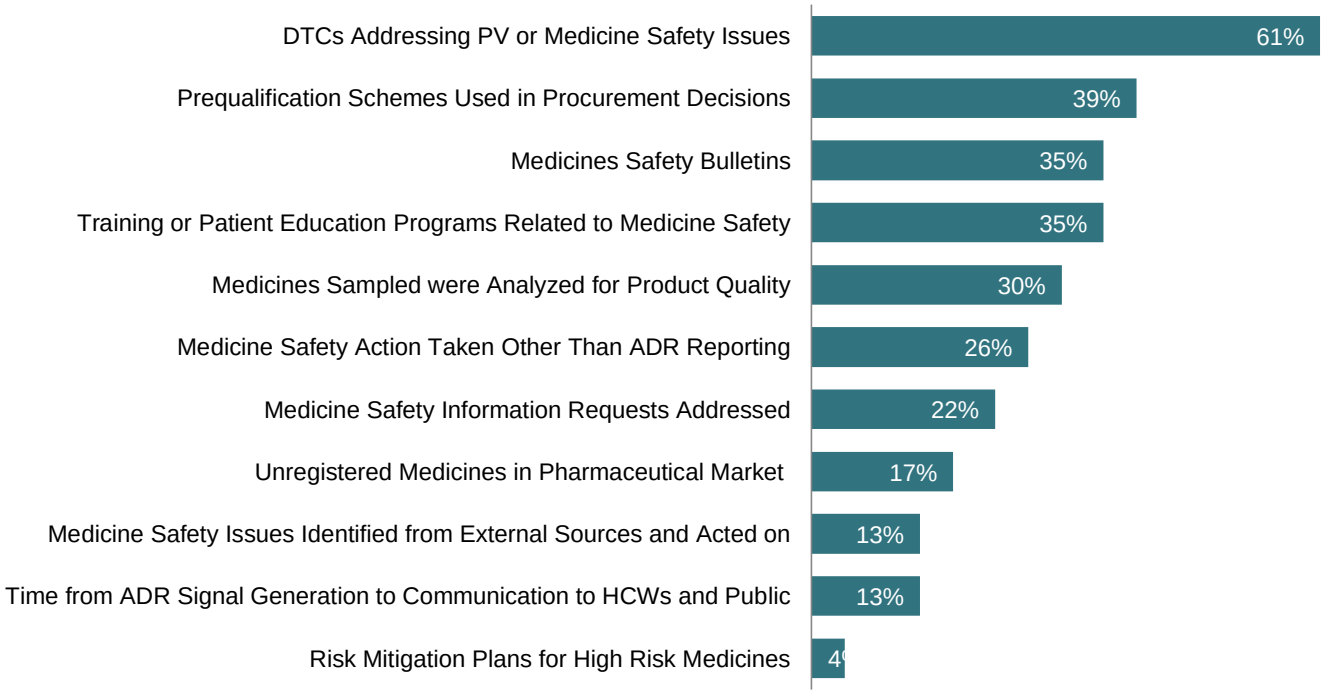


Figure 8. Percentage of respondent with risk management and communication within selected health facilities

Recommendations

- PHPs should have access to an FDA-led medicine safety information center that compiles medicine safety information from local and external sources.
- Service providers should adopt a more systematic prequalification scheme used in the procurement decision.
- The National PV Center should further improve its turn-around time for reporting ADR signal generation and providing feedback to service providers by defining specific items that needs to be reported.
- FDA should strengthen advisory strategies to promote information update among service providers.
- Service providers should develop risk mitigation plans and FDA should encourage all institutions to update this regularly.

The PV Situation at the Service Delivery Level

The figures below represent the findings and responses received from respondent at the service delivery level (PHP, health facility, pharmacy). Figure 9 shows that the PHPs have a high score for policy and law regulation, however, signal generation and data management, risk assessment and evaluation, and risk management and communication scored low.

Figures 10 and 11 show the chart score for health facilities and pharmacies and in both cases, especially the health facilities, the scores are relatively low with the exception of one high score in pharmacy on their knowledge on policy and regulations.

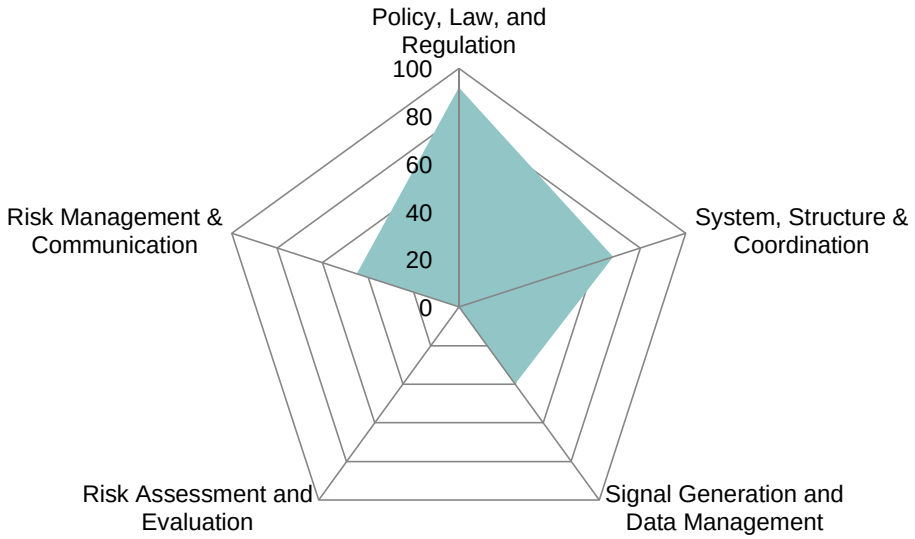


Figure 9. Medicines safety situation in National PHPs

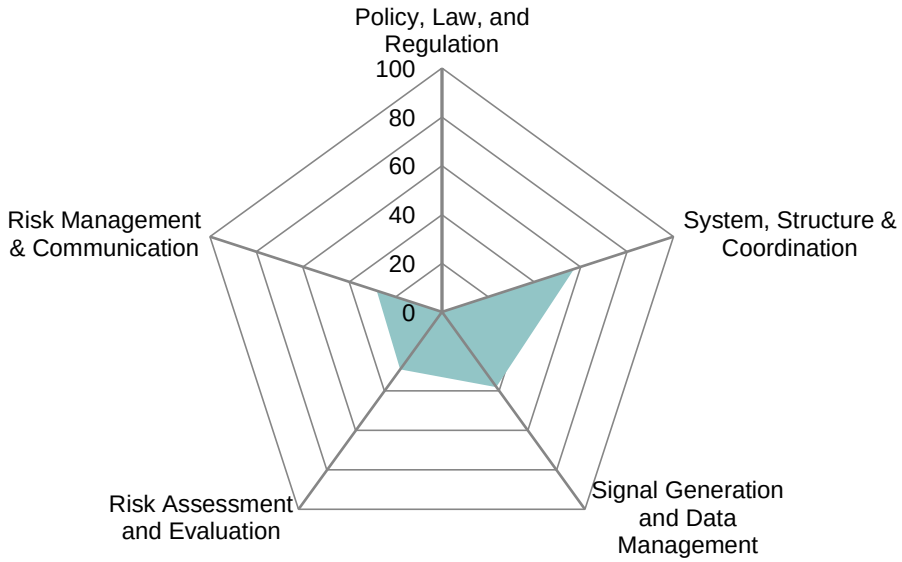


Figure 10. Medicines safety situation in selected health facilities

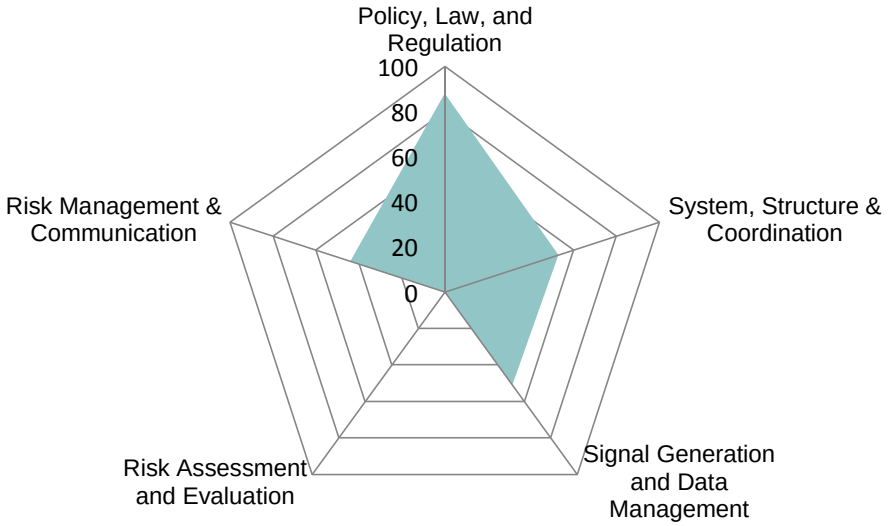


Figure 11. Medicines safety situation in selected pharmacies

PHARMACOVIGILANCE IN THE PHARMACEUTICAL INDUSTRY— PHARMACEUTICAL COMPANIES, MEDICAL DEVICE COMPANIES, CLINICAL RESEARCH ORGANIZATIONS

Introduction

The pharmaceutical industry is one of the multiple stakeholders who share the responsibility for ensuring safety of medicines and medical devices within a country. A MAH must establish appropriate medicine and device safety systems to ensure responsibility and liability for its products and must also monitor and report ADEs related to the use of its products wherever they are marketed. Stringent regulatory authorities such as the European Medicines Agency (EMA) and the US FDA require MAHs to report ADRs or device-related ADEs that occur in all countries where their products are marketed. According to the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) guidelines, these agencies also require companies to conduct post marketing safety studies or risk minimization activities for high-risk medicines and products with unresolved safety concerns.[17,18]

Description of Study Sites

The investigating team interviewed three multinational innovator, three multinational generic, and three local pharmaceutical manufacturing companies in the Philippines.

Table 12 shows the FDA data of the number of reported ADR by different types of industry. Of the total 1,302 reported ADRs, multinational generic companies 2 and 3 had the highest number of ADRs reported.

Table 12. Number of Products in Market vs. Reported ADRs

Industry	Number of products in the market				Number of Reported ADRs
	1–50	51–100	101–200	>200	
Multinational Innovator 1	–[a]	–	169	–	21
Multinational Innovator 2	–	–	–	209	17
Multinational Innovator 3	–	–	114	–	18
Multinational Generic 1	–	–	–	438	0
Multinational Generic 2	–	–	–	433	932
Multinational Generic 3	–	83	–	–	300
Local Generic 1	–	60	–	–	0
Local Generic 2	–	–	–	479	11
Local Generic 3	–	55	–	–	3

a. The dash (–) signifies no product in the market, according to FDA.

[17] EU. 2004. *Legislation Volume 9: Guidelines for Pharmacovigilance for Medicinal Products for Human and Veterinary Use.* Available at http://ec.europa.eu/health/files/eudralex/vol-9/pdf/vol9_10-2004_en.pdf

[18] FDA. 2001. *Draft Guidance for Industry: Post-marketing Safety Reporting for Human Drug and Biological Products Including Vaccine.* Available at http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Vaccines/ucm074850.htm#INTRODUCTION

At the time of the assessment, all fourteen pharmaceutical industries have PV units and designated staff, SOPs in reporting, and reporting forms. Only the three medical device companies have not sent ADR reports to regulatory authority and did not carry out post-marketing surveillance (table 13).

Table 13. PV Activities within Industry

	Multinational Innovator (N = 3)	Multinational Generic (N = 3)	Local Manufacturer (N = 3)	Medical Device Company (N = 3)	Clinical Research Organization (N = 2)	Total
With PV unit or Staff	3	3	3	2	2	13
With SOP or reporting form	3	3	3	3	2	14
That have sent ADR reports to regulatory authority in 2011	3	3	2	–[a]	2	10
That have carried out post-marketing surveillance in 2011	3	3	2	–	–	8

a. The dash (–) signifies no PV activities.

Policy, Law, and Regulation within Selected Pharmaceutical Companies

Findings and Implications

Generally, pharmaceutical industries have policies, laws and regulations to implement PV activities within their institutions, though not all institutions link their policies to FDA. The policy within the organizations is usually updated every 1 to 2 years. All the industries interviewed have internal procedures addressing PV in the quality system. However, 33% of those interviewed did not submit development safety updates reports for premarketing PV activities and one company did not submit development safety updates reports (DSUR) for post-marketing surveillance.

The majority of the industries interviewed comply with the policy, laws, and regulations pertaining to PV and medicine safety. Most companies have existing policies as well as legal provisions that govern medicine safety related activities, ADR reporting, and quality assurance. Only few pharmaceutical companies do not have procedures for addressing mandatory expedited reporting. One of nine pharmaceutical companies did not reference the legal provision requiring post-marketing surveillance activities for products as required by FDA. Pre- and post- marketing seem to have low priority with all interviewed companies.

All medical device organizations sampled have internal policies on device safety, including procedures addressing product quality, safety, and promotion. Although 33% does not require reporting ADRs to the FDA, internal controls are present in all these organizations to ensure confidentiality of patients who reports.

The clinical research organizations (CROs) have internal policies on PV which seem to be regularly updated. In addition, they have procedures addressing quality standards and the mandatory reporting requirement of worldwide safety experience for MAH in the quality

system. Development safety updates reports are submitted for pre-marketing but this information is submitted directly to the product sponsor and not the FDA (figure 12).

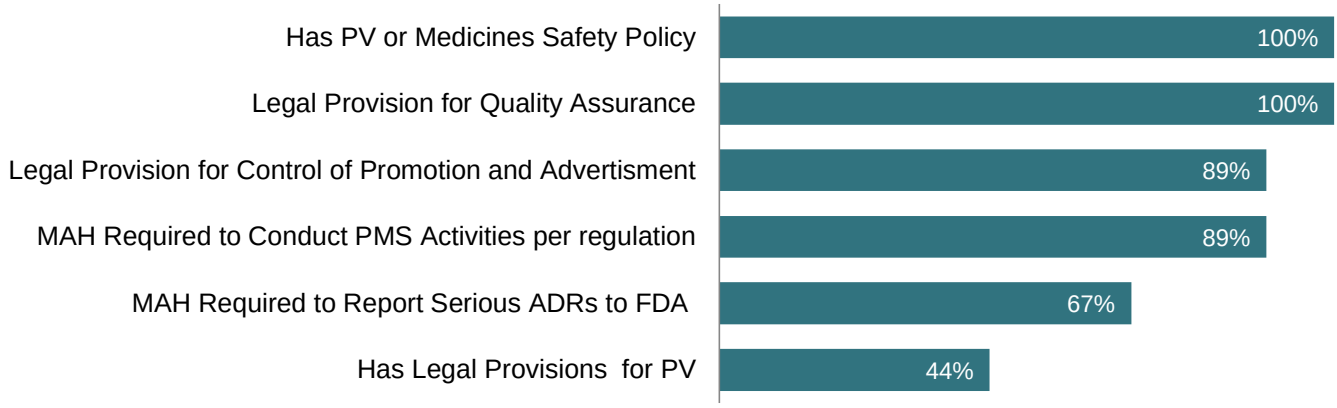


Figure 12. Percentage of respondents with policy, law, and regulation within selected pharmaceutical companies

Recommendations

Pharmaceutical industries should regularly update and revise PV policies and ensure compliance with the FDA's regulatory requirements; improve detection system and the identification of inferior, spurious, adulterated medicines in the market; and improve transparent reporting of ADR.

System, Structure, and Stakeholder Coordination

Findings and Implications

Figure 13 shows that all of the pharmaceutical companies have PV units within the company with a clear mandate, and structure, and clear roles and responsibilities. This unit manages all PV-related activities including training, product complaints, ADR reporting to FDA, and patient-oriented programs. A high percentage has regular audits and inspections with written procedures for each.

All device companies sampled have teams within the organization responsible for PV activities. They all have documented procedures, roles, and reporting lines for device safety. One out of the three device companies did not have a quality control unit or a quality control laboratory; however, the investigators were informed that their quality control unit/ laboratory are present in their manufacturing sites.

Two of the three companies have local SOPs surrounding PV, the other company relies on their regional/main office for safety queries and information. Communication tools for PV-related information are all available as references. Less than 5% of the staff has been trained on PV.

CROs have PV units responsible for PV related activities, with a clear mandate and role, and structures and responsibilities. All CROs are obliged to inform patients directly through an patient-doctor agreement about the medicine safety. They also have SOPs for product quality, ADRs reporting, follow up on missing information, duplicate reports detection, and clinical assessment for causality. The CROs also have a process for expedited serious adverse drug reaction reporting during clinical trials; identify safety signals of changes in severity, characteristics, or frequency of expected ADR. All CROs included in the assessment also assessed any increase in frequency of expected ADR as a potential risk. Tools and technology for reporting are available and reports are sent via email. Staff members are trained in PV.

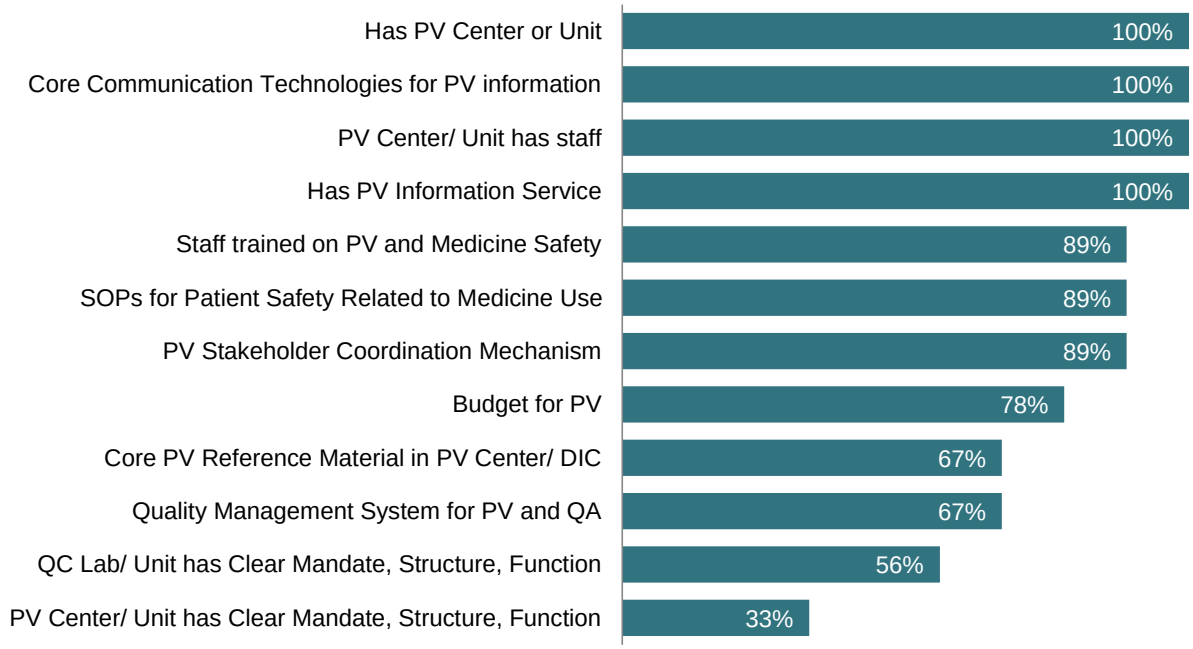


Figure 13. System, structure, and stakeholder coordination within selected pharmaceutical companies

Recommendations

The National PV Center should take the lead and coordinate with all the pharmaceutical industries to define responsibilities for PV inspections, report suspected AEs, and promote the safe use of their products.

Signal Generation and Data Management

Findings and Implications

All medical device companies store information on device safety. A form exists for spontaneous reporting of suspected device adverse events but only one organization has a form for reporting medication error.

CROs have system for archiving and storing PV-related documents and coordination. They have forms for spontaneous reporting of ADRs which complies with the Council for International Organizations of Medical Sciences(CIOMS) standards. Forms for reporting product quality, treatment failure, and medication errors are available at one CRO, as seen in figure 14. Eight out of nine pharmaceutical companies have a system for archiving and storage of PV information. But not all databases are compliant with the E2B standard format of reporting to ICH and UMC. All of the pharmaceutical companies have forms for product quality and reporting errors; however, there is not 100% compliance with reporting medication errors and lack of efficacy concerns.

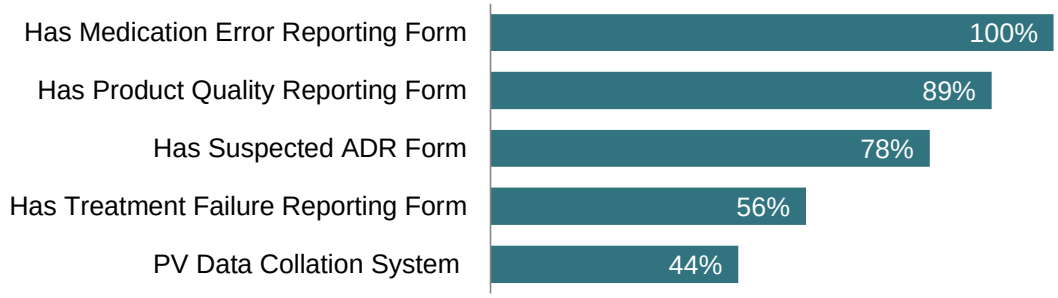


Figure 14. Signal generation and data management within selected pharmaceutical companies

Recommendations

The National PV Center should make all forms for reporting including standardization of reporting format available.

Risk Assessment and Evaluation

Findings and Implications

All CROs received ADRs in 2011 that were reported to FDA. Figure 15 showed that none of the CROs assessed conducted any active surveillance in the last five years, but they mentioned that they use and have data mining tools or signal detection tools.

All medical device companies have received adverse event reports, which are stored in the companies' device safety databases. There are no surveys conducted regarding the quality of their products in 2010, as well as no surveys regarding device errors, yet one company reported that they received one report of an adverse event. No utilization review surveys have been conducted. Two of the three organizations have conducted active surveillance.

Multinational pharmaceutical companies have generally good practices in reporting adverse events. Most have ADR reports which they submit to FDA, although one respondent from a local pharmaceutical company do not have ADR reports. There is generally good documentation of ADRs experiences, ICSR received and causality studies. Surveys for product quality and medication errors can be improved. Implementation of active surveillance and post-authorization safety studies needs to improve.

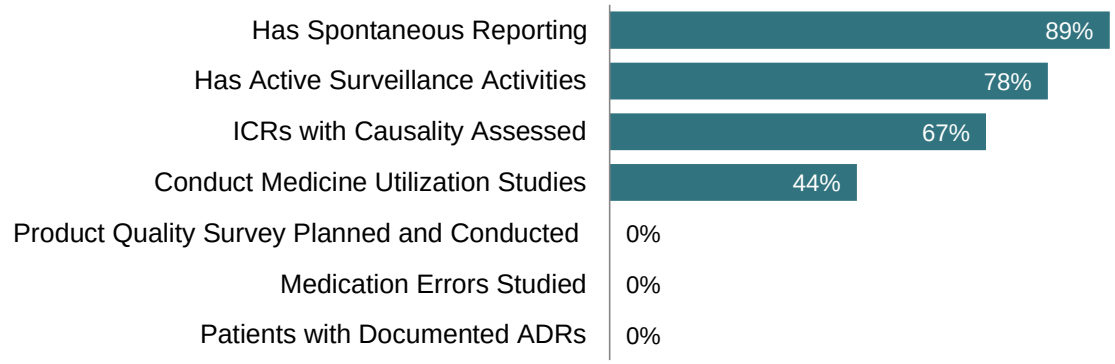


Figure 15. Risk assessment and evaluation within selected pharmaceutical companies

Recommendations

- Industry should adopt policies and procedures to meet legislative mandates and increase reporting rates.

- FDA should develop systems for audits and inspections to ensure that industry complies with legislations and fulfills its responsibility for monitoring the safety of products they are licensed to market.

- Industry should collaborate with the FDA to implement post-authorization safety studies for products with safety uncertainties, particularly where such products and studies are required by stringent regulatory authorities.

Risk Management and Communication

Findings and Implications

Of the nine pharmaceutical industry respondents, only three pharmaceutical companies have received requests for safety information; Challenges from the perspective of the pharmaceutical companies are that patients are not aware that ADRs could be reported. Similarly to medical device companies, pharmaceutical companies suggest that there be a public information campaign on PV and safety of health products (figure 16).

Of the medical device companies, 67% received requests of information regarding their products. Sampling for product quality analyses was not conducted for any of the devices and risk management plans were not submitted. Two of three respondents have controlled distribution and use of class II and III devices due to concerns of safety when improperly used. However, there are no activities to mitigate risk of such high-risk devices. Average time lag between identification of safety signal and communication is 2 to 4 weeks. Two of three devices developed safety alerts and dear doctor letters. Two of three have required changing labels or updating promotional information.

One of the two CRO respondents submitted risk management plans and both respondents have a system of monitoring safety reports. One of two CROs has developed safety alerts and

"dear doctor letters" or drug information letters disseminated to the doctors. No risk management plans were submitted and no assessments performed for decision making.

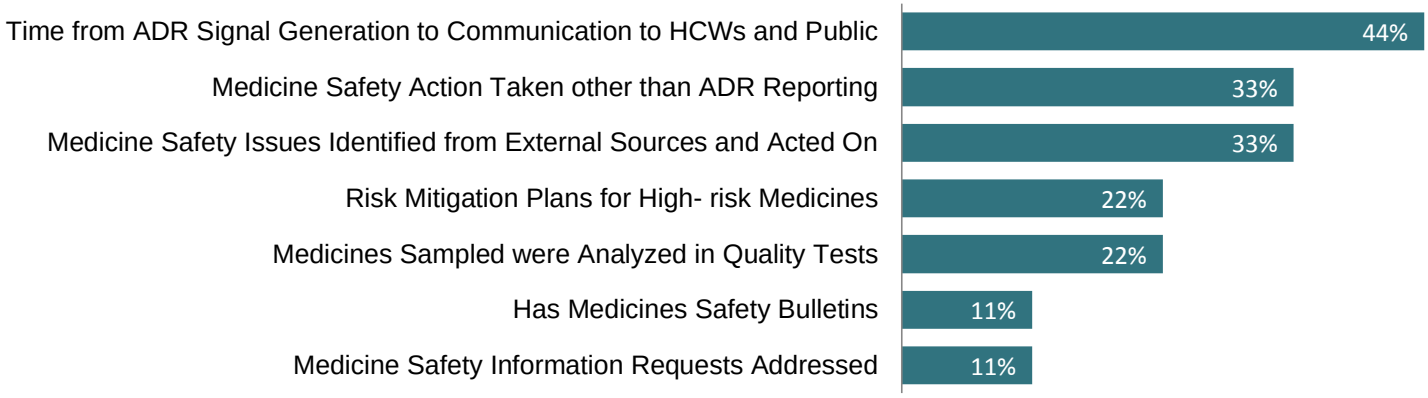


Figure 16. Risk management and communication within selected pharmaceutical companies

Recommendations

Industry should review its risk management and communication strategies, particularly related to risk management plans and strategies for providing patients with medicine safety information, given the patients' and pharmacies' reliance on industry for information on medicine safety.

The PV Situation in Philippines within Industry

The following figures show where the strengths and weaknesses in PV implementation in the industry. For the pharmaceutical companies and devices, the risk assessment and evaluation and risk management and communication seem to be weak. The policy, law, and regulation; systems and structures and coordination; and signal generation and data management relatively score high. The clinical research organization chart indicates strong systems, structures and coordination.

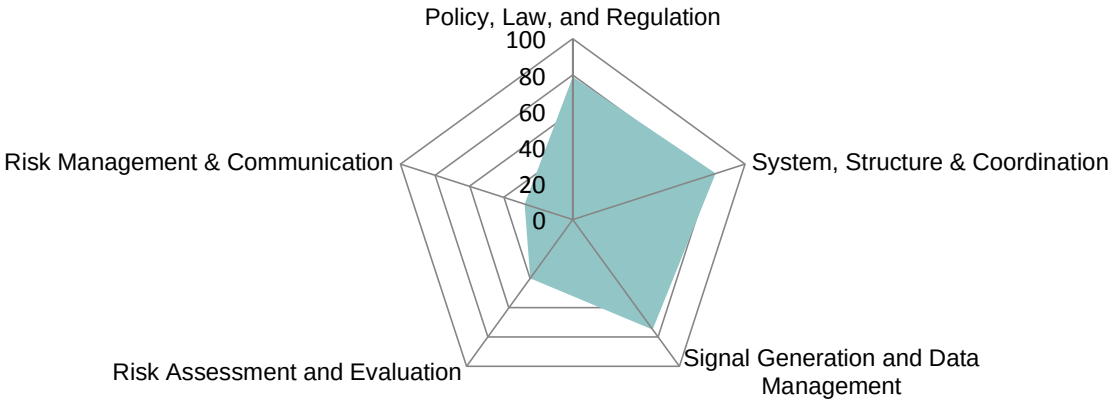


Figure 17. Pharmacovigilance situation within pharmaceutical companies

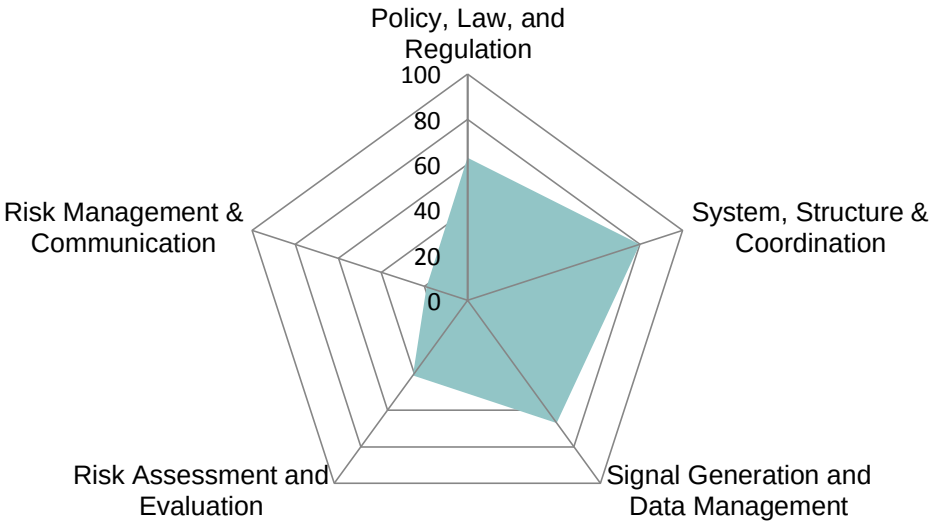


Figure 18. Pharmacovigilance situation within medical device companies

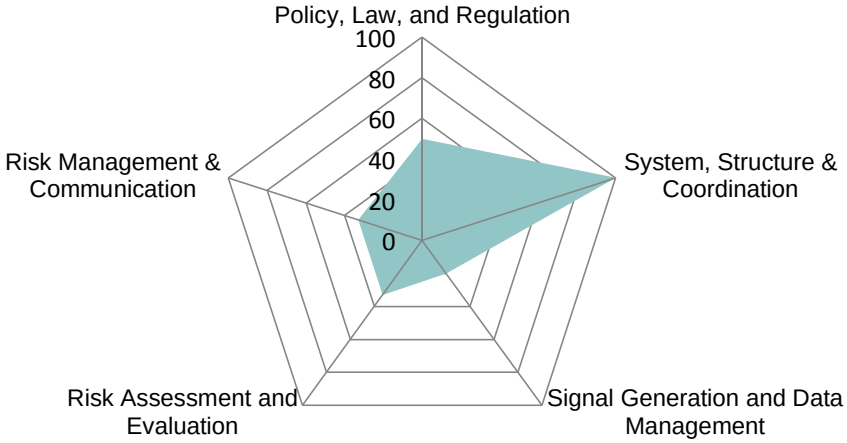


Figure 19. Pharmacovigilance situation within clinical research organizations

PHARMACOVIGILANCE IN CIVIL SOCIETY ORGANIZATIONS— ACADEMIA, PROFESSIONAL ASSOCIATIONS, CONSUMER GROUPS

Introduction

Civil societies play a critical role in advocating for patient safety and for pushing forward the national medicine safety and PV agenda. Members of civil society are critical stakeholders and should be included in national committees, introduction of pre- and in-service training, and to consult with to solve medicine safety challenges.

Findings and Implications

Civil societies are not represented in the National Pharmacovigilance Advisory Committee . The findings showed that only one of three consumer groups was aware of the existence of the PV policy or the National PV Center. None of the groups were trained in PV, though when asked of their role in ensuring medicine safety, two of three cited their role in reporting ADRs to the concerned government agencies. Two of three consumer groups were aware of consumer reporting forms for ADRs and encouraged their members to report ADRs directly to FDA. No consumer groups sampled received any medicine safety bulletins nor were they aware of strategies or plan to mitigate use of high-risk medicines. None received safety information materials and none was aware of any mechanism to report inappropriate or violations in promotional materials. One consumer group conducted safety information orientations within their membership and through efforts of MeTA on medicine safety but commented that there are no more trainees and popular education materials for distribution. Consumer groups commented that within the FDA and the National PV Center, there is no centralized area for distribution of alerts, and public information is limited and does not cover license withdrawals. Consumer groups recommended having forums for patients' awareness, participation, and capacity building.

All respondents representing academic institutions from pharmacy, medicine, and public health academia include some PV and medicine safety topics as part of the curriculum. Topics include overview of PV system, national drug policy, drug interactions, monitoring drug utilization, ADR, medication errors, and therapeutic errors reporting. Almost all of the respondents were aware of their role in the medicine safety, except for one who pointed that their role is only theoretical. Two of seven academic institutions are not aware of any platform for PV coordination in the country.

One of seven academic institutions respondents participated in a short review of ADR in the hospital setting. Two respondents reported monitoring medication errors in their affiliated hospitals. Of this, one major hospital reported 10%–15% major medication errors from the wards, which they have addressed. The pharmacy departments in two of the academic institutions study drug utilization as part of their pharmacy department. Active surveillance is carried out by the pharmacy departments of their affiliated hospitals.

Most respondents from medical professional associations answered that 60% of patients and 90% of consumers are not aware of the policy and laws surrounding PV. The Philippine Pharmacist Association and the Board of Pharmacy developed a policy for medication safety and it is planning to communicate and present to the consumers and patients; 60% of the

groups are aware of the existence of the PV Center in FDA. Only 40% are aware of the existence of the national guidelines for PV. Less than half of the academic groups include PV as part of the curriculum or as a continuing education programs in their field. Only 50% conducted trainings for PV. Only one of 10 was aware of their role in the PV system.

Recommendations

- The FDA should ensure that medicine safety advisory committees and related expert committees are established or revived and include representatives from consumer groups and civil society.

- Health care workers should be trained to monitor and report ADRs either through pre-service and in-service training or through the Drug and Therapeutic Committees, with clear delegation of line of reporting.

The PV Situation in Philippines within Civil Society

Figures 20 and 21 represent Philippine's PV system at the civil society level. Higher scores are depicted by points further from the center of the diagram, on a scale of 0 to 100 for each of the five components.

The consumer groups were not asked about indicators for risk assessments and evaluation. The chart shows their strength in signal generation. Their perception is a weakness in the other indicators especially in the risk management and communication.

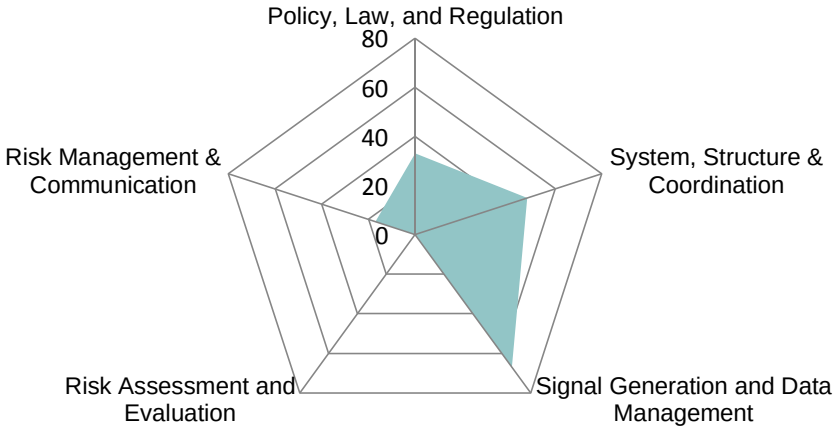


Figure 20. Pharmacovigilance situation in selected consumer groups

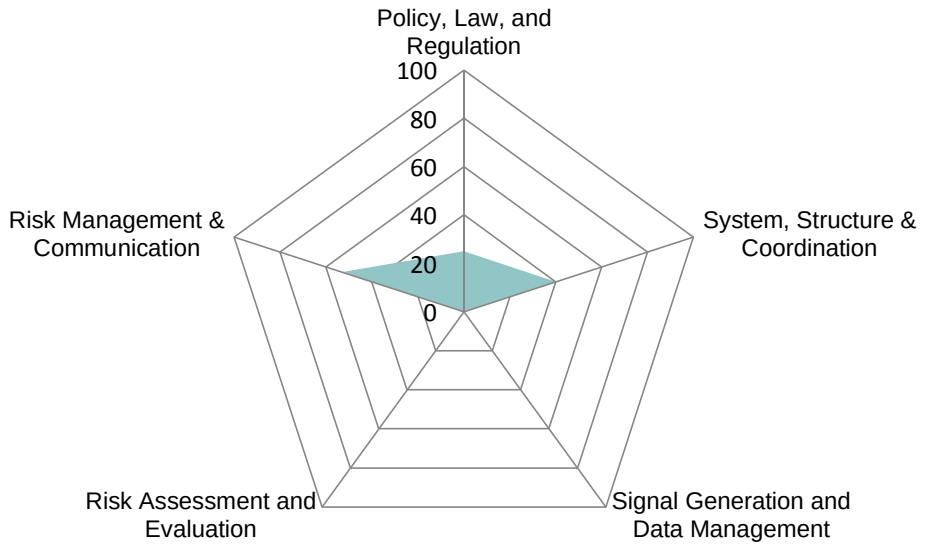


Figure 21. Pharmacovigilance situation in selected professional associations

Professional associations scored the PV systems low in the three components. The highest score is below 50% in risk management and communication.

For academia, questions were directed in the systems, structures and coordination, and the risk assessment and evaluation. Figure 22 shows weakness in both indicators, especially in the risk assessment and evaluation.

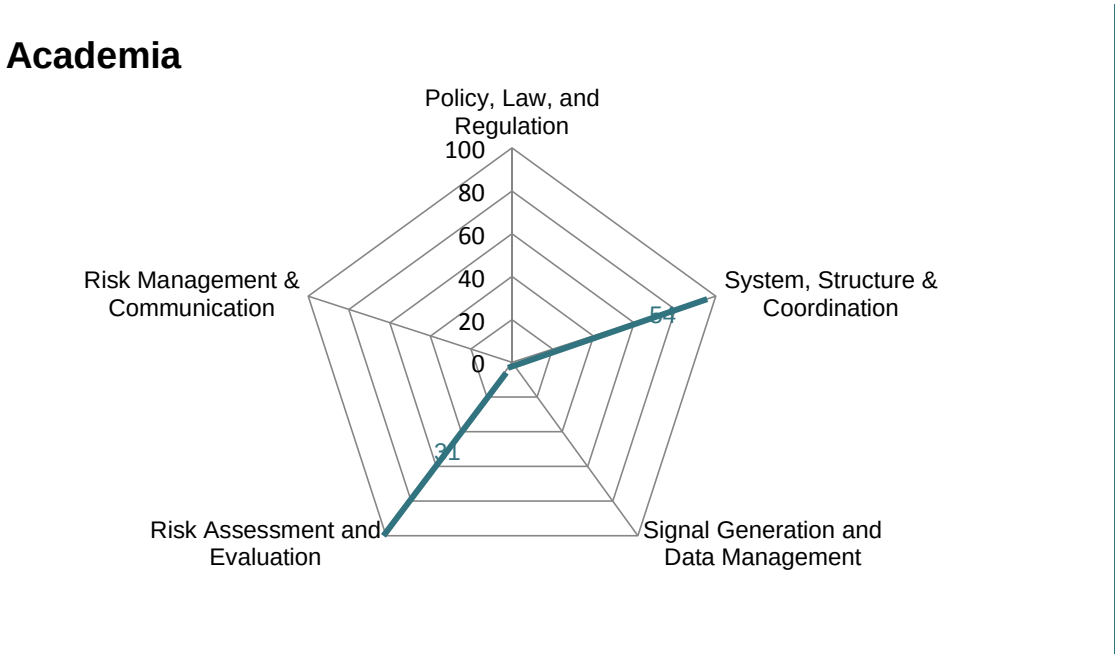


Figure 22. Pharmacovigilance situation in selected academic institutions

CONCLUSION

The assessment of the Philippines PV system showed that there is a foundation for a comprehensive PV system in place, which includes—

- National laws, policy and regulation and governance that specifically address medicine safety systems and PV
- Most systems, structures, and stakeholder coordination activities required
- Strong signal generation and data management

The assessment identified some risk assessment and evaluation and some risk management and communication activities, but the assessment authors recommend that investments be made to improve the conduct of related activities.

In the Philippines, a PV policy is in place that addresses medicine safety. MAHs are required by FDA to report suspected ADRs to the FDA, and are required by law to conduct post-marketing studies under certain circumstances. Legal provisions for medicine product quality assurance and control of product promotion and advertising are in place. Supportive governance structures include a regulatory framework, regulatory registers for medical products, and enforcement of governance structures.

The Philippines has invested significantly in the establishment of structures and systems related to medicine safety including having a PV center within the FDA with a dedicated staff member, PV information service, quality control laboratory, and other core elements necessary for the functioning of a national PV system. The assessment found that a National Medicines Safety Advisory Committee and a National Quality Control Advisory Committee are not yet in place. A standardized national ADR form is in place and includes fields to collect suspected ADR data as well as product quality concerns, medication error, and treatment failure. Consumers are encouraged to report suspected ADR or medicine safety concerns to the FDA directly or through service providers.

However, although risk assessment and evaluation activities in the Philippines are in place, they require strengthening. ADR reports are collected and causality is assessed for only one-third of reports. Risk management and communication activities are being done, but they could be improved through systematic and routine publication and distribution of an electronic medicine safety bulletin.

The Philippines has established a PV system with many elements required to ensure the ability of the FDA to detect and address medicine safety in the Philippines through regulatory action. Some functions of the PV system in the Philippines need to be improved. Medicine safety is a significant issue in the Philippines. There may be preventable harms that occur but the size of the problem is not sufficiently known due to barriers and challenges in the system. Fully addressing medicines safety for the Filipino people should continue to be included as a priority for the DOH and the FDA and should be fully integrated into national PHPs, industry practice, and points of contact with the patient and health care providers.

In the last few years, the Philippines economy has grown at a rate of 7% a year, surpassing most of economies in the West Pacific Region. The pharmaceutical and medical industries are capitalizing on this growth by reaching out to consumers to offer medicines of similar

formulations, discounts, and aggressive advertising campaigns. The retail pharmacies are competing for clients' available out-of-pocket pesos and will sell and dispense (with or without prescriptions) medicines and medical products to make ends meet. The abundance of medicines in the market brings health risks if not checked or legislated by FDA.

In addition, the Philippines is a member of the Association of Southeast Asian Nations and Asia-Pacific Economic Cooperative communities and signed agreements to improve quality of medicines, combat counterfeit, and reduce cross border smuggling of poor quality medicines. Several neighboring countries in the region have taken important measures to improve quality and reduce risks due to ADR. The Philippines will join this group of nations with the important reforms currently ongoing at FDA. By empowering the FDA to strengthen its structures, it gives a clear signal to the industry that no deviation to the norms of quality will be tolerated.

To achieve this objective the FDA has to strengthen the PV system nationally and regionally and strive to empower the health workers of the impending risks of overprescribing and self-medication. The FDA has to reach out to the health workers, provide the direction and the tools to monitor ADR cases and assure them that them that they are not alone in this fight. FDA also need to empower the consumer through focused group discussions, town hall talks and advertisement campaigns and ensure that the message about quality and safety of medicines is required and necessary by law to ensure public health.

The findings of the assessment suggest that the FDA will strongly benefit in achieving all the above by strengthening PV unit in particular the analysis of data and risk management components.

ANNEX A. BACKGROUND

Definition and Scope of Pharmacovigilance

WHO defines pharmacovigilance PV as the science and activities relating to the detection, assessment, understanding, and prevention of adverse effects or any other possible medicine-related problems.[19] At the time of medicine registration and availability in the market, there is an incomplete understanding of the safety of new medicines. Data on the safety of new medicines are mainly derived from pre-market clinical trials to determine whether or not the drug will be approved for use. However, clinical trials are limited by restricted exposure, narrow perspective, and short duration, making it essential to monitor for safety and effectiveness even after approval, particularly when the product is used in large populations.[20] Post-marketing surveillance is crucial to quantify previously recognized ADRs, identify unrecognized adverse drug events (ADEs), and evaluate the effectiveness of medicines in real-world situations to ultimately decrease mortality and morbidity associated with adverse events.[21] ADR is defined by WHO as "one which is noxious and unintended, and which occurs at doses normally used in man for the prophylaxis, diagnosis, or therapy of disease, or for the modification of physiological function," The US FDA defines ADE as "any adverse event associated with the use of drug in humans, whether or not considered drug related, including the following: an adverse event occurring in the course of the use of a drug in professional practice; an adverse event occurring from a drug overdose, whether accidental or intentional, an adverse event occurring from drug abuse; an adverse event occurring from drug withdrawal; and any significant failure of expected pharmacological action."

A medicines safety or PV system is comprised of the systems, structures, and stakeholders necessary to ensure the safety and effectiveness of medicines and protect public health (figure A1). It is the coordinated and interdependent functioning of activities to improve health outcomes and reduce harm related to the use of medicines by the public through the efficient mobilization of various stakeholders and resources at all levels and in all sectors.[22] A country's PV system should incorporate activities and resources at the facility, state, national, and international levels; and foster collaboration among a wide range of partners and organizations that contribute to ensuring medicine safety. The scope of PV has broadened over the recent years to include additional critical issues such as medication errors, product quality, and treatment failure in addition to the traditional focus on ADRs. ADEs are common, but many of them are also preventable. The growing problem of poor quality or counterfeit medicines is yet another reason why PV needs to be proactive. The implementation of a comprehensive PV system requires efforts beyond passive data

[19] WHO. 2004. *WHO Policy Perspectives on Medicines (Pharmacovigilance: Ensuring the Safe Use of Medicines)*. Available at http://whqlibdoc.who.int/hq/2004/WHO_EDM_2004.8.pdf

[20] Nwokike, J. 2009. Technical Assistance for the Establishment of a Pharmacovigilance and Medicine Safety System in Rwanda. Submitted to the U.S. Agency for International Development by the Strengthening Pharmaceutical Systems (SPS) Program. Arlington, VA: Management Sciences for Health.

[21] Eguale, T., et al. 2008. Detection of adverse drug events and other treatment outcomes using an electronic prescribing system. *Drug Safety* 31(11): 1005–16.

[22] Strengthening Pharmaceutical Systems (SPS) Program. 2009. Indicator-Based Pharmacovigilance Assessment Tool: Manual for Conducting Assessments in Developing Countries. Submitted to the U.S. Agency for International Development by the SPS Program. Arlington, VA: Management Sciences for Health. Available from http://pdf.usaid.gov/pdf_docs/PNADS167.pdf

collection on AEs and should include mechanisms for risk identification, risk evaluation, and risk management and communication. Spontaneous ADR reporting and other forms of data collection for early warning on medicine safety are part of the risk identification process through the generation and detection of safety signals. Active surveillance is a key tool in risk evaluation. Risk management and communication include strategies for mitigating known risks, communication of medicine safety information, and promotion of the rational use of medicines. PV activities in many low- and middle-income countries, however, are fragmented and often do not address all components of a comprehensive PV and medicine safety system.[23]

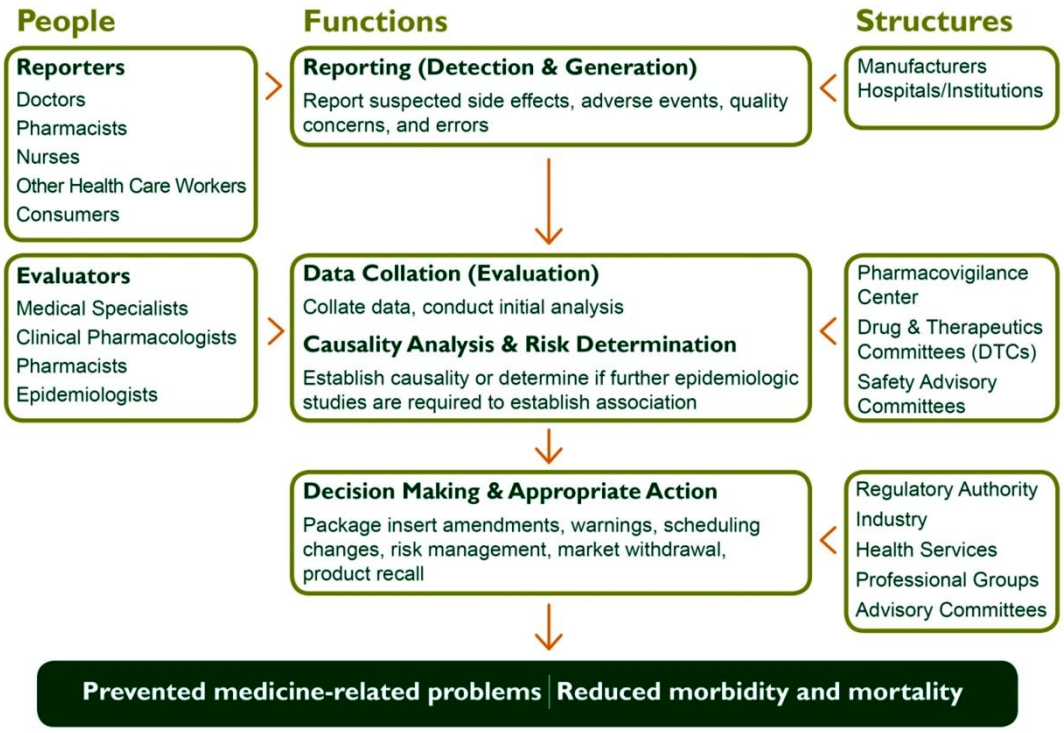


Figure A1. Pharmacovigilance framework[24]

The aims of PV are to[25]—

- Improve patient care and safety in relation to the use of medicines and all medical and paramedical interventions.
- Improve public health and safety in relation to the use of medicines.
- Detect problems related to the use of medicines and communicate the findings in a timely manner.

[23] Olsen, S., S. Pal, A. Stergachis, and M. Couper. 2010. "An Analysis of Pharmacovigilance Activities in 55 Low- and Middle Income Countries." *Drug Safety* 33:689–703.
[24] Strengthening Pharmaceutical Systems (SPS). 2009. *Supporting Pharmacovigilance in Developing Countries: The Systems Perspective*. Submitted to the U.S. Agency for International Development by the SPS Program. Arlington, VA: Management Sciences for Health.
[25] WHO. 2006. *The Safety of Medicines in Public Health Programmes.* Geneva: WHO

- Contribute to the assessment of benefit, harm, effectiveness, and risk of medicines, leading to the prevention of harm and maximization of benefit.

- Encourage the safe, rational, and more effective (including cost-effective) use of medicines.

- Promote understanding, education, and clinical training in PV and its effective communication to the public.

What Is a Pharmacovigilance System?

Figure A2 presents the framework for a comprehensive PV system that identifies the structures, people, and functions that are needed for making national and local decisions that aim to prevent medicine-related problems and reduce associated morbidity and mortality. This approach highlights the need for building capacity to carry out both passive and active methods and the complementariness of these approaches in ensuring a robust system for addressing medicine safety issues.

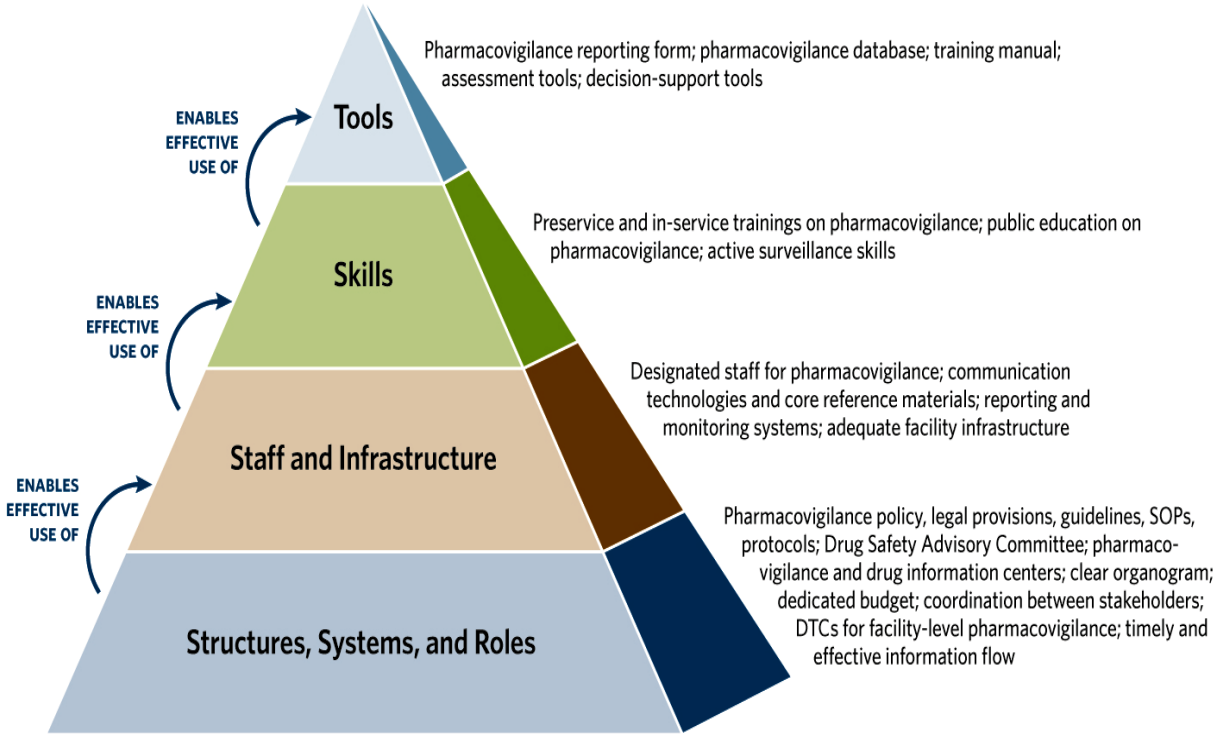


Figure A2. Capacity-building model for pharmacovigilance[26]

In the absence of a robust PV system, adverse drug events occur but the size and magnitude of the problem remains largely or entirely undetected and therefore unknown. Besides the

[26] Source: Adapted from Potter, C., and R. Brough. 2004. "Systemic Capacity Building: A Hierarchy of Needs." Health Policy Planning 19:336–45.

impact of ADEs on morbidity and mortality and the attendant costs to health systems, ADEs also have other associated costs in terms of the loss of confidence in the health system, economic loss to the pharmaceutical industry, non-adherence to treatment, and development of drug resistance.

Consequences of weak PV systems include the occurrence of preventable ADRs and the escalation of costs of health care delivery. Over 70% of ADRs that resulted in hospitalization are estimated to have been potentially avoidable. Inappropriate use of medicines can also occur either on the part of the patient or the health care provider; WHO estimates that worldwide more than 50% of all medicines are prescribed, dispensed, or sold inappropriately, while 50% of patients fail to take their medicines correctly. Other consequences include increases in therapeutic switches, use of more expensive regimens, drug resistance, higher patient drop-out, and non-adherence. Unsafe and poor quality products in the supply chain may result in harm to patients or even death.[27]

Global Standards for Pharmacovigilance

The International Conference on Harmonization (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use develops guidelines to facilitate the harmonization of regulatory requirements to ensure that safe, effective, and high quality medicines are developed and registered in the most resource-efficient manner. In particular, the ICH guidelines E2A through E2F cover guidelines for the design, planning, reporting, and evaluation of pre- and post-authorization safety data and the establishment of PV systems.[28] The topics include clinical safety data management for expedited reporting, individual case safety reports (ICSR), periodic safety update reports, post-approval safety data management, PV planning for industry, and development safety update reports from clinical trials.

These international guidelines are adopted by stringent regulatory authorities (SRAs) such as the EMA and US Food and Drug Administration (FDA). Standardization and harmonization of guidelines offers benefits as they prevent duplication of effort, enhance information sharing, minimize risk to public health, and reduce the time and resources for medicines development. Countries can benefit from the ICH guidelines by modeling their PV regulations and guidelines to the ICH or in the minimum ensuring that their guidelines are equivalent to the ICH ones.

[27] Strengthening Pharmaceutical Systems (SPS) Program. 2011. Safety of Medicines in Sub-Saharan Africa: Assessment of Pharmacovigilance Systems and their Performance. Submitted to the US Agency for International Development by the Strengthening Pharmaceutical Systems (SPS) Program. Arlington, VA: Management Sciences for Health. Available from http://www.msh.org/projects/sps/SPS-Documents/upload/SPS-FDA-PV-Report-March-2012.pdf

[28] The International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use. Efficacy Guidelines. Available at http://www.ich.org/products/guidelines/efficacy/article/efficacy-guidelines.html

US Food and Drug Administration Medicine Safety System

In the United States, the reporting of ADEs is mandated by the Federal Food, Drug, and Cosmetic Act Sub-Chapter H Section 760 and 761. The regulations governing drug safety are covered by Title 21 of the Code of Federal Regulations.[29] Title IX of the Food and Drug Administration Amendments Act (FDAAA) of 2007 provided FDA with enhanced authorities regarding post-marketing safety of medicines including statutory powers to demand post-authorization safety studies.

The FDA's Drug Safety Oversight Board mandated by the FDAAA advises on how to handle and communicate important and emerging drug safety issues. The Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, is responsible for post-marketing PV, pharmacoepidemiology, risk management, and medication error prevention and analysis. FDA implements the MedWatch program,[30] which provides clinically important safety information and a mechanism to report serious problems with human medical products. Through MedWatch, health professionals and consumers can voluntarily report serious AEs (SAEs), product quality problems, medication errors, and treatment failure through online reporting using FDA 3500 reporting form. Importers, distributors, and manufacturers can report through the FDA 3500A mandatory reporting form.

FDA also maintains a database for spontaneous reporting through the Adverse Event Reporting System (AERS)[31] and its structure is in compliance with international safety reporting guidance (ICH E2B).[32] The AERS database was designed to support the FDA's post-marketing safety surveillance program for all approved drug and therapeutic biologic products. Adverse events in AERS are coded using the Medical Dictionary for Regulatory Activities (MedDRA) terminology. The AERS database contained nearly four million records as of December 31, 2010.[33] The FDA, in collaboration with the US Centers for Disease Control and Prevention, also administers the Vaccine Adverse Event Reporting System which is the national vaccine safety surveillance program collecting information about adverse events that occur after vaccines are given. The program's data can be obtained either searching the online database or by sending a freedom of information request to FDA.[34]

In addition to its newly increased authority to require post-marketing surveillance activities, the US FDA supports active surveillance in accordance with its FDAAA Section 905 mandate. The FDA developed the Sentinel Initiative as an electronic proactive system to monitor post-marketing performance of medical products by accessing existing automated health care data sources such as insurance claims databases, electronic health records, and registries.[35]

[29] 27 Sections of 21 CFR addressing safety reporting include 310.305, 314.80, 314.81, 314.90, 314.98, 314.99, 314.540, and 314.630.
[30] FDA Medwatch: The FDA Safety Information and Adverse Event Reporting Program. Available at http://www.fda.gov/Safety/MedWatch/default.htmTable
[31] FDA. Adverse Event Reporting System. Available at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/default.htm
[32] International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use. 2001. Maintenance of the ICH Guideline on Clinical Safety Data Management: Data Elements for Transmission of Individual Case Safety Reports E2B. available at http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E2B/Step4/E2B_R2__Guideline.pdf
[33] FDA Adverse Events Reporting System. Available from http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/ucm070434.htm
[34] Vaccine Adverse Event Reporting Systems. Available from http://vaers.hhs.gov/data/data
[35] FDA's Sentinel Initiative. Available from http://www.fda.gov/Safety/FDAsSentinelInitiative/ucm2007250.htm

European Medicines Agency Medicine Safety System

The EMA recently performed a significant update of its PV legislation after commissioning a detailed review which culminated in the *Assessment of the European Community System of Pharmacovigilance* report published in 2006 by the Fraunhofer Institute for Systems and Innovation Research.[36] Critical success factors were identified including general factors such as sufficient number of staff with sufficient expertise and integration of PV to the larger public health strategy, as well as factors specific to certain phases of PV including having sufficient and quality data. This process of review and reform serves as an example to countries such as the Philippines with established PV systems in developing a process for continual review and improvement of existing systems.

The new legislation, which was instituted on July 2, 2012, is intended to make the European Union (EU) PV system more robust and more transparent to so as to better safeguard patients and public health. The new legislation has introduced wide-spread reform including—

- Establishment of the Pharmacovigilance Risk Assessment Committee (PRAC)
- Clarification of the roles and responsibilities of all actors involved in the monitoring of the safety and efficacy of medicines in Europe
- Strengthened coordination leading to more robust and rapid EU decision-making;
- Engagement of patients and health care professionals in the regulatory process, including direct consumer reporting of suspected adverse drug events
- Improved collection of key information on medicines such as through risk-proportionate, mandatory post-authorization safety and efficacy studies
- More transparent and better communication, including publication of agendas and minutes of the PRAC.[37]

The EMA has subsequently published and put on its website a series of guidelines related to PV contained in the EMA Good Pharmacovigilance Practice (GPP). As of July 2012, the EMA GPP governs PV systems in regulatory authorities in EU member states and pharmaceutical companies. The EU regulatory PV system includes the member states' competent authorities, the European Commission as the competent authority for medicinal products authorized centrally in the EU, and the EMA which coordinates PV systems in the EU.
The EMA's Pharmacovigilance and Risk Management Sector manages EudraVigilance, a central database that contains case reports received from over 40 regulatory agencies in member states and pharmaceutical companies. The MAHs are required to electronically submit ADR reports and periodic safety update reports via NRAs to EMA. Under new regulations, MAHs will be able to submit the reports directly to EMA's electronic database.
The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance, established by the EMA in 2006 to strengthen post-authorization monitoring of medicinal products in Europe,[38] comprises EU research institutions, databases, and registries covering

[36] Fraunhofer Institute for Systems and Innovation Research, *Assessment of the European Community System of Pharmacovigilance*, 2006
[37] European Medicines Agency. New pharmacovigilance legislation comes into operationhttp://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2012/07/news_detail_001553.jsp&mid=WC0b01ac058004d5c1
[38] ENCePP website. Available at http://www.encepp.eu/events/index.html

rare diseases, therapeutic fields, and adverse events of interest. In addition to facilitating multicenter, independent post-authorization studies that focus on risk-benefit, the network launched the E-Register in 2010, which provides a publicly accessible resource for the registration of pharmacoepidemiological and PV studies.[39]

The member states, the EMA, and the European Commission exchange information regarding new safety concerns, particularly those resulting in major changes to the marketing authorization status, revocation, or withdrawal of a product through EU rapid alert and incident management systems. A rapid alert is circulated for those requiring urgent action to protect public health (e.g., when a member state suspends the marketing and use of medicinal products) within one day. The rapid alert system is also used to send notifications concerning medicine quality defect or counterfeits.[40] The EMA has a risk management system complying with the ICH-E2E guideline requiring MAHs to submit an EU risk management plan for all newly authorized medicines that contains safety specification, a PV plan, an evaluation of the need for risk minimization activities, and, if there is a need for additional risk minimization activities, a risk minimization plan.[41,42] To advance the goal towards improved transparency, the EMA recently launched a website for the online publication of suspected side effect reports.[43]

Review of Published Literature on the Philippines' Pharmacovigilance System

A literature search was conducted to identify literature published in peer-reviewed journals related to medicine safety or PV in the Philippines. Search terms included the following: ("adverse drug reaction" OR "adverse event" OR "adverse effect" OR "side effect monitoring" OR "drug safety" OR "drug toxicity" OR "adverse events following immunization" OR "pharmacovigilance" OR "pharmacoepidemiology" OR "medicine safety" OR "active surveillance study" OR "adverse reaction study" or "post marketing surveillance" OR "product surveillance") AND "Philippines"[all]. Only studies published after 1997 were included. Titles and abstracts were reviewed for relevance, and articles not reporting effectiveness, efficacy or safety (including adverse event reporting) of a medicine or pharmacologic product were removed.

Findings and Implications of Literature Review

Using the above search methodology, a total of 29 publications were identified in published peer-reviewed literature that included medicine safety or adverse events associated with pharmacological treatment as an outcome of interest or reported result. Of these, 16 (55%) are clinical studies, 8 (28%) are observational studies, 1 (3%) is a mixed review of

[39] ENCePP Electronic Register of Studies. Available at http://www.encepp.eu/encepp/studySearch.htm
[40] EMA. 2011. Compilation of Community Procedures on Inspections and Exchange of Information. Available at www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2009/10/WC500004706.pdf
[41] Regulation (EU) No 1235/2010 of the European Parliament and of the Council of 15 December 2010. Available at http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2010:348:0001:0016:EN:PDF
[42] The European Commission. 2008. Volume 9A of the Rules Governing Medicinal Products in the European Union: Guidelines on Pharmacovigilance for Medicinal Products for Human Use. Available at http://ec.europa.eu/health/files/eudralex/vol-9/pdf/vol9a_09-2008_en.pdf
[43] European database of suspected adverse drug reaction reports. http://www.adrreports.eu/EN/index.html

observation and clinical studies, and 4 (14%) are commentary analysis on issues related to medicines safety or PV in the Philippines.

Treatment area of the studies varied and some addressed the overall pharmaceutical system in the Philippines. Of the studies reviewed, 10 address vaccine safety; two address multidrug-resistant tuberculosis; four address medicine safety for neglected tropical diseases including dengue, leprosy, and lymphatic filariasis; and eight address medicines safety for other conditions. Four studies address medicines safety and PV in the context of the general Philippines health system.

Literature from clinical trials and studies in the Philippines on medicines safety or PV exists but the literature but not robust. Few active or passive surveillance studies with medicine safety or PV outcomes were identified in published peer-reviewed journals. Of these, two post-marketing surveillance studies and two active surveillance components were noted. However, several studies were identified with medicines or vaccine safety or effectiveness endpoints either in observational or clinical trials or studies.

The Philippines disease epidemiology is transitioning towards a double burden of both communicable and non-communicable diseases. The publications found during a literature search focused on vaccine safety and efficacy and infectious disease such as multidrug-resistant tuberculosis and various neglected tropical diseases. Several studies also addressed interventions with safety outcomes for chronic conditions including kidney disease, dystonia, sterilization, erectile dysfunction, and smoking cessation.

An opportunity exists to build on available literature and research capacities in the Philippines, to promote additional active and passive surveillance studies with medicines safety and PV outcomes. In addition, observational studies are likely to examine elements of the PV system, for example at national, regional, and community-based service delivery points including health facilities and pharmacies. Opportunities for collaboration on such studies with industry and with civil society organizations including academic institutions, consumer groups, and professional associations should be explored.

Review of Clinical Trials Database

A search was conducted of the clinical trials database, ClinicalTrials.gov, which is supported by the US National Institutes of Health through its National Library of Medicine. The database contains a registry of clinical trials conducted in the United States and abroad that are funded either by private institutions or through the government. Three-hundred and sixty one ongoing and completed clinical trials (phases III and IV) with safety outcomes were identified in the Philippines. This includes three trials related to malaria, one trial related to tuberculosis, and 39 trials related to immunization safety.[44]

[44] Clinicaltrials.gov

Indicator-Based Pharmacovigilance Assessment Tool

In 2009, the USAID-funded Strengthening Pharmaceutical Systems (SPS) Program, implemented by Management Sciences for Health (MSH), developed the indicator-based pharmacovigilance assessment tool (IPAT) for the systematic and longitudinal monitoring of country capacity and performance in ensuring the safety and effectiveness of health products registered in the country.[45] IPAT is a comprehensive performance metric for monitoring and evaluating PV systems in developing countries. The tool supports evidence-based options analysis and development of relevant and feasible recommendations reflecting each country's local realities, existing regulatory capacity and priorities, system gaps, and resource availability. Additionally, the tool's standardized and indicator-based approach allows longitudinal measurement of progress after recommended interventions are implemented.

The assessment tool used to conduct the PV systems assessment in five Asian countries was adapted from the IPAT and from performance indicators that covered a range of quality and safety systems for essential medicines. The assessment tool includes 49 indicators across five key PV and medicine safety system components:

- Governance, policy, law, and regulation
- Systems, structures, and stakeholder coordination
- Signal generation and data management
- Risk assessment and evaluation
- Risk management and communication.

Local Adaptation of the IPAT

Key stakeholders in the Philippines reviewed the IPAT before its use for the Philippines PV assessment. The reviewers made locally-relevant adaptations, while ensuring that data results would still be comparable across countries. Such adaptations include:

- Changed the word "consumer" to "patient/consumer." Differentiated "consumer" as impersonal buyer of pharmaceuticals from "patient" who is the person who takes and experiences the effects of the medicine.

- Determined that respondents should be member(s) of the drug therapeutic committees or PV committee or be the safety officer of the organization they represent.

- Determined that representatives from academia include both training institutions and purely academic institutions.

- Determined that both pharmacy schools and public health schools be included.

In addition, the IPAT was independently reviewed by the local consultant and an expert on PV. The consultant noted that some indicator questions were not applicable to the Philippine

[45] Strengthening Pharmaceutical Systems (SPS) Program. 2009. *Indicator-Based Pharmacovigilance Assessment Tool: Manual for Conducting Assessments in Developing Countries*. Submitted to the U.S. Agency for International Development by the SPS Program. Arlington, VA: Management Sciences for Health.

setting. The consultant also observed that the assessment tool uses knowledge-based type of questions and that some respondents may not be familiar with some of the indicator questions. These were addressed by the local consultant by slight customization of some questions, such as terms that are used locally .

Assessment Methodology

The assessment of the PVand medicine safety system in the Philippines included the use of structured interviews using the study assessment tool and supporting document review. Relevant literature was searched for on PubMed, EbscoHost, scientific journals, the FDA's website, and the US National Institutes of Health clinical trial registration website. The data gathering of the PV assessment in the Philippines was conducted from May 16, 2012, to July 31, 2012.

- Documents reviewed included the National Drug Policy (1987), Food and Drug Administration—National Policy Program on Pharmacovigilance law: AO 2011-0009, RA 9711 – Strengthening the role of FDA-Philippines, and AO 2012 0008 – Adaption and Implementation of the Pharmaceutical Inspection Cooperation Scheme GMP for medicinal plants.

- The consultant and data collectors conducted structured interviews using the data collection tool. Prior to that, the data collectors were trained on the use of the structured interview tool to ensure the consistency and accuracy of data among several data collection teams.

- A total of 128 questions were used for data collection to form 49 indicators. Seventeen forms were used as a data collection tool, with questions tailored to the individual respondent type. This included questionnaires for gathering data from the DOH and FDA (one form for DOH and 6 forms for various units within the FDA), the national PHPs (one form each for the HIV and AIDS, malaria, tuberculosis, and immunization programs), health facilities, pharmacies, pharmaceutical companies, medical device companies, clinical research organizations, academia, consumer groups, and medical professional associations. Open-ended questions were also included in selected questionnaires.

- Several forums for review of assessment findings and recommendations were convened to solicit additional feedback from respondents, key opinion leaders, and other stakeholder to capture and address other locally relevant factors related to pharmacovigilance systems and capacity in the Philippines. Two such forums with key leaders were conducted on July 9, July 24, and August 2, 2012, in Manila.

Selection of Study Sites

The study selected sites represent the national, regional and sub-regional levels.

At the national level, the following institutions and agencies were included: FDA and its national pharmacovigilance unit, the NCPAM, pharmaceutical companies, medical device companies, medical professional associations, consumer groups, universities, contract

research organization, and PHPs. Public health programs included the HIV and AIDS, TB, malaria, and immunization programs.

Regions and sub regions within the Philippines were selected to ensure balanced representation of each of the three island groups—Luzon, Visayas, and Mindanao. This included the regional health offices' -Centers for Health Development. Representatives of pharmacies and health facilities in each of the three island groups, including primary, secondary, tertiary, referral, private, government, and specialty hospitals that provide direct health services to patients, were included in the sampling model. At the health facility level, data was collected from the Drug and Therapeutic Committees, pharmacovigilance units, and patient safety or medication safety unit.

The data from the pharmaceutical industry included multinational innovators, multinational generic, and local manufacturers, medical device companies, and clinical research organizations.

In accordance with the study design, convenience sampling was used to identify study sites. For the health facilities, those with history of ADR reporting to FDA were considered as respondents. Efforts were made to follow as much as possible and logistically feasible the above mentioned guidelines to identify sites and respondents.

Table 14. List of Sites Assessed

Data Collection Sites	Location	Number of Respondents
DOH and FDA-Philippines		
Food and Drugs Administration Philippines	Luzon	7
NCPAM	Luzon	1
Center for Health Development (regional)	Luzon/Mindanao	2
Public Health Programs		
National TB Program	Luzon	1
Expanded Program on Immunization	Luzon	1
National HIV/AIDS control Program	Luzon	2
National Malaria control Program	Luzon	1
Health Facilities		
Tertiary Health Facilities		
Quirino Memorial Hospital	Luzon	1
Southern Philippines Medical Center	Mindanao	1
Philippine General Hospital	Luzon	2
District/Sub district Hospitals		
Ospital ng Sampaloc	Luzon	2
Sta. Ana Hospital	Luzon	1
Maribojoc District Hospital	Luzon	1
Regional Hospitals		
Bicol medical Center	Luzon	2
Bicol Regional and Training Hospital	Luzon	2
Corazon Montelibano Memorial Hospital	Visayas	1
Cebu City Medical Center	Visayas	1
Mariano Marcos Memorial Hospital	Luzon	3
Davao Regional Medical Center	Mindanao	1
Vicente Sotto memorial Hospital	Visayas	1
Private Hospitals		
Makati Medical Center	Luzon	1
St. Luke's Hospital	Luzon	1

Data Collection Sites	Location	Number of Respondents
Sto. Tomas University Hospital	Luzon	1
Aquinas Hospital	Luzon	1
St. Paul's Hospital	Visayas	1
Chong Hua Hospital	Visayas	1
Velez Hospital	Visayas	1
Iloilo Mission Hospital	Visayas	1
Cagayan De Oro Polymedic Hospital	Mindanao	1
Government/Specialty Hospitals		
Philippine Children's Hospital	Luzon	1
National Center For Mental Health	Luzon	1
Pharmacies	Luzon, Visayas, Mindanao	
Mercury Drug Corporation		15
Watson		10
Rose Pharmacy		4
Generika		1
The Generics Drug Store		2
National level institutions		
Academia	Luzon/Visayas/Mindanao	7
Pharmaceutical companies	Luzon	9
Medical device companies	Luzon	3
CROs	Luzon	2
Consumer groups	Luzon	3
Professional Organizations Phil Society of Anesthesiologist Marikina Valley Medical Society Phil Pediatric Society Misamis Oriental Medical Society Phil Society of Digestive Endoscopy Phil Society of Otolaryngology	Luzon, Visayas, Mindanao	9

Analysis

The data of this assessment were collated and entered onto a database along with responses and findings collected from key stakeholders. In addition a literature review was also done. A rating scale was applied to classify the performance of each system. Based on the scoring of the five components of the PV system in the data collection tool, specific gaps were identified. A bar-style chart and tables was used to compare indicators within the same component. A radar-style chart was used to illustrate the situation of various pharmacovigilance functions or attributes within each component.

Limitations

The assessment did not collect data from a fully representative number of stakeholders beyond the national level, particularly in Mindanao where, for security reasons, data collectors visited only two key cities, Cagayan de Oro city and Davao city. Respondent data was used to inform and provide context for data collected from the DOH and FDA regarding the national PV system and to suggest potential gaps and opportunities. Hence, the situational analysis of the medicine safety system in health facilities, pharmacies, industry, and civil society may not be generalizable or comparable across regions.

Other limitations that may affect the findings of this assessment include the inability to fully verify responses to assessment questions, potential for conflicting feedback from respondents, reliance on the data collectors' technical competence and judgment in asking and recording assessment questions and responses, and accuracy in transcribing responses to quantitative forms. To address this limitation, review of supporting documents to verify responses and review of transcribed data with original data collection forms were conducted.

ANNEX B. PHILIPPINES PROFILE

Table B1. Philippines Pharmaceutical Profile

Medicines Policy	
Existence of National Medicines Policy	Foods, Drugs and Devices, and Cosmetics Act, 1987[46]
Legal Provision for Medicines Legislation	Universally Accessible Cheaper and Quality Medicines Act, 2008[37]; The Generics Act, 1988[47]
Pharmaceutical Market	
Population (million, 2012)[a]	96.71 million, 2012
Gross domestic product per capita (USD, 2012)[a]	2,587.88
Number of medicines registered (2012)[b]	32,069
Total expenditure on healthcare per capita (USD, 2010)[d]	77.33
Total pharmaceutical expenditure per capita (USD, 2006)[c]	21.3
Public expenditure on pharmaceuticals per capita (USD, 2006)[c]	2.1
Total pharmaceutical expenditure as percentage of total expenditure on healthcare per capita	27%
Health workforce per 10,000 population (2011)[e]	10.2 physicians; 53.1 nursing and midwifery personnel; 5.4 licensed pharmacists 11.0 pharmaceutical technicians / assistants
Patent provisions	Universally Accessible Cheaper and Quality Medicines Act, 2008[48] Intellectual Property Code of the Philippines, 1997[49]
Pharmaceutical Production Status	
Pharmaceutical manufacturing plants[f]	301 (2012)
Number of pharmaceutical manufacturing plants[f]	301 (2012)
Number of pharmaceutical manufacturing plants:	
producing pharmaceutical active ingredients (2011)[f]	0
producing finished pharmaceutical dosage forms[f]	93 (2012)
packaging finished pharmaceutical dosage forms[f]	22 (2012)
Number of research-based pharmaceutical industries[f]	24 (2012)
Number of generic pharmaceutical products (including branded generics) manufacturers[f]	70 (2012)
Number of nationally owned pharmaceutical industries (government and private)(2012)[f]	4[g]

[a] World Bank. http://data.worldbank.org/country/philippines
[b] Directorate General of Drug Administration
[c] WHO World Medicines Situation 2011 Annex
[d] WHO National Health Account Database, 2010

[46] Executive Order No. 175
[47] Republic Act No. 6675
[48] Executive Order No. 17
[49] Republic Act No. 667

[e] WHO World Health Statistics 2012
[f] FDA database as of June 2012
[g] Includes only data from government-owned – Philippines Institute of Traditional and Alternative Health Care (PITAHC)

Table B2. Pharmacovigilance Profile

Policy, laws, and regulations	Food, Drugs, Devices and Cosmetics Act , 1987 National Policy and Program on Pharmacovigilance, 2011 Philippine Medicines Policy–Draft Generics Act of 1988 Universally Cheaper and Quality Drug Act of 2008
Name of regulatory authority/website	Food and Drug Administration Philippines, www.fda.gov.ph
Mandate of regulatory authority	Registration, licensing and import control, inspection, quality control, PV, control of promotion, control of clinical trials
How products get into the market	Preclinical tests, clinical trial approval, drug approval, post marketing surveillance
Joined the WHO program	1995
E2B compliance	YES clinical AO 2012 0007
Medical terminology used	WHO–antiretroviral therapy
Type of reports in PV database	With FDA: Spontaneous reports, product quality reports, periodic safety update reports (PSURs) With Immunization program: Adverse-event following vaccination reports
Total # of ICSRs in the database	9,865 total ICSRs submitted to VigiLyze as of December 2012.
Newsletter or bulletin published	No, medicine safety alerts published on the website

ANNEX C. PUBLISHED PHARMACOVIGILANCE AND MEDICINE SAFETY STUDIES IN THE PHILIPPINES

Title	Authors	Journal	Study Design	Condition area/ Intervention type	Identifiers
Everolimus with reduced-dose cyclosporine versus full-dose cyclosporine and mycophenolate in de novo renal transplant patients: a 2-year single-center experience.	Santos SM, Carlos CM, Cabanayan-Casasola CB, Danguilan RA.	Transplant Proc. 2012 Jan; 44(1):154-60	Retrospective cohort study	Other	PMID: 22310603
Observational study of safety and efficacy of varenicline for smoking cessation among Filipino smokers.	Park PW, Casiano EM, Escoto L, Claveria AM.	Curr Med Res Opin. 2011 Oct; 27(10): 1869-75	Observational study	Other	PMID: 21838412
Frequency and type of microbiological monitoring of multidrug-resistant tuberculosis treatment.	Kurbatova EV, Gammino VM, Bayona J, Becerra M, Danilovitz M, Falzon D, Gelmanova I, Keshavjee S, Leimane V, Mitnick CD, Quelapio MI, Riekstina V, Taylor A, Viiklepp P, Zignol M, Cegielski JP.	Int J Tuberc Lung Dis. 2011 Nov; 15(11)	Retrospective analysis	TB	PMID: 22008772
Longitudinal ocular survey of 202 Filipino patients with multi-bacillary (MB) leprosy treated with 2 year WHO-multiple drug therapy.	Ravanes JM, Cellona RV, Balagon M, Abalos RM, Walsh GP, Walsh DS.	Southeast Asian J Trop Med Public Health. 2011 Mar; 42(2):323-30	Longitudinal survey	Neglected Tropical Disease—(NTD) Leprosy	PMID: 21710853
Immunogenicity of HBV vaccine during stated shelf-life.	Gloriani NG, Srinivasa K, Bock HL, Hoet B.	Southeast Asian J Trop Med Public Health. 2010 Jul; 41(4):876-82.	Single-blind, randomized study	Vaccine	PMID: 21073062
A new DTPw-HBV/Hib vaccine: immune memory after primary vaccination and booster dosing in the second year of life.	Gatchalian S, Reyes M, Bermal N, Chandrasekaran V, Han HH, Bock HL, Lefevre I.	Hum Vaccin. 2008 Jan-Feb; 4(1):60-6. Epub 2007 Sep 23.	open, randomized immune memory and booster study	Vaccine	PMID: 18376148
Factors associated with the acceptance of mass drug administration for the elimination of lymphatic filariasis in Agusan del Sur, Philippines.	Amarillo ML; Belizario VY; Sadiang-Abay JT; Sison SA; Dayag AM	Parasit Vectors. 2008 May 27;1(1):14.	stratified cluster survey	NTD—Lymphatic filariasis	PMID: 18505577
Lack of efficacy of high-dose intravenous immunoglobulin treatment of severe thrombocytopenia in patients with secondary	Dimaano EM, Saito M, Honda S, Miranda EA, Alonzo MT, Valerio MD, Mapua CA, Inoue	Am J Trop Med Hyg. 2007 Dec; 77(6):1135-8.	RCT	NTD - Dengue	PMID: 18165536

Title	Authors	Journal	Study Design	Condition area/ Intervention type	Identifiers
dengue virus infection.	S, Kumaori A, Matias R, Natividad FF, Oishi K.				
Adverse events in the treatment of multidrug-resistant tuberculosis: results from the DOTS-Plus initiative.	Nathanson E; Gupta R; Huamani P; Leimane V; Pasechnikov AD; Tupasi TE; Vink K; Jaramillo E; Espinal MA	Int J Tuberc Lung Dis; 8(11): 1382-4, 2004 Nov.	Active surveillance	TB	PMID: 15581210
Immunogenicity and safety of a varicella vaccine, Okavax, and a trivalent measles, mumps and rubella vaccine, MMR-II, administered concomitantly in healthy Filipino children aged 12-24 months	Gatchalian S, Leboulleux D, Desauziers E, Bermal N, Borja-Tabora C	Southeast Asian J Trop Med Public Health. 2003 Sep; 34(3):589-97.	RCT	Vaccine	PMID: 15115135
Quinacrine sterilization (QS) experience in the Philippines: a preliminary report.	Alfonso LA, Albano HA.	Int J Gynaecol Obstet. 2003 Oct; 83 Suppl 2:S121-3.	Clinical trial	Other	PMID: 14763198
A post-marketing surveillance study of a combined diphtheria, tetanus, whole-cell pertussis, and hepatitis B vaccine in the Philippines.	Ducusin J, Dayrit E, Simbulan A, Tuazon A.	Southeast Asian J Trop Med Public Health. 2000 Sep; 31(3):487-92.	Post-marketing surveillance	Vaccine	PMID: 11289007
Safety and efficacy of generic cyclosporine arpimune in Filipino low-risk primary kidney transplant recipients.	Pamugas GE, Danguilan RA, Lamban AB, Mangati VB, Ona ET.	Transplant Proc. 2012 Jan; 44(1):101-8	Prospective cohort study	Other	PMID: 22310590
Randomized controlled study of fractional doses of inactivated poliovirus vaccine administered intradermally with a needle in the Philippines.	Cadorna-Carlos J, Vidor E, Bonnet MC.	Int J Infect Dis. 2012 Feb; 16(2):e110-6	Randomized controlled study	Vaccine	PMID: 22153001
Challenges of drug risk communications in the Philippines	Hartigan-Go K.	Drug Saf. 2012 Nov 1; 35(11):995-1004.	Other	Pharmaceutical Systems	PMID: 23061777
The broadening application of chemodenervation in X-linked dystonia-parkinsonism (Part II): an open-label experience with botulinum toxin-A (Dysport®) injections for oromandibular, lingual, and truncal-axial dystonias.	Rosales RL, Ng AR, Santos MM, Fernandez HH.	Int J Neurosci. 2011; 121 Suppl 1:44-56	Open-label study	Other	PMID: 21348790
Safety and immunogenicity of a tetravalent meningococcal serogroups A, C, W-135 and Y conjugate vaccine in adolescents and adults.	Bermal N, Huang LM, Dubey AP, Jain H, Bavdekar A, Lin TY, Bianco V, Baine Y, Miller JM.	Hum Vaccin. 2011 Feb;7(2):239-47. Epub 2011 Feb 1.	Phase 3 open, randomized multi-center study	Vaccine	PMID: 21343698
Rabies post-exposure prophylaxis with purified	Quiambao BP, Dy-Tioco	Vaccine. 2009 Nov	Vaccine	Vaccine	PMID: 19925947

Title	Authors	Journal	Study Design	Condition area/ Intervention type	Identifiers
equine rabies immunoglobulin: one-year follow-up of patients with laboratory-confirmed category III rabies exposure in the Philippines.	HZ, Dizon RM, Crisostomo ME, Teuwen DE.	27; 27(51):7162-6	safety surveillance		
Efficacy of an 11-valent pneumococcal conjugate vaccine against radiologically confirmed pneumonia among children less than 2 years of age in the Philippines: a randomized, double-blind, placebo-controlled trial.	Lucero MG, Nohynek H, Williams G, Tallo V, Simões EA, Lupisan S, Sanvictores D, Forsyth S, Puumalainen T, Ugpo J, Lechago M, de Campo M, Abucejo-Ladesma E, Sombrero L, Nissinen A, Soininen A, Ruutu P, Riley I, Mäkelä HP.	Pediatr Infect Dis J. 2009 Jun; 28(6):455-62	Randomized, double-blind, placebo-controlled trial	Vaccine	PMID: 19483514
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Title	Authors	Journal	Study Design	Condition area/ Intervention type	Identifiers
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Double-blind placebo-controlled study of concurrent administration of albendazole and praziquantel in schoolchildren with schistosomiasis and geohelminths.	Olds GR, King C, Hewlett J, Olveda R, Wu G, Ouma J, Peters P, McGarvey S, Odhiambo O, Koech D, Liu CY, Aligui G, et. al	J Infect Dis. 1999 Apr; 179(4):996-1003.	Double-blind placebo-controlled study	NTD - Schistosomiasis and geohelminths	PMID: 10068597
A single blind comparative study between Itraconazole and Fluconazole in the one-day treatment of vulvo-vaginal candidiasis.	Singson-alday AP, Ortega AR.	Philipp J Obstet Gynecol. 1998 Oct-Dec;22(4):119-21	Single-blind comparative study	Other	PMID: 12179666
Resistance in gonococci isolated in the WHO Western Pacific Region to various antimicrobials used in the treatment of gonorrhoea, 1997. WHO Western Pacific Gonococcal Antimicrobial Surveillance Programme-WHO WPR GASP.	[No authors listed]	Commun Dis Intell. 1998 Dec 24; 22(13):288-91.	Other	Other	PMID: 9893340