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Regulatory Reliance and Post-Marketing Surveillance Systems for Safe and Accelerated Introduction of New Medical Products in Low- and Middle-Income Countries

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Regulatory Reliance and Post-Marketing Surveillance Systems for Safe and Accelerated Introduction of New Medical Products in Low- and Middle-Income Countries

by

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AUTHOR'S DECLARATION

At no time during the registration for the degree of Doctor of Philosophy has the author been registered for any other University award without prior agreement of the Doctoral College Quality Sub-Committee.

Work submitted for this research degree at University of Plymouth has not formed part of any other degree either at the University of Plymouth or at another establishment.

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ABSTRACT

Though delayed access to medicines is still common, disease outbreaks in the past three decades has driven speedier introduction of innovative medical products. Yet, successful models for safe and accelerated introduction of new medical products in low- and middle-income countries are scarcely documented. Recent viral diseases outbreaks like Ebola, COVID-19, and Monkeypox has further highlighted the need for regulatory preparedness for health emergencies. Well-resourced countries have developed expedited regulatory pathways for such situations, while LMICs are not as prepared. They lack models for adopting best practices for implementing regulatory reliance and integrated post marketing surveillance (PMS). Experiences gained from our work strengthening regulatory systems for HIV/AIDS, Tb, and malaria may inform the development of best practices and models for accelerated introduction of future medical products.

Chapter 1 of this thesis provides summary of research outputs which documents my published work on introduction of new medical products in global health. Chapter 2 is an integrative literature review of pharmaceutical access, regulatory reliance, and PMS, concluding that regulatory reliance and PMS are critical for safe and accelerated introduction of new medical products in LMICs. However, gaps and challenges exist, and they lead to delayed access which

costs lives. To address those gaps, in Chapter 3 we developed Model Integrated Quality and Safety Review (IQSR) checklist, reliance-based review, and tools for integrated surveillance.

Evolution in medicines regulation is typically predicated by access campaigns or mishaps. Stronger regulatory systems with well-established approaches for implementing reliance and post market surveillance have the capability to ensure safe and accelerated introduction of new medical products. To ensure that best practices are implemented, we recommended practical tools for the operationalization of reliance practices and post marketing surveillance systems. The tools identified will help regulators, industry, global health experts in advancing timely access to address unmet medical needs.

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ACRONYMS

AEFI	Adverse events reports following immunization
APQR	Annual product quality reports
ARV	Antiretroviral drugs
CMC	Chemistry, manufacturing and controls
CRP	WHO Collaborative Registration Procedure
CTD	Common Technical Document
FAERS	Adverse Event Reporting System, FDA
FDA	Food and drug administration
FRP	Facilitated regulatory pathways
GBT	Global benchmarking tool
GMP	Good manufacturing practices
HIV/AIDS	Human immunodeficiency virus/acquired immunodeficiency syndrome
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IPAT	Indicator-based Pharmacovigilance Assessment Tool
IQSR	Integrated quality and safety review
ISS	Integrated Summaries of Safety
LMICs	Low- and middle-income countries
PASS	Post authorization safety studies
PIC/S	Pharmaceutical Inspection Co-operation Scheme
PMC	Post marketing commitments
PMR	Post marketing requirements
PSUR	Periodic safety update reports
PQ	Prequalification
PV	Pharmacovigilance
QOS	Quality overall summary
SRA	Stringent regulatory authority
SCE	Summaries on efficacy
SCS	Summary of clinical safety
VAERS	Vaccine Adverse Event Reporting System
WHO	World Health Organization

CHAPTER 1: SUMMARY OF RESEARCH OUTPUTS

Selection of papers for inclusion in this summary of research outputs was influenced by the interest to document aspects of my work that support safe and accelerated introduction of new medical products in low- and middle-income countries.

1.1. Paper 1 – Comparative Analysis of Pharmacovigilance Systems in Five Asian Countries

1.1.1. Background and objectives

The development of performance metrics for measuring pharmacovigilance (PV) systems in developing countries preceded the publication of this paper on the Comparative Analysis of Pharmacovigilance Systems in Five Asian Countries. First, new medicines were increasingly being introduced in countries without pharmacovigilance systems. The spread of the HIV/AIDS epidemic in the late 90s and early 2000s, not only brought attention to the challenges of access to medicines but also highlighted the weak capacity to regulate medical products in low- and middle-income countries (LMICs). Through global health initiatives, most of those countries eventually started seeing the influx of new antiretroviral drugs raising concerns in some quarters about the capacity to monitor the adverse events that may be associated with those products. At the time, there were no established guidelines and tools for assessing pharmacovigilance capacity. There was no consensus about the attributes of a functional pharmacovigilance system and no universally adopted performance metrics for assessing pharmacovigilance systems. It was critical to measure the performance of the systems given the importance of pharmacovigilance to

prevent harm associated with the use of medical products. Pharmacovigilance is most relevant for the introduction of new medicines and vaccines. As disease outbreaks like HIV/AIDS, SARS, H1N1, Ebola, COVID-19, and Monkeypox become more frequent, the time to access for new products in developing countries has shrunken further highlighting the importance of pharmacovigilance or post marketing surveillance. Pharmacovigilance is crucial to quantify previously recognised adverse drug reactions, to identify unrecognised adverse drug events, to evaluate the effectiveness of medicines in real-world situations, and to decrease mortality and morbidity associated with adverse events.[1]

To address the lack of performance measures for pharmacovigilance systems, we developed the Indicator-based Pharmacovigilance Assessment Tool (IPAT). We described IPAT as a manual for conducting assessments in developing countries that is "suitable for evaluating the current state of collection, analysis, and interpretation of data on the safety aspects of medicine regulation as well as to ensure safe use of medicines at public health programmes, health facilities, and the health care worker and consumer levels. The analysis of data derived from IPAT could be used to develop recommendations and identify priority interventions to improve critical aspects of the pharmacovigilance and medicine safety system." This paper on the Comparative Analysis of Pharmacovigilance Systems in Five Asian Countries used the IPAT to conduct a comprehensive review of the pharmacovigilance and safety surveillance systems in Bangladesh, Cambodia, Nepal, Philippines, and Thailand. In the context of the rapid introduction of new medicines in LMIC, this paper was timely and relevant and had the prospects to add new knowledge to the field.

1.1.2. Study method

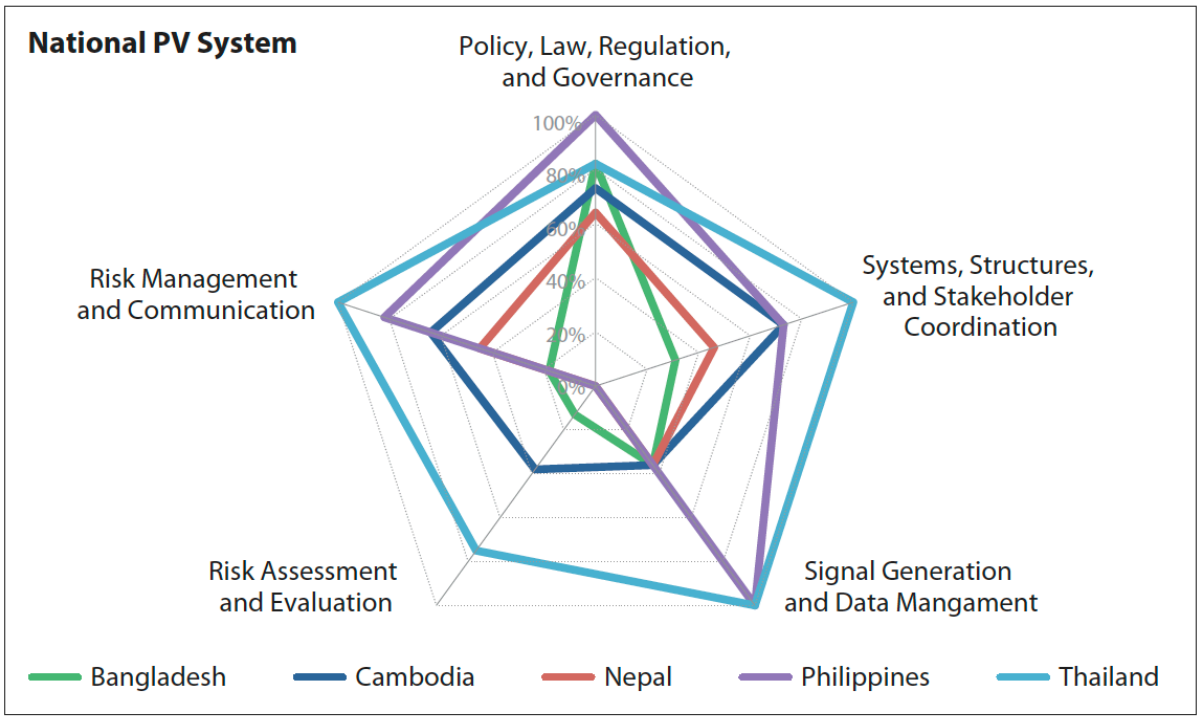
The study reviewed regulatory and PV systems literature in the Asia region, conducted expert-led comprehensive assessment of the PV system using the IPAT, and conducted comparative analysis of the five components of the PV system including Governance and Policy, Law, and Regulation; Systems, Structure, and Stakeholder Coordination; Signal Generation and Data Management; Risk Assessment and Evaluation; and Risk Management and Communication. Those five components were determined as the components of a comprehensive PV systems. Previous assessments had not recognised those 5 components. Researchers focused narrowly on measuring the effectiveness of the passive reporting systems. Often, they conceded that the inability of the passive reporting system to function effectively is attributed to the absence of regulations, systems, and infrastructure most of which are consistent with the IPAT's 5 components of comprehensive PV system. The use of desk review followed by expert-led key informants' interview was an adequate methodology for this study. However, it does not completely remove the response bias typically seen in this sort of studies.

1.1.3. Results

The study found common limitations in capacity for risk assessment and evaluation and risk management practices. They were not explicitly required in the countries' legislations. Risk assessment and evaluation was identified as the weakest component of the PV system across all the countries. Those capabilities are essential for decision making on the approval of new medical products as well as for post approval regulatory action following adverse events. The primary objective of pharmaceutical regulation is to enable timely access and safeguard the

public from unsafe medical products. Capacity for risk assessment and evaluation together with adequate regulations on risk management plans for new products are fundamental for regulatory agencies to meet those primary objectives. In terms of the systems and structures that support PV and post marketing surveillance activities, it was only Thailand, as of the time of the study, that had a WHO pre-qualified quality control laboratory. All countries had standardised national adverse events (AE) form. Thailand AE form could be used for all health products to collect data on suspected ADRs, product quality issues, medication error, and treatment failure. That indicated that Thailand was developing an integrated and comprehensive post marketing surveillance system. The study found that the regional post-marketing alert (PMA) system for information sharing on defective or unsafe medicinal products was underutilised. It provided an untapped opportunity for collaboration to safeguard the supply chain in the member countries. Adverse events reporting in the public health programs were low and uncoordinated with the national PV system. Which is a significant gap given that most new products including vaccines that are introduced in LMICs are managed by the public health programmes. As at the time of the study only Bangladesh reported that the national immunization programme collected 1,100 adverse events reports following immunization (AEFI) in 2011 against a patient population of 3.7 million children vaccinated. To assess pharmacovigilance systems in the pharmaceutical industry, the study reviewed five clinical research organizations (CROs), seven medical device companies, and 38 pharmaceutical companies. The study found that PV performance within the pharmaceutical industry was below expectation. The industry operated within a weak regulatory environment and did only the minimum that was required by the existing law. For instance, more than one third of companies did not submit adverse events reports in E2B formats. Across board, the industry was in rudimental stages in the adoption of international standards for

pharmacovigilance. Risk assessment and evaluation was not required in country laws and was not being implemented. As shown in Figure 1, it was the least performing pharmacovigilance function in the national pharmacovigilance systems studied. Risk assessment and evaluation refers to the capacity for active surveillance and comparative observational studies. The common weakness seen across Asia in risk assessment and evaluation as at the time of this study, means that the safeguards necessary for the introduction of new medical products were weak overall in both the public health agencies as well as within the pharmaceutical industry operating in the 5 Asian countries that were studied.



Source – Comparative Analysis of Pharmacovigilance Systems in Five Asian Countries. October 2014
Figure 1.1: National PV systems capacity in five Asian countries

The above findings from the paper - Comparative Analysis of Pharmacovigilance Systems in Five Asian Countries – are important because the introduction of new medical products require strong pharmacovigilance systems. In the countries studied, the PV systems were fragmented,

weak, and unable to protect the public adequately. One of the major recommendations from the study was to develop organizational structure that will lead to an integrated safety and quality surveillance systems. A comprehensive and sustainable quality assurance system is one way to achieve that. A quality assurance system is comprised of the structures, functions, and processes, including both managerial and technical activities that monitor the quality of pharmaceuticals throughout all stages of the product cycle, from production to use. PV is part of such a system, but alone is not sufficient. Quality assurance includes inspections for compliance with good manufacturing practices (GMP), assessment of documentation on product quality submitted by manufacturers for registration as well as procurement, sampling, and testing of pharmaceutical products from the market and other entry points and systematic evaluation of reported product quality problems through the PV system. We advised countries to integrate adverse events reporting for all health products and consolidate post-marketing surveillance department to bring together PV, product quality surveillance, routine inspections, and control of advert and promotion into a single unit. Such infrastructure will help ensure strong safety and quality surveillance systems that ensures timely access and protects the supply chain from substandard and falsified medical products.

1.1.4. Limitations

The study limitation includes the methodology for the classification of countries into four performance groups. It was based on higher weighting of the core indicators and a calculated total of >60% for each component for that component to be met. The criteria for the >60% cut off seem to have been set arbitrarily. Based on the classification systems, the Group 4 countries have PV systems that can detect, evaluate, and prevent medicine safety issues. They have basic

structures for both passive and active surveillance and capacity to evaluate risks. In Group 4 countries, PV activities inform regulatory actions that results in improved treatment outcomes. The study found that Thailand is classified as Group 4. It was not clear how to verify that Thailand is truly able to achieve such outcomes. The study did not measure the timeliness of approval of new medical products in Thailand or the speed at which they removed products with notable adverse events from the market. Granted Thailand was the only country studied that has a programme for the investigation of new medicines. The Safety Monitoring Programme (SMP) "is intended to confirm the safety of new medicines in Thai patients by generating earlier safety signals and gathering more safety information before granting unconditional registration approval. It monitors all new medicines, including products with new chemical entities, new indications, new combinations, and new delivery systems. Under SMP, the Thai FDA grants conditional approval for registration of new medicines for a period of two years. Products with conditional status must have a blue triangular emblem displayed on the product packaging and can only be distributed through hospitals or healthcare facilities under the close supervision of physicians. During the two-year safety monitoring period, reporting of adverse drug reactions is mandatory for the pharmaceutical companies seeking full marketing authorization." Another limitation is that the study was not able to verify the validity of the data collected and the extent to which they truly predict the robustness and sustainability of countries PV system.

1.1.5. Influence and related studies

The use of the IPAT and its 5 components of comprehensive pharmacovigilance system was controversial about the time of this study. According to the IPAT, a comprehensive PV system is comprised of (1) governance, policy, law, and regulation, (2) system, structure and stakeholder

coordination; (3) signal generation and data management, (4) risk assessment and evaluation; and (5) risk management and communication. Much earlier WHO had defined the minimum requirements for a functional national PV system to include a national PV center, a spontaneous reporting system, a national database, a national PV advisory committee, and a communications strategy. All of which seemed to belong to the IPAT's #2 component - system, structure, and stakeholder coordination. In addition, WHO guidelines did not provide detailed description of those minimum requirements and did not provide indicators for measuring them. The lack of attention to the other critical aspects of a PV system was glaring. For instance, the need for regulatory reforms to include stringent requirements for adverse event reporting, the need for RMPs, development of capacity for active surveillance, etc. were greatly overlooked. The Asia assessment study therefore seemed to have been ahead of its time in evaluating the countries against benchmarks higher than what WHO was proposing as at that time. In addition, the methods for the evaluation of performance of pharmacovigilance systems varied throughout the years. Much after the publication of the IPAT in 2009, WHO came out with the WHO Pharmacovigilance Indicators: A Practical Manual for the Assessment of Pharmacovigilance Systems published in 2015. The new manual included indicators on risk management, active surveillance, and product quality, signally a shift from the traditional focus on spontaneous reporting systems only. For 6 years prior to the publication of the WHO manual, the IPAT was used to conduct nearly 20 regional and national pharmacovigilance assessments. Till date, more than 100 of those assessments has been conducted with the use of the IPAT alone or in combination with the WHO manual. The Comparative Analysis of Pharmacovigilance Systems in Five Asian Countries itself has been reference in dozens of peer reviewed publications.

This paper may have resurfaced the discussions on the relationship between pharmacovigilance and surveillance. Is pharmacovigilance a subset of surveillance? For some, pharmacovigilance is a regulatory function good enough for generating data for regulatory decision. The spontaneous reporting systems and WHO's earlier focus on the subject thrived under that construct. So, the sort of assessment that the Asia study undertook was perceived as over the board. However, other groups consider pharmacovigilance critical for surveillance of products throughout the lifecycle. In that mindset, pharmacovigilance is a surveillance science. For example, Brazil used the overarching public health surveillance system methodology to measure the performance of their Brazilian Notification System for Health Surveillance of adverse drug-related effects.[2] The argument is that the key criteria relevant to the generic public health surveillance should be considered for health products surveillance systems. The paper has also been referenced in recent publication from Bernabe et al in their paper on regulatory oversight on the use of experimental therapies during a pandemic: The case of early access to convalescent plasma therapy in three LMICs.[3]

1.2. Paper 2 – Actions of the National Regulatory Authorities in 10 Low- and Middle-Income Countries Following Stringent Regulatory Authority Safety Alerts on Rosiglitazone

1.2.1. Background and objectives

Critiques have warned that introducing new medical products in low- and middle-income countries immediately after licensure denies those countries the opportunity of learning from resourced markets on the risk and real-life experiences with the products. However, timely

access ensures that LMICs are not left behind in the benefits of innovation. Timely access is an equity imperative. The current COVID-19 pandemic presents a good example. Previously the introduction of vaccines in low- and middle-income countries occurred years after successful deployment in the US and EU. All that changed with the emergence of the COVID-19 pandemic. New vaccines for COVID-19 were deployed in LMICs within weeks of emergency use authorization in developed countries. That meant that developing countries must have systems ready to go for immediate deployment, vaccination, and safety surveillance. Vaccines regulatory capacity in Africa is very limited. Only 4 African countries including Tanzania, Ghana, Nigeria, and Egypt have achieved WHO Global Benchmarking Tool, GBT Maturity Level 3. Capacity for Lot Release regulatory function is even more limited. Most countries lack the capacity to review dossiers and summary protocols, conduct independent testing of samples, and conduct adequate post marketing surveillance for vaccines. Even before the COVID-19 pandemic, most LMICs lack the capacity to generate own new knowledge on adverse events or take action based on data from other countries. Most LMICs are unable to undertake benefit-risk analysis and follow up with timely regulatory decisions. That means that they are not able to review the continued usefulness of products. Products withdrawn by stringent agencies are available in the Africa and Asia. The inability to take timely regulatory action to protect public health costs lives.

The study on the Actions of the National Regulatory Authorities in 10 Low- and Middle-Income Countries Following Stringent Regulatory Authority Safety Alerts on Rosiglitazone, evaluated the timeliness of regulatory action in LMICs. We reviewed the extent to which LMIC regulatory agencies have the capacity to consider data on emerging safety risks against benefits in determining what medicines should be available in their countries and under what circumstances.

Strong pharmacovigilance system conducts benefit-risk analysis throughout product lifecycle including during the post-approval phase. The study reviewed the timely uptake of the decisions of the US FDA and the EMA following safety signals on the GSK's thiazolidinedione class oral anti-diabetic drug, Avandia, approved by the US FDA on 5/25/1999. Concerns about the cardiovascular risk of Avandia was highlighted with the publication of the 2007 Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of Glycaemia in Diabetes (RECORD) study that assessed the cardiovascular safety of rosiglitazone combined with metformin or sulfonylurea. Our study on the actions of LMICs, documents that with several reports of myocardial infarction associated with rosiglitazone, the FDA announced on September 23, 2010, announced that it will require restricted access programme for the elevated cardiovascular risk associated with rosiglitazone. The same day, the European Medicines Agency (EMA) recommended marketing suspension for medicines containing rosiglitazone. Before these regulatory actions, safety concerns had impacted global sales of Avandia® to slide dramatically from $2.2b in 2006 to $1.2b in 2009. Other authors have also studied the impact of safety alerts on trends in the sale of rosiglitazone and other oral antidiabetic drugs. Timeliness of regulatory action to protect patients from medication harm and safeguard the population is an important public health function. This paper was therefore relevant to the field and had the prospects to add new knowledge.

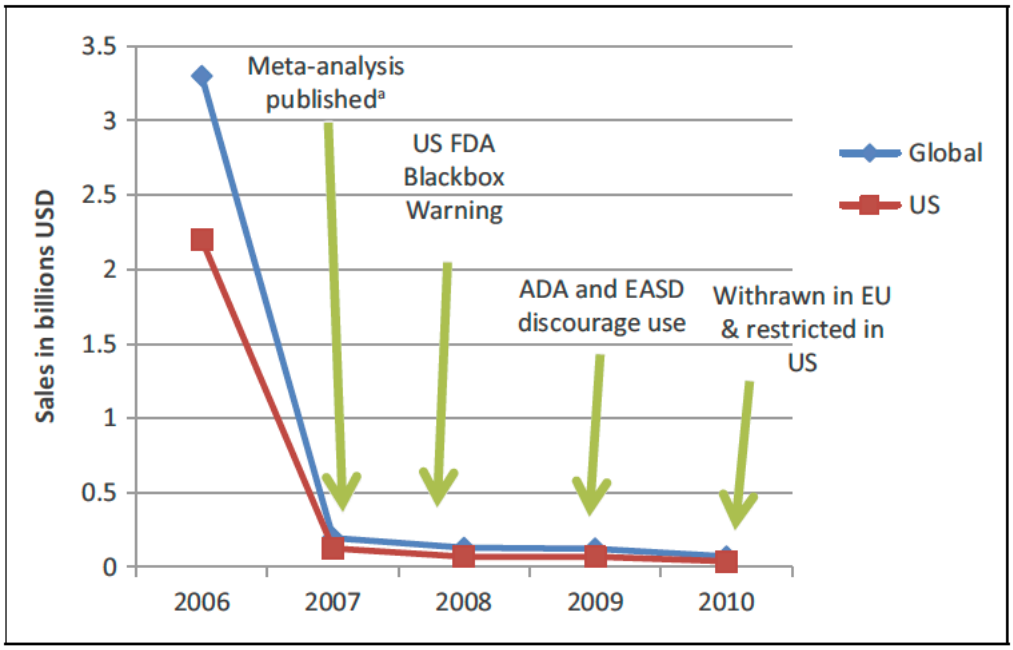
1.2.2. Study method

Our study monitored the actions of LMIC regulators in relation to rosiglitazone using a metric from the Indicator-based Pharmacovigilance Assessment Tool (IPAT). One of the core indicators of the IPAT is the average time lag from safety signal to communication to the public. Several information sources were reviewed to document relevant publications related to rosiglitazone

risks and safety communications. The average time lag for safety communication was calculated in days from date of first announcement by FDA and EMA (index date) to date of regulatory action (defined as any regulatory communication) by LMIC regulatory agency. The method was appropriate to meet the study objectives. However, studies that review change in prescription patterns after regulatory decisions using time series analysis would have provided more reliance result of the impact of the regulatory actions.

1.2.3. Results

Two regulatory agencies outside Africa took regulatory actions related to safety of rosiglitazone within 2 weeks of FDA and EMA safety alerts. For the 7 of the 8 African regulatory agencies that acted, the median time lag before some regulatory action was 43 days, although there was considerable variability in time to regulatory action. From 2007 to 2010, the percentage of sales of Avandia in the US and EU declined, while there was modest increase in the rest of the world. As seen from the Figure 2 below, key safety milestones were associated with the global and US sales of rosiglitazone-containing products. The study proposed a process for national regulatory authorities to react to emerging safety issues. The authors recommended that LMICs should strengthen systems for timely consideration and management of emerging safety issues for products that they have registered.



Sales dynamics of rosiglitazone-containing products, 2006-2010.[4] ADA, American Diabetes Association; EASD, European Association for the Study of Diabetes.

Source - Actions of the National Regulatory Authorities in 10 Low- and Middle-Income Countries Following Stringent Regulatory Authority Safety Alerts on Rosiglitazone. 2015

Figure 1.2: Global and US sales of rosiglitazone-containing products across safety milestones

1.2.4. Limitations

Critiques may argue that our study was not able to study the reason for the inaction. Also, the study did not review the impact of the regulatory actions in countries where they were taken. The documentation of regulatory action does not address the main issue of determining the regulatory impact and effectiveness of the interventions for safeguarding public health. As new medical products get introduced in LMICs much quicker than it was previously, question arises on the capacity of these countries regulatory and PV systems to generate and share reliable data that can be used for timely benefit and risk decision making. Inability to collect real-world data impairs those countries' ability to safeguard their population as well as limit the ability of the global community to fully understand the benefit and risks of the new medical product. Advocates for improved access to medicines in LMICs countries use a metric called drug lag—to indicate how long it takes before an essential medicine licenced by SRAs is introduced by developing

countries. Similarly, we argue for safety lag—how long it takes for developing countries to react to emerging safety alert for products marketed in their country. One of the new challenges of PV is to reduce safety lag globally. The harmonization of standards, use of common terminologies, and sharing information can help reduce safety lag and reduce continued exposure to harmful products.

1.2.5. Influence and related studies

Several other authors have studied related topics and posed questions about how safety concerns may cause drug approval lag. Some have concluded that drugs having longer lag have fewer safety issues post approval compared with drugs with shorter launch lag. Delays in regulatory actions to remove an unsafe drug from the market costs lives. Benfluorex (Mediator®)– a fenfluramine-derivative marketed in France by Servier as a diabetes drug for over 33years was claimed to be responsible for around 3100 hospitalizations and 1300 deaths due to valvular insufficiency. The French agency as at then (AFSSAPS), now National Agency for the Safety of Medicines and Health Products (MSNA) was accused of "inexplicably tolerant of a drug with no real therapeutic value" for allowing Mediator® to remain in the French market after safety concerns were raised. The Mediator event contributed to the reform of the French regulatory system with the enactment of new legislation to strengthen drug safety, including benefit/risk assessment throughout product life cycle, public declaration of conflict of interest by regulators, promotion of independent research on the safety of health products, and government funding of the new MSNA through the Ministry of Health.

In another study titled, Rosiglitazone in Namibia Medicines Register: Evidence for regulatory decision, we reviewed leading treatment guidelines, statements from notable diabetes associations, systematic reviews, drug bulletins and comparative effectiveness review reports. Our findings indicate that older oral anti-diabetic agents already in the Namibia medicines register, example metformin and sulfonylureas are still preferred as monotherapy and combination products in the management of type 2 diabetes. There have been recent concerns about the cardiovascular safety particularly myocardial infarction with rosiglitazone. There are also other safety concerns that warranted boxed warnings on rosiglitazone by notable regulatory authorities including the FDA and EMA. The study identified registered products that do not add value to the already congested anti-diabetic medicines available in Namibia. Except for use in cases of metformin/sulfonylurea intolerance, rosiglitazone's therapeutic role in type 2 diabetes seemed uncertain. The recommendation was to establish criteria for therapeutic novelty prior to evaluation of the registration application. Also, with its comparative efficacy but seemingly higher safety concerns (though inconclusive) rosiglitazone use suggests reduced utility compared to metformin and sulfonylureas in the treatment of type 2 diabetes.

1.3. Paper 3 – Registration timelines on antiretroviral medicines in Ghana and Kenya

1.3.1. Background and objectives

Regulatory review is a resource intensive undertaking. The current system for pre-approval process is disparate and time consuming. Most LMICs lack the resources. Review experiences from the FDA, EMA, and WHO are treasured by almost all LMICs. The review work products

and public assessment reports are highly valuable and instructive for less resourced regulatory agencies. Many studies have documented that regulatory agencies review times for new products are typically long and have negatively impacted on timely access particularly to life saving medicines. One way to address that is through adoption of reliance and facilitated regulatory pathways. The introduction of reliance pathways in the regulatory process, has resulted in reduction in the review timelines. WHO defined reliance as the act whereby the regulatory authority in one jurisdiction takes into account and gives significant weight to assessments performed by another regulatory authority or trusted institution. The relying authority remains independent, responsible, and accountable for the decisions taken, even when it relies on the decisions, assessments, and information of others.

To understand the application of reliance by developing countries, we studied the registration timelines of antiretroviral medicines (ARVs) in Ghana and Kenya, to assess whether prior reviews by the US FDA through the Tentative Approval programme or review by the WHO prequalification (WHO/PQP) affect in-country approval timelines. FDA tentative approval means that the drug meets FDA's standards for safety, effectiveness, and manufacturing quality. The approval is tentative only because of existing patents and exclusivity.

1.3.2. Study method

The study question was to find out prior reviews by FDA and the WHO PQ affect the approval timelines in Ghana and Kenya. Data was collected from national registers of approved products and from online databases in the case of FDA and WHO. Products that are FDA tentatively

approved can be procured by USAID and donated to countries benefiting from the PEPFAR programme. FDA tentative approval products are also listed in amongst the WHO PQ list of products that can be procured by UN agencies including the Global Fund, UNICEF, UNAIDS, and UNITAID. None of the two countries have databases like the FDA's Drug@FDA or related databases like the Orange Book. The study measured the median in-country review period. We evaluated the extent to which FDA tentative approval and WHO prequalification impacted on the approval timelines by calculating the time (in months) between those stringent approvals and national approval from Ghana and Kenya.

Regulatory action that grants timely access to medicines for serious conditions like HIV/AIDS is an important public health function. This paper was therefore relevant to the field and had the prospects to add new knowledge.

1.3.3. Results

The study found that FDA tentatively approved and WHO prequalified ARVs did not have shorter in-country review timelines as would have been expected. Additionally, those products did not receive expedited review. There was no significant difference in the median review period of WHO prequalified and non-WHO prequalified ARVs and similarly in Kenya FDA tentative approval and WHO prequalification did not significantly affect the median in-country review periods.

1.3.4. Limitations

Due to the paucity of reliable datasets in regulatory agencies, particularly as at the time of this study, there were missing data that could have introduced bias.

1.3.5. Influence and related studies

Earlier in 2013, Doua and Geertruyden[5] reviewed how suitable the stringent review procedures of the World Health Organization, FDA, and the EMA are in registering medicines in LMICs. The study focused on the productivity of those pathways rather than on their use for reliance. The authors established that medicines reviewed and approved through FDA tentative approval, WHO prequalification and EMA Article-58 has improved access to ARVs. In was not certain how the authors confirmed their conclusion that those mechanisms have facilitated medicines registration in LMICs. In 2017, Chahal et al[6] had published on the FDA's tentative approval process and the global fight against HIV. The study reviewed the FDA's tentative approval process for antiretroviral medicines (ARVs) and its importance on the procurement of those products by USAID and UN agencies. The establishment of the WHO Collaborative Registration Procedure (CRP) is a very significant effort to ensure that the review work of stringent agencies are not duplicated. The CRP has resulted in significant engagement by many LMICs to rely on stringent decision to achieve timely approval of critical public health medicines in their countries.

CHAPTER 2: INTEGRATIVE LITERATURE REVIEW ON PHARMACEUTICAL ACCESS, REGULATORY RELIANCE, AND POST MARKETING SURVEILLANCE

2.1. Introduction

This Chapter provides an integrative review of literature on regulatory reliance and post-marketing surveillance systems for safe and accelerated introduction of new medical products in low- and middle-income countries. The integrative review approach allows to focus on select published literature on the topic to generate combined perspectives and create new theoretical models. The review integrates own work into the context of related literature and summarise current approaches and conclusions. Over the past 3 decades, published literature about drug approval and post approval systems in low- and middle-income countries have been increasing in number. That increase is associated with the improvement in access to new medical products for global health programmes. Subjects covered have extended to include drug development for neglected tropical diseases, pharmaceutical policy reforms, access initiatives, regulatory approvals, quality assurance systems, and delivery systems. Those publications jointly explain how strong pre and post approval systems enable early access and safeguard patients from adverse events. As the society learns more about ways to overcome the challenges of late-phase drug development, regulatory approval, and monitoring use throughout the product's lifecycle, time to access continues to improve.

2.2. Study method

The integrative review approach involved the search and review of published and gray literature as well as databases and websites of notable organizations working in access to medical products. We searched for articles from databases for biomedical and life sciences literature - Pubmed, ScienceDirect, Scopus Global Research, and from technical reports and databases from US FDA, EMA, WHO, World Bank, United Nations Industrial Development Organization (UNIDO), Cortellis Regulatory Intelligence, Drugbank, and Google. Seminal papers on the subject provided snowballing opportunity, an approach that involves using a key document on the subject as a starting point to identify other relevant papers. Fifteen years of scientific and public health literature related on the topic from 2007 to 2022 were collected using the following search terms – pharmaceutical regulation, regulatory reliance, pharmacovigilance, safety surveillance, post marketing surveillance, expedited regulatory pathways, and drug registration. Nearly 80% of the search hits across Pubmed, ScienceDirect, Scopus Global Research were published in the last 15years. In the case of searches with key word – Expedited regulatory pathways, more than 95% of the hits were for articles published in the last 10-15 years. The literatures included journal articles, book chapters, technical standards, normative guidelines, implementation and evaluation reports, white papers, practice guidelines, and product reviews. The outputs from the review were synthesised and discussed in this Chapter's subthemes within the subject of regulatory reliance and post marketing surveillance systems. In some instances, we synthesised the guidelines recommendations from FDA, EMA, MHRA, WHO and other stringent agencies. The review focused on key global health issues, HIV/AIDS, TB, Malaria, Ebola, COVID-19 and how regulatory systems have reacted or reformed to meet the needs of those diseases.

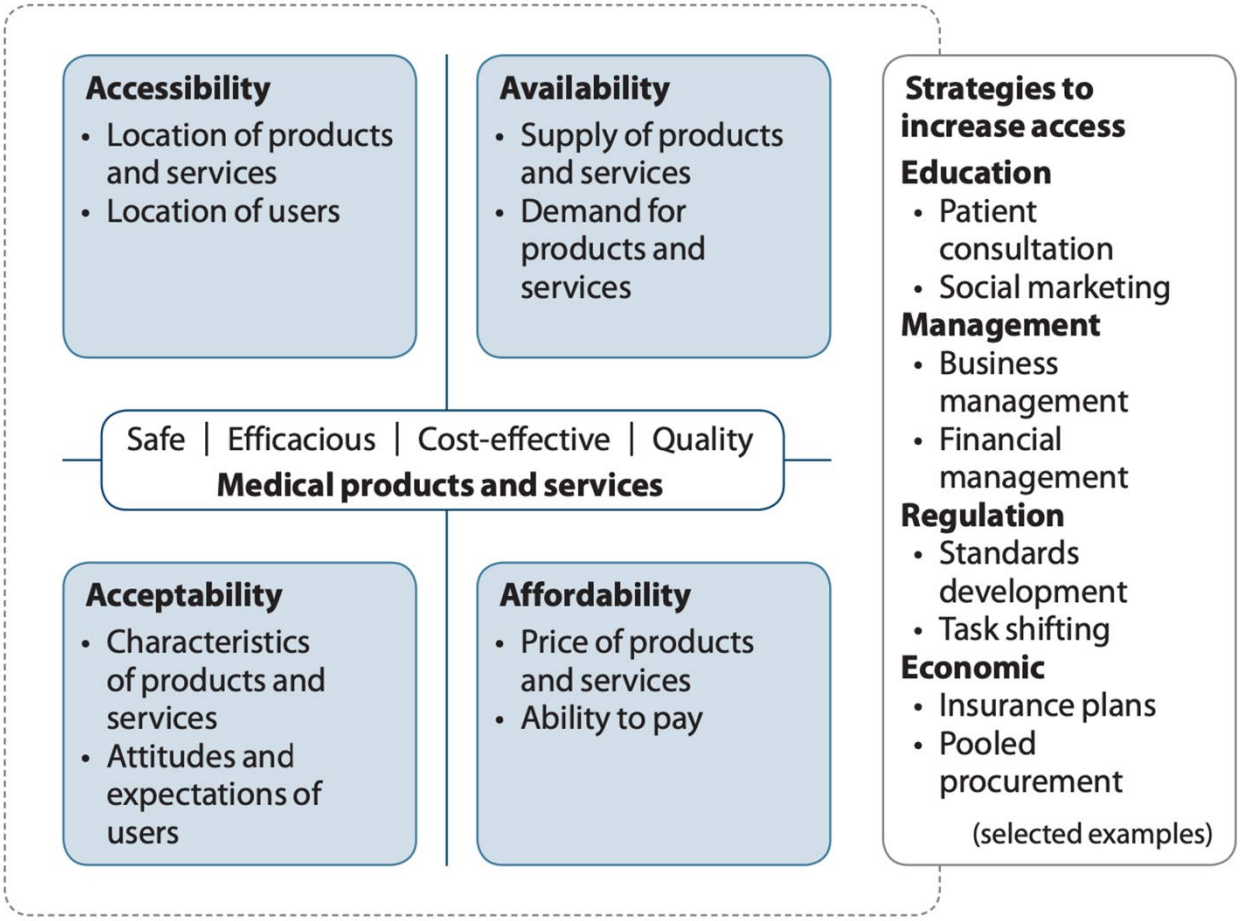
2.3. Pharmaceutical policies and access frameworks

Patients in resource-rich countries may benefit from innovative medical products almost immediately. Though the systems for timely access to promising news treatment is far from perfect in developed countries, patients are guaranteed to receive those medicines many years ahead of the rest of the world. That was the case in the mid-1980s with the outbreak of the HIV/AIDS disease. Epidemics and other global health challenges in the past three decades have dramatically brought into sharp attention the issues of delayed drug approval process and lack of timely access to patients. For example, in the 1980s, the world was desperate in the face of the devastation that HIV/AIDS was wrecking in the US and as cases in other countries were beginning to emerge. The lack of access to antiretroviral drugs at the beginning of that epidemic caused global uproar. AIDS activist and patient communities in the US mounted tremendous pressure on the US Food and Drug Administration (FDA) leading to the approval of azidothymidine or zidovudine in March 1987. Conversely, newly developed medical products for life threatening diseases are often not available to those most in need in low- and middle-income countries. It took until the establishment of the President's Emergency Plan for AIDS Relief (PEPFAR) under the United States Leadership Against HIV/AIDS, Tuberculosis, and Malaria Act of 2003 for access to antiretroviral medicines to reach less-resourced countries. Current reports indicate that a total of 5.5 million babies have been born HIV-free because of PEPFAR and nearly 20million people are on lifesaving antiretroviral treatment.[7] In a study to quantify the societal benefits and costs of HIV treatment coverage and effectiveness from 1995 through 2030, Forsythe and co. estimated that access to antiretroviral therapy averted 9.5 million

deaths worldwide in 1995–2015, with global economic benefits of $1.05 trillion.[8] Since inception in 2000 through 2020, the Global Alliance for Vaccines and Immunisation (GAVI) has provided vaccines to more than 888 million children in 77 countries and prevented more than 15 million future deaths through its support for routine immunization programmes.[9] The Global Fund to Fight AIDS, Tuberculosis and Malaria (Global Fund) which has also been in operation since 2000, has invested more than US$4.4 billion to save 50 Million lives and mitigate the impact of HIV, TB and malaria.[10] All those three global health initiatives, PEPFAR, GAVI, and Global Fund have led the introduction of new medical products in LMICs. Without those programmes those products would have taken decades to arrive and would have never reached millions.

Lack of timely access to medical products for serious health conditions costs lives. While, expanding access to quality-assured medicines safe millions of lives annually. It has been estimated that every year that drug approval is shortened for new anticancer drugs, a median of 79,920 life-years is saved per drug with documented improvement in survival.[11] Accelerating access by only two years for a heat-stable formulation of oxytocin used in the management of postpartum hemorrhage and an orally dispersible antibiotic for pneumonia in children under five years old could save more than 23,000 lives in eastern and southern Africa alone.[12] New medical products are first approved in the US, EU, Japan, and other developed countries but at different time points. Delays that occur after first approval between countries is often referred to as drug lag. It could take from 4 to 7 years from approval in high-income country to approval in low-and-middle income countries in Sub-Saharan Africa.[13] The United Nations Sustainable Development Goal (SDG) identifies global goals that could facilitate timely access to medicines

including SDG 3.b aimed at supporting the research and development of vaccines and medicines for the communicable and non-communicable diseases that primarily affect developing countries and providing access to affordable essential medicines and vaccines.[14] Pharmaceutical access has been a dominant topic in many global health discussions. That is because of the high value and importance of medical products compared to other aspects of health expenditures. Medicines account for three of the ten leading sources of inefficiencies in health systems which results from underuse of generics, higher than necessary medicine prices, substandard and falsified medical products, and inappropriate and ineffective use. Several frameworks have been developed on access to essential medicines, most addressing the need for availability of essential medicines at affordable prices. Figure 3 below shows the access framework from Management Sciences for Health (MSH) which identifies 4 dimensions to access including availability, affordability, acceptability, and accessibility.[15] The MSH access framework also lists some examples of the strategies for improving access.



Source – Increasing access framework, MDS-3: Managing Access to Medicines and Health Technologies.[14]

Figure 2.1: Access framework

The WHO framework for improving access to essential medicines identifies rational selection, affordable prices, sustainable financing, and reliable health and supply systems as the critical components of an access framework. WHO defines essential medicines as "those that satisfy the priority health care needs of the population. They are selected with due regard to public health relevance, evidence on efficacy and safety, and comparative cost-effectiveness. Essential medicines are intended to be [always] available within the context of functioning health systems in adequate amounts, in the appropriate dosage forms, with assured quality and adequate information, and at a price the individual and the community can afford. The implementation of the concept of essential medicines is intended to be flexible and adaptable to many different

situations; exactly which medicines are regarded as essential remains a national responsibility."[16] Other authors have also approved the access construct from different dimensions. Laura J. Frost & Michael R. Reich proposed that in addition to the traditional dimensions of access – availability, affordability, adoption, and architecture which is the organizational structure required for coordinating the other three activity streams to produce access to new health technologies.[17] Attridge and co who examined alternative frameworks for empirical analysis of supply side of manufacturing and distribution of medicine.[18] In our study on expanding access to essential medicines: investment priorities for sustainable strengthening medical products regulatory systems, we identified three critical challenges to access to medical products and that impedes efforts to confront substandard and falsified medicines. They include the lack of implementation of value-added regulatory practices that best utilise available resources, lack of timely access to new, quality medical products, and limited evidence-based data to support post-marketing regulatory actions.[19] The lack of access to new medical products was one of the main issues addressed by the Lancet Commission on Essential Medicines Policies.[20] The Commission identified five key areas that are crucial to essential medicines policies including paying for a basket of essential medicines, making essential medicines affordable, assuring the quality and safety of medicines, promoting quality use of medicines, and developing missing essential medicines. The report of the Commission dwelt extensively on the need for the pharmaceutical industry to align its R&D priority setting with global health needs and develop access strategies to make medically important innovations available to all in need.

The availability dimension in the access framework reviewed marginally touched on the regulatory approval issues. Besides that, most of the authors focused more on the supply chain

management of the availability dimension and did not adequately address product regulation. Table 1 provides a synthesis of the literature on access framework by identifying the dimensions of access that are common to the respective frameworks.

Table 2.1: Analysis of literature on access dimensions

Specific dimensions of Access	WHO	MSH	Frost & Reich	Bigdeli & Co.
Availability (manufacturing, supply and demand management)	√	√	√	√
Affordability (pricing, ability to pay)	√	√	√	√
Acceptability (characteristics of product, use/expectations from product)	√	√		√
Accessibility (supply location, health system)	√	√		√
Overarching dimensions				
Adoption			√	
Architecture (organizational relationships at national and international levels)			√	
Quality and safety		√		
Health systems and human resources				√

The same issue is at the heart of the Global strategy and plan of action on public health, innovation and intellectual property focus on a sustainable, needs-driven, essential health research and development that is relevant to diseases that disproportionately affect developing countries. The pharmaceutical industry constitutes a critical stakeholder in the access discussions. Through trade associations, the industry acknowledges the unequitable nature of the current access paradigm. Activities recommended for the industry for improving access to essential medicines in LMIC goes beyond the need to develop medicines for neglected diseases. It includes the importance of transferring technologies for medicines and vaccines and the use of voluntary licensing for the production of health products in developing countries. An example of successful technology transfer is the Gilead Sciences technology transfer to South Africa's Aspen Pharmacare for the manufacture and distribution of generic versions of Gilead's viread

and Truvada antiretroviral medicines. Several bilateral voluntary licensing and pooled patent are now in place. The Medicines Patent Pool has played a significant role in negotiating most of those agreements that have allowed generic manufacturers to make new innovative medicines and distribute to low-income and middle-income countries.

Besides commercial considerations, several other factors including inadequate approval pathways, review process, and safety concerns contribute to delay in access. Zidovudine was approved in record time as the first HIV/AIDS medicine after one clinical trial. At the point of approval, several safety and efficacy concerns about zidovudine was remaining. Likewise, the outcry that vaccines used for the prevention of childhood diseases in developed countries take years to be introduced to developing countries and results in the loss of millions of lives, contributed to the establishment of the UNICEF's Expanded Programme on Immunization in the 1980s and GAVI in 2000.[21] Scarcity of cancer drugs is a very known cause of disparity in access to essential medicines. As newer cancer drugs that substantially improve survival are introduced in developed countries, the disparities in cancer survival between the rich and poor countries widen even further.[22] Many of the biosimilar products that are included in the WHO Essential Medicines List (EML) are not available in LMICs. Many of the monoclonal antibodies approved in the US and EU and included in the EML face delays in regulatory review and approval thereby contributing to gaps in access for patients in need. Those scientific and non-commercial factors of access can be addressed and their impact on delayed access reduced. To accomplish such objectives will require the strengthening of the drug review process and consolidation of quality and safety data throughout the product lifecycle. Integrated analysis of pre- and post-approval quality and safety data may enable timely access and proactively safeguard patients.

2.4. Regulatory systems that support timely introduction of new drugs

Nearly one-third of the world's population lacks timely access to quality-assured essential medicines. Weak and ineffective regulatory systems are an impediment to access and can expose patients to substandard and falsified medical products. The primary objective of regulatory systems is to improve access and safeguard the public from unsafe medical products. Every country requires the capacity to regulate medical products in their market to ensure access to products for the diseases in their country as well as to ensure they can protect their population from substandard and falsified products. Medical products regulation covers all the processes involved in the pre-marketing evaluation (non-clinical, clinical, and pharmaceutical development), marketing authorization, and post-marketing review of medicines, vaccines, devices, and other health products to ensure compliance to established standards of quality, safety, and efficacy. To meet that capacity, most countries have established a regulatory framework and guidelines on how medical products can be introduced in their market. However, according to the World Health Organization (WHO), only 30% of regulatory agencies have the capacity to regulate medical products effectively and efficiently in their countries.[23] To address that, the World Health Assembly Resolution 67.20 determined that effective regulatory systems are an essential component of a well-functioning health system and contribute to improved health outcomes. That Resolution requested WHO to support countries in regulatory system strengthening, including, as appropriate, to evaluate national regulatory systems, apply WHO evaluation tools, generate, and analyse evidence of regulatory system performance, facilitate the formulation and implementation of institutional development plans, and provide technical support to national regulatory authorities and governments. WHO fulfills this mandate through

the implementation of the Global Benchmarking Tool (GBT) to evaluate the regulatory framework and the component regulatory functions of national regulatory systems. Countries undergo self-benchmarking and verification process, then followed by formal benchmarking by WHO to evaluate the participating agency's regulatory functions using the computerised version of the GBT (cGBT). Findings from the benchmarking exercise is used to develop institutional development plans (IDP) for addressing the gaps in the regulatory system. However, questions have remained on the priority interventions that are needed to ensure that national regulatory authorities have the capacity to ensure timely introduction of new medical products. Some of those new products are introduced for disease outbreaks including the last Ebola disease outbreak in Africa and the current COVID-19 pandemic. To answer that question, the paper - *Expanding global access to essential medicines: investment priorities for sustainably strengthening medical product regulatory systems* brough together global experts to review several normative documents and build upon existing best practices to provide new recommendations. The normative documents reviewed were acknowledged as representing the best ideas from global health organizations and global health experts within the last 10 years, on interventions for health system strengthening and improving access to medicines -

1. WHA Resolution 67.20.[24]
2. Towards access 2030: WHO essential medicines and health products strategic framework 2016-2030.[25]
3. Lancet Commission report on Essential medicine for universal health coverage
4. USAID's Vision for Health System Strengthening.[26]
5. US National Academies report on Ensuring Safe Foods and Medical Products Through Stronger Regulatory Systems Abroad.[27]

Based on the analysis, the authors identified 7 strategies and 13 recommendations. Those recommendations were classified into 4 groups of analytics, collaboration, system development, and workforce development. Reliance, risk-based approaches, and post marketing surveillance are some of the recommendations that can impact on access to new quality-assured medical products.

Several indicators of the WHO GBT can be used to review a regulatory system's capacity to support timely introduction of new drugs. Broojerdi and co. in their study, used 10 of the GBT's 268 sub-indicators to review the regulatory preparedness of LMICs to approve medical products during public health emergencies. Those ten GBT sub-indicators were considered directly relevant to regulatory preparedness for public health emergencies.[28] Notable that 4 amongst those sub-indicators are those related to reliance. They address the existence of legal provisions to recognise or rely on decisions of other agencies and the policies, procedures, and mechanisms for implementing reliance and recognition.

Many of the literature on the topic have similarly recommended that regulatory agencies should implement reliance strategies for new active substances and expedite review timelines as measures of regulatory performance.[29,30,31] Those measures extend to the need to prioritise applications based on their potential for impact on the public health issues in their country. They established that the approval timelines in South Africa in two time periods 2015–2017 and 2018 was more than the 330 calendar days set by the SADC-Zazibona regional harmonization initiative of which South Africa is a member. The review timeline did not ensure timely access to medicines for patients in South Africa. O'Brien and co listed 10 pillars to strengthen regulatory

review systems. Of those pillars, they identified the need for commitment to prioritization of applications. They cited the prioritization of applications based on potential to impact public health issues of the country as an example of performance metric under that pillar.[32] In the paper on how to accelerate supply of vaccines to all populations worldwide, McGoldrick et al., identified four areas for accelerating access to vaccines, 1) science and risk-based approaches, 2) global regulatory harmonization, 3) use of reliance, work-sharing, and recognition processes, and 4) digitalization. They argue that these strategies can contribute to streamlining regulatory process in future pandemics as well as increase efficiency of regulatory activities for vaccines at normal times.

A synthesis of the literature discussed above identified the following as the key capabilities required for measuring regulatory preparedness for health emergencies. As shown in Table 2, the parameters that define key capabilities of agencies necessary for ensuring timely access are described and examples provided.

Table 2.2: Key capabilities amongst regulatory agencies that ensure timely access to new medical products

Parameter	Description	Examples
WHO Maturity Level 3&4	WHO ML3 defines a stable, well-functioning and integrated regulatory system, focus on 10 WHO GBT sub-indicators for regulatory preparedness for public health emergencies.	GBT sub-indicators relevant to emergency preparedness. Five indicators are related to regulatory flexibilities, 4 on reliance, and 1 on safety.
International standards and guidelines	Adoption of international standards to guide regulatory functions.	ICH, PIC/S, WHO, Pharmacopeial standards
Regulatory flexibilities	Defines regulatory pathways for expedited approval.	Allowing for the submission of process validation data, long term stability data, etc. after initial emergency authorization.
Reliance practices	Use of reliance in review and approval of new medicines; avoiding duplication of regulatory reviews, inspections, and quality control testing.	WHO CRP-PQP, PIC/S GMP inspection reliance, WHO National Control Laboratory Network for Biologicals (WHO-NNB).

Good regulatory practices	Describes how to most effectively and efficiently achieve public health objectives (access to medical products and protection of public from SF)	Application of these principles - Legality, consistency, independence, impartiality, proportionality, flexibility, clarity, efficiency, and transparency.
Risk-based approaches	Risk-based reviews, inspections, and post marketing surveillance	Risk-based resource allocation framework for pharmaceutical quality assurance.[33]
Post approval systems	Post marketing quality and safety surveillance, managing post-approval changes and variations.	Changes to approved new and generic drugs.[34]
Information Technology infrastructure	Provides for electronic submission of applications and exchange of regulatory information.	Electronic submission gateway, eCTD, online review

2.5. Access programmes

Overcoming the challenges of late-phase drug development and approval process for the purposes of timely access to drugs for life threatening diseases has received attention recently. Countries have developed pharmaceutical access policies and regulation to facilitate timely introduction and use of medicines for serious conditions. The policies differ in each country but can be generally described as programmes designed to expedite the approval of a new medical product and those to facilitate early access and emergency use of unapproved products. The expedited programmes in the US are categorised as Priority Review, Breakthrough Therapy, Accelerated Approval, and Fast-track. Expedited review programmes may allow for 'rolling review' which means that the sponsor is allowed to submit sections of the new drug application for review rather than waiting for the entire application to be ready. The Expedited Programmes make new drugs to treat life threatening diseases available earlier than the traditional or regular review process particularly for a product that provide the first available treatment for a disease or offer significant advantages over existing treatments.

Early Access pathways on the other hand, enable access to investigational products still undergoing clinical trials for patients that are not recruited into those trials. The terms used to

qualify programmes used for speeding the review and approval of new medicines and the granting of access to investigational products to patients who are not participating in clinical trials differ across countries. In most countries' sponsors are expected to have completed phase III studies to apply for review. Early access and emergency use authorization can be granted for products in Phase II based on data available at that point on the safety and efficacy of the product. In some countries this is referred to as compassionate use. WHO has recommended that compassionate use that offers unlicensed therapeutics is ethically appropriate and justified when clinical trials cannot be initiated.[35] Table 3 below lists some examples of access programmes in the US and EU. The main objectives of the respective programmes are also provided.

Table 2.3: Expedited programmes of US FDA and early access programs of EMA

Expedited Programmes (US)	***Objectives***
Accelerated approval	Approval of drugs based on either a surrogate endpoint or an intermediate clinical endpoint for – • Serious or life-threatening diseases or conditions • Provide a meaningful advantage over available therapies • Requires post-approval confirmatory studies be conducted to confirm anticipated clinical benefit.
Breakthrough therapy designation	Expedites development and review of drugs – • Intended to treat a serious condition • Preliminary clinical evidence indicates drug may demonstrate substantial improvement on a clinically significant endpoint over available therapy.
Fast track designation	Facilitates development and expedites review of drugs - • Intended to treat serious conditions • Demonstrate the potential to address unmet medical needs.
Priority Review	Expedite the review process for drugs – • Treats serious condition • Provides significant improvement in safety or effectiveness • For qualified infectious disease products.
Early Access Programmes (EU)	***Objectives***
Accelerated approval	Reduce assessment time for potentially innovative products; 150 days instead of 210 days.
Compassionate use	Access to unauthorised drugs for life threatening diseases for which there are no available alternatives.
Hospital exemption	Permission for use of unauthorised advanced therapy medicinal products on a named patient basis in hospital setting.
Conditional approval	Accelerated approval for therapies fulfilling a significant unmet need prior to the availability of mature clinical trial data.
PRIME	Priority medicines that benefit from early scientific advice and eligibility for an accelerated assessment.

As shown in the Table above, early access makes medicines for unmet needs available to patients faster than in the standard approval process. Adaptive pathways programme that was launched by the EMA in 2014 has similar objective. Products authorised through the adaptive pathways are allowed a narrow indication in well-defined patients. The expansion of indication is then predicated on outcomes of post-approval and real-world data obtained through prescription databases, patient registries, and similar observational data.

In Table 4 below, we analyzed early access regulations in selected countries to check for the availability of regulations and guidelines for expedited pathways and emergency use authorization. From content analysis, we document guidelines with 6 measures including 2 that are relevant for pharmacovigilance. The guidelines may or may not be similar to the US FDA's Guidance for Industry, Expedited Programmes for Serious Conditions – Drugs and Biologics. The analysis excluded regulations for the importation of drugs for personal use or for compassionate use. It focuses only on early access programmes that allow for use of the unapproved drugs in a greater number of people in the population particularly during health emergencies.

Table 2.4: Content analysis of emergency authorization guidelines in selected countries

Country/Region	Regulation exists for:		Guidelines covers:				PV responsibilities	
	Expedited/fast track programmes	**Emergency authorization**	Submission req.	Reliance	Clinical trials data	CMC/long-term stability)	Risk Mgt Plans	Phase IV studies
India	Yes	**Yes**[1]	Yes	Yes	No	Yes	No	No
South Africa	Yes	**Yes**[2]	Yes	Yes	No	Yes	Yes	No
Canada	Yes	**Yes**	Yes	Yes	No	No	No	No
USA	Yes	**Yes**[3]	Yes	No	Yes	Yes	Yes	Yes
European Union	Yes	**Yes**[4]	Yes	Yes	Yes	Yes	Yes	Yes
Australia	Yes	**No**	No	No	No	No	No	No
Brazil	Yes	**Yes**[5]	Yes	Yes	Yes	Yes	Yes	No
Ethiopia	No	**Yes**[6]	No	No	No	No	No	No
Nigeria	No	**Yes**	No	No	No	No	No	No
Pakistan	No	**Yes**	No	Yes	No	No	No	No

India[1]- Guidance for Approval COVID-19 Vaccines in India for Restricted Use in Emergency Situation which are already Approved for Restricted Use by USFDA, EMA, UK MHRA, PMDA Japan or which are listed in WHO Emergency Use Listing (EUL)
South Africa[2] - Section 21 of Medicines and Related Substances Act
USA[3] - Emergency use authorization can be granted by the FDA in circumstances involving a heightened risk to the public or US military force under section 564 of the Federal Food, Drug, and Cosmetic Act as amended.
EU[4] - PRIME – provides for enhanced enhance interaction and early dialogue to support the development of medicines that target an unmet medical need.
Brazil[5] – On Jul 15, 2022, Anvisa granted emergency use authorization for Sinovac Biotech's Covid-19 vaccine, CoronaVac, in children aged three to five years.
Ethiopia[6] - Guideline for Emergency Use Authorization of COVID-19 Vaccine

2.6. Regulatory flexibilities and reliance practices

Access to medicines depends on multiple factors of which timely and efficient regulatory approval are critical elements. The primary objective of the regulatory review process is to determine that a new product works as it claims and that its benefits outweigh the known risks.

The regulatory review process can be a burden to both the health authorities charged with new drug approval as well as to the pharmaceutical industry. In most instances, the current regulatory process for approving new drugs does not work for patients. During disease outbreaks and public health emergency, it is important to have available regulatory pathways and flexibilities to access new medical products that are indicated for the health problems. Those products could be authorised for use and rapidly manufactured at scale. Regulatory agencies need to have systems in place for timely authorization of medical products indicated for public health emergencies – part of those systems will include emergency use regulations (specifying flexible regulatory pathways), detailed guidelines, and post authorization requirements. Over the past 3 decades, the outbreak of several infectious diseases like HIV/AIDS, tuberculosis, malaria, H1N1, SARS, Zika, ebola, and currently SARS-CoV-2 have reinforced the need for clear pathways for expedited authorization of innovative medical products as they become available. Same urgent demand is seen for new products for cancer and other life-threatening conditions where they are unmet medical needs. Developed countries have established expedited pathways for making innovation products that meet unmet medical needs to be available timely. According to Liberti and colleagues,[36] the goal of facilitated regulatory pathways is to speed the development, marketing authorization, and patient access to new drugs with positive benefit-risk balances. FRPs shift the burden of generating clinical evidence of benefit and safety from the pre-authorization to the post-authorization phase. In their 2015 study, Liberti and colleagues[37] assessed the characteristics of currently implemented facilitated regulatory pathways used by regulatory authorities in emerging economies to speed access to important new medicines. They reviewed 33 FRPs in 29 countries to understand how often they addressed any of the 27 characteristics. They grouped those characteristics under 5 sequential regulatory activities:

agency assistance, acceptance criteria, review process, decision criteria, and post-authorization and disengagement. In their findings, 79% reported that approval can be based on a surrogate or intermediate clinical endpoint. Also 73% required that the agency must respond to an FRP request within 30 days. The authors however warned that while timeliness is important, agencies must ensure a quality review. Another interesting finding is that the sponsor must commit to conducting post authorization studies (78%). Leading to the conclusion that effective FRP combines expedited pre-authorization review procedures with robust post-authorization monitoring.

Reviews from expedited processes should not be duplicated particularly in cases on health emergencies and in environment of limited resources. For LMICs, it's important that the regulation includes provisions for reliance and recognition of decisions of mature agencies. Hence, several initiatives have been developed to facilitate the review process and encourage the adoption of efficiency mechanisms like work-sharing, reliance, and mutual recognition to ensure timely access. The World Health Organization, WHO defines regulatory reliance as the "act whereby the regulatory authority in one jurisdiction takes into account and gives significant weight to assessments performed by another regulatory authority or trusted institution, or to any other authoritative information, in reaching its own decision. The relying authority remains independent, responsible, and accountable for the decisions taken, even when it relies on the decisions, assessments and information of others." Common features of reliance practices are that they are usually stated in the regulations, defines reference countries, are targeted at achieving efficiency and avoiding duplicative work, and could lead to 2 pathways – Verification

and Abridged review. Reliance is needed the most by LMICs as new innovative and complex medical product are introduced in developed countries.

Other experts have discussed the increasing complexity in the new therapeutic modalities as it relates to flexible regulatory approaches. Klein and colleagues[38] proposed the concept of regulatory density which they defined as the relative number of obligatory standards, measures, and procedures applied to certain medicinal products or product classes and the resources required to meet these requirements. Complexity in this context were described from the perspective of the product's complicated molecular structures and sophisticated manufacturing processes, the complexity of the 'process' which they refer to healthcare delivery process and the complexity of the 'patient' - target patient population. Similar to the conditions for adaptive licensing and FRPs, the authors posit that regulatory density accepts a higher level of risk and uncertainty at time of authorization and relies on post approval data to reduce the uncertainty over time through data generated in real world use. Another area of concern relates to the consequences of relying on decisions from facilitated review pathways. As seen in cancer clinical trials, there may be weak association between surrogates and life extension. Davis and co. found that up to 57% of drugs' indications approved by EMA did not have evidence of overall survival (OS) or quality of life (QoL) improvement at the moment of marketing authorization.[39] Post approval studies particularly those that are targeted at treatments approved without clinical outcome data and limited evidence of benefit on survival are good candidates for investigation in post marketing studies. Such products are often granted conditional marketing authorizations because at the point of authorization, the sponsor does not have comprehensive data and need to generate additional evidence to answer unresolved safety and efficacy questions

in the post marketing period. Well resources agencies that are often relied upon must understand that their decisions have implications beyond their borders.

Another aspect of the access problem is with regards to timely access to medical products that have recently shown promise in managing life threatening diseases. These medicines are usually new chemical entity in phase II/III clinical trials for the serious conditions and are awaiting filing by the sponsor. Patients who have not received those products through participation in the clinical trials and who may have failed other existing therapies look forward to these new drugs as their only hope. Such patients fervently hope that the drug development and approval process should be accelerated so they can obtain promising treatment on time. Yet, the regulatory agency must balance the benefit and risks of the products before granting market approval and extensive use in the population. An effective approval system combines expedited pre-authorization review process with robust post authorization monitoring. The most important challenge for the regulators is therefore to find the right balance between timely access and risk to the patient. For most products with proof of efficacy for the indication they are being studied for, additional delays in approval are usually attributed to safety concerns. Due to the limitations of clinical trials, it is not possible to fully characterise all the safety issues that could be related to the use of the product particularly long-term adverse events. Similarly, real-time stability data, manufacturing variation, impurities, and other product quality issues may not be completely understood at the point of approval. Drug approval does not constitute a singular moment of clarity about the safety and efficacy of the product. Gaps may remain in knowledge due to lack of completeness of ascertainment, inadequate characterization of safety, and quality issues that may occur during storage and distribution. Strong post approval surveillance system should be

able to fill those gaps in knowledge. It is very important to acknowledge strong pharmacovigilance system as a pre-requisite for the introduction of new products in global health. Table 5 provides features of reliance guidelines of WHO, EU, Brazil, Pakistan, and South Africa.

Table 2.5: Reliance guidelines and their features

Reliance program	Illustrative feature
WHO	WHO prequalification relies on the decision of stringent agencies, The collaborative regulatory pathway (CRP) enables LMICs to rely on decisions of the prequalification programme and of the SRA-CRP. Reliance is also encouraged in the WHO NNB for lot release testing for vaccines.
EU Decentralised Procedure	Assessment of a new medicine by a Reference Member State on behalf of a group of other Member States.
Brazil	ANVISA uses the term Equivalent Foreign Regulatory Authority and define them as a foreign regulatory authority that has regulatory practices like ANVISA's and that "ensure the same level of health protection, including in terms of regulatory action, considering the adoption of good regulatory practices, and what should be considered for decision-making, including requirements, criteria, measures and controls adopted, and that meets all the requirements set out in this Resolution."
Pakistan[40]	Includes a review of the Certificate of Pharmaceutical Product and conditions for withdrawal of the product based on similar action in the reference agency country. Withdrawal is the responsibility of the manufacturer in Pakistan.
South Africa[41]	Requires full and unredacted evaluation reports from the reference regulatory agency where the product is registered.

To implement reliance, countries identify reference countries. The reference regulatory agency (RRA) is usually stated in the regulations. The relying agency build on the decision of the trusted RRA agency. Examples of RRA for South Africa are US FDA, EMA, PMDA, MHRA, TGA, Health Canada, Swissmedic, and WHO. South African Health Products Regulatory authority (SAHPRA) also consider decision of the regional harmonization initiative, the ZaZiBoNa Collaborative Medicines Registration pathway. To support regulatory reliance on its work product, the WHO developed the collaborative registration procedure (CRP). By providing access to the assessment conducted in the prequalification programme, WHO intends to use the CRP to facilitate the assessment and approval of medical products for resource-limited agencies.

The same principle extends to the use of review experiences and products of well-resources agencies or agencies that conduct stringent reviews. The countries previously listed as stringent regulatory agencies (SRA) are examples. Through the SRA-CRP, WHO facilitates the access and use of SRA assessments for medical products that represent unmet public health needs, including those not in the scope of the WHO prequalification programme.

Many regulatory agencies are also involved in work sharing arrangements, usually through the regional economic community agreements. Examples include the GCC, EAC, SADC-ZaZiBoNa, the Southern African Development Community (SADC) collaborative medicines registration initiative, CRS – CARICOM. Member States participate in joint review and joint inspections. The results of such joint activities are expected to lead to marketing authorization decision within a specified timeline. WHO defines work-sharing as the process by which NRAs of two or more jurisdictions share activities to accomplish a specific regulatory task.

Reliance does not mean outsourcing of regulatory function as the country still retains the sovereignty for the final decision. There are 3 review types that products being assessed through reliance will have to undergo -

- Verification review – determines sameness of product specifications with previously authorised product.
- Abridged review – considers local factors, local benefit-risk determination, local epidemiology and medical practice
- Full review – requires full review though product may have been previously reviewed by an SRA.

For each of the 3 above review types, the Table 6 below have specified the data that are most critical to be reviewed. In all cases a full review of the labeling as well as a review of module 2 or the module 3 may be required for all product types.

Table 2.6: Required data for reliance review

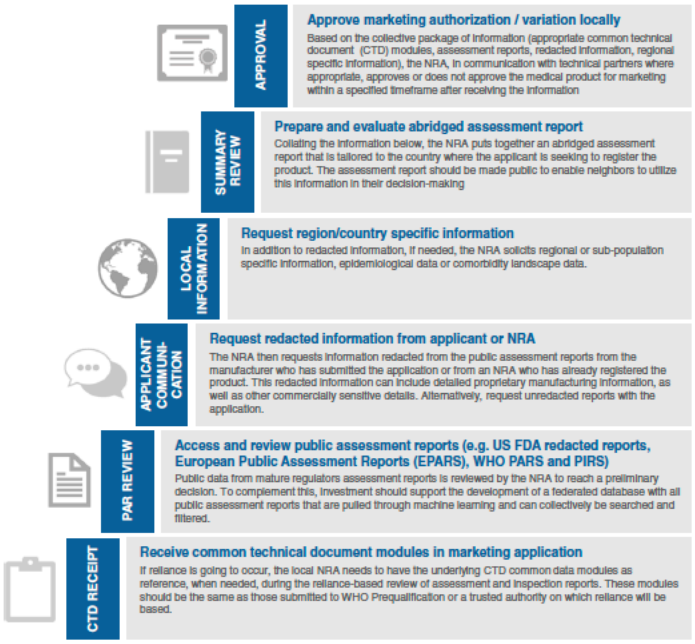
Review type	Labeling (M1)	CMC (M2&3)	BE (M5)	Clinical data (M5)
Verification	✓	✓		
Abridged	✓	✓	✓	
Full review	✓	✓	✓	✓

Having systems, procedures, and capacity to conduct those types of reviews listed above is critical for the utilization of opportunities created by reliance. Most LMICs lack those systems and are therefore unable to fully take advantage of reliance opportunities. To understand the application of reliance by developing countries, we studied the registration timelines of antiretroviral medicines (ARVs) in Ghana and Kenya, to assess whether prior reviews by the US FDA through the Tentative Approval programme or review by the WHO prequalification (WHO/PQP) affect in-country approval timelines. The study[42] found that the median time between FDA approval and the approval by those countries was 21 months and median time of 19 months between WHO prequalification and NMRA approval.

The question then is, why are the opportunities for reliance not utilised? They are not because the infrastructure to support the operationalization of reliance practices are not well developed. Defining reliance is not enough, it must be operationalised. For LMICs to implement concrete reliance practices the infrastructure and needs for reliance-based secondary review should be in

place. Secondary review - considers multiple pieces of secondary data to create a coherent as possible picture on a specific topic.

Regulatory agencies conduct reviews on primary data submitted by the product sponsor. That primary review typically ends with approval decisions by mature agencies. Given the huge resources deployed for primary reviews they should not be duplicated. Well-resourced agencies have a role to play in that regard. Lumpkin et al argues that FDA was ill equipped to serve in the role of reference agency to LMICs during COVID-19 pandemic due to limitations imposed by the agency's transparency practices.[43] For efficient use of resources, stringent reviews can be considered are global public good. Producers should therefore ensure that they are presented in ways that facilitate use by secondary reviewers. In this context, secondary review refers to the evaluation of primary reviewer's report alongside other related documents to arrive at decisions that aligns with primary review or raise questions for further clarification. Operationalizing reliance practices will require the development of guidelines, procedures, manuals, secondary review toolkits and processes, information systems, and training that is needed by regulators and industry in LMICs. Figure 4 below describes a reliance process that could be applied in LMIC to facilitate timely authorization and products and approval of variations.



Source – Roth et al. Expanding global access to essential medicines: investment priorities for sustainably strengthening medical product regulatory systems

Figure 2.2: Operationalizing regulatory reliance for registration

The current lack of these defined processes and tools in LMICs have meant that many agencies are not implementing reliance while having access to data from reference regulatory authority. In some instances, the reason may go beyond the absence of infrastructure and systems but may include a preference to conduct own reviews due to legal, sovereignty, demographic reasons. McGoldrick et al proposed for the case of COVID-19 vaccines, a reliance procedure for regulatory approvals and post-approval changes, that is based on the acceptance of an approval from a reference authority and defined target time (e.g.,15–30 working days). The authors stated that industry received thousands of CMC questions which relate to the same product and exact same data package.

Several authors have documented challenges that confront the adoption of reliance. The bullets below summarise the most critical challenges to reliance.

2.7. Summary of challenges with operationalizing reliance

1. Regulatory requirements - differences in regulatory systems and lack of equivalent regulatory requirements.
2. Operational issues – lack of guidelines, procedures, manuals, review toolkits and processes to support the operationalization of reliance.
3. Information systems - effective reliance depends on the exchange of large data in secure environment. The lack of secure information technology systems and procedures and manuals for reviewers on the use of nonpublic information limits the adoption of reliance
4. Autonomy - reviewers concern that it reduces their autonomy and may mean the outsourcing of their responsibilities. “We are trained to review data and not how not to review”.
5. Public health risk - concern that LMICs lack the resources for quick action in the event of errors arising from the approval of an ineffective or unsafe products by a reference agency.
6. Redaction of data – public assessment reports and drug approval package from stringent agencies in some instances are heavily redacted, thereby dramatically limiting their usefulness.
7. Lack of context – limited competency in the relying agency to independently recognise all the considerations of the reference agency’s reviewer.

Increasingly, the challenges listed above are being overcome. The impetus is the urgency for timely access to innovative products. Most of those products have been reviewed by mature agencies. Their review products can be considered as public goods. Expedited review pathways

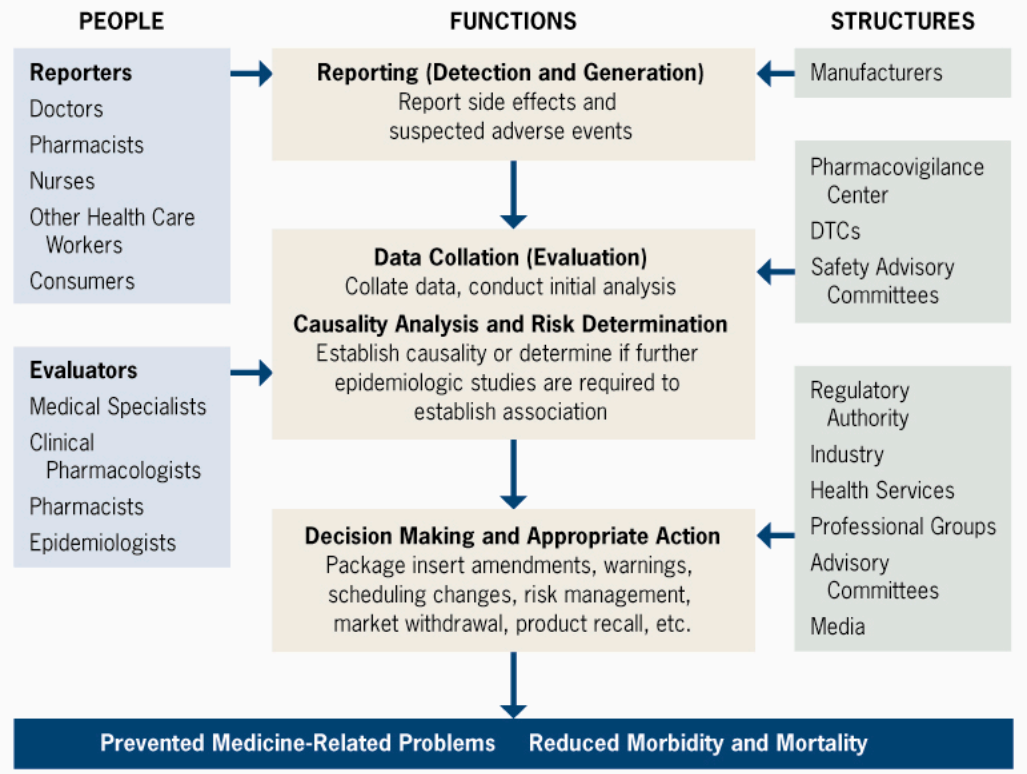
are important to LMICs given that several global health initiatives are introducing new products to those countries.

2.8. Facilitating the introduction of new products with strong surveillance system

In the paper Global pharmacovigilance for antiretroviral drugs: overcoming contrasting priorities[44] we highlighted the critical need for improving the global drug safety system as increasing numbers of people worldwide are placed on antiretroviral drugs. A report of the safety and surveillance working group[45] provides detailed description of how strong pharmacovigilance systems can support the introduction of new medical products in global health. Many developing countries are now recognizing the need to set up systems for safety surveillance of newly introduced medical products and increasingly the decision to grant accelerated access, like the case of COVID-19 vaccine, is conditioned on follow-up through strong post approval surveillance systems. Practical approaches for the conduct of active surveillance studies on newly approved products have been proposed as part of the pharmacovigilance systems that supports the introduction of new medical products for global health programmes including HIV/AIDS, Tb, malaria, and vaccines. To conduct an active safety surveillance for the introduction of new antiretroviral drugs we used probabilistic records method to study adverse effects of antiretroviral therapy in sub-Saharan Africa. The study on Records linkage of electronic databases for the assessment of adverse effects of antiretroviral therapy in sub-Saharan Africa[46] was a first of its kind in Sub-Sahara Africa that introduced the data linkage study of electronic medical records for active safety surveillance. Strong post marketing surveillance for quality and safety is critical for new medicines. No amount of pre-market studies will ever elucidate all the information about the safety and risks of a new drug. Therefore, post-marketing

surveillance is extremely important. Adverse effects that are not detected during clinical trials are identified after approval through post-marketing clinical trials, spontaneous reporting of adverse events, or observational studies based on more widespread use of the product following approval.[47]

Supporting Pharmacovigilance in Developing Countries: The Systems Perspective[48] outlined the urgent need for strong regulatory systems given the increasing influx of new products for HIV/AIDS, Tb, and malaria into low- and middle-income countries without adequate pharmacovigilance systems. The paper's central message is that global supply chains influx of new products without strengthened pharmacovigilance systems "can diminish the significant improvements in access and compromise the success of public health programmes." Every country should have regulations and guidelines to cover the scope of pharmacovigilance or post marketing surveillance to include adverse drug reactions, medication errors and product quality problems. The pharmacovigilance system is the "coordinated and interdependent functioning of activities to improve benefits 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." The framework for a comprehensive pharmacovigilance system therefore describes the people and structures that support the pharmacovigilance functions of reporting (detection and generation), data collation (evaluation), causality analysis and risk determination, and decision making and appropriate action according to Figure 5 (below).



Source: 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.

Figure 2.3: Pharmacovigilance system

During implementation, countries can progressively mature from a basic passive surveillance system to incorporate active surveillance methods to address priority safety concerns, such as the use of registries, sentinel sites, and follow-up of defined patient cohorts. Active surveillance is a defined systematic and proactive approach to detect and evaluate medicine-related risks, is important in identifying and quantifying long-term toxicities of new products introduced in global health programmes. A study on the ongoing and completed active surveillance activities from 46 countries over a period of 5 years found that 48% of the countries have ongoing active surveillance activity through academic institutions, public health programmes, hospitals, and various international organizations. Most of the active safety surveillance that was ongoing were those conducted in collaboration with institutions in Europe and the United States and focused on antiretroviral drugs and antimalaria.[49]

2.9. Expanding scope of pharmacovigilance

Product quality surveillance and other quality assurance measures can contribute to efforts to contain antimicrobial resistance.[50] Besides being a regulatory intervention, "including medicines quality assurance in national action plans and key normative guidance documents for antimicrobial resistance is critical to containment, especially for low- and middle-income countries, where weak regulatory controls may increase the potential for poor-quality antimicrobials to be widely available." Addressing the issues of substandard medical products - those that fail to meet quality standards and/or specifications – is particularly important from a public health perspective as subtherapeutic levels of an antibiotic can promote development of resistant bacterial strains. Poor quality antimicrobials could be fueling the common clinical practices of retreatment, use of increased dosage strengths, relatively higher use of broad-spectrum antibiotics, and general overuse of antimicrobials. Current pharmacovigilance systems are skewed towards reporting only events that lead to immediate harm and hospitalization. The regulatory framework and scope of post marketing surveillance that can contribute to the containment of AMR should include the monitoring of therapeutic ineffectiveness and quality concerns within the pharmacovigilance system. With the right regulation and guidelines in place, healthcare providers can be trained to have an index of suspicion that the quality of antimicrobial drugs may be unreliable and requesting for investigation before switching to more expensive alternatives. Another drawback is that pharmaceutical data on antibiotics are often siloed, separated by healthcare providers' roles and by functions in the health facility. Hence, prescribers and lab scientist focus mainly on drug sensitivity tests and antibiogram, and pharmacists and pharmacies on drug quality tests. All healthcare providers are better served

when they have information on prescription pattern and utilization, susceptibility pattern, and antibiotic quality test results. Ensuring that quality surveillance systems provide timely and reliable data on drug quality should be part of the comprehensive infrastructure for antimicrobial resistance surveillance systems. These systems should work together, especially since product quality issues can signal the risk of potential development of antimicrobial resistance and vice versa.

Defining an adequate regulatory framework and scope of pharmacovigilance system is only one part of the problem. Many LMICs do not have the resources and often struggle to identify the priorities for having such a system in place. Donors and development partners that introduce new medical products for global health diseases are also eager for a strong regulatory system.

2.10. Measuring post marketing surveillance systems

Post marketing surveillance (PMS) is a systematic process for monitoring all aspects of the performance, use, and adverse events of medical products in large number of populations after marketing authorization or approval. A functional PMS system is critical for both old and for new medical products. For products introduced through expedited process, regulators may require authorization holders to generate more evidence of benefits and safety post authorization. Measuring the performance of PMS or pharmacovigilance systems that covers the scope of both the previously and the recently introduced medical products is challenging. The Indicator-Based Pharmacovigilance Assessment Tool (IPAT)[51] was developed as a comprehensive performance metric for pharmacovigilance systems to benchmark stakeholders' functions; diagnose system strengths, weaknesses, and gaps; and monitor and evaluate interventions. Prior to the

development of IPAT in 2009, no universally adopted performance or outcome metrics existed for assessing pharmacovigilance systems.

2.11. Delphi method and research studies

The Delphi method used for the development of the IPAT involved 3 consultations for 12 respondents in 8 countries. The process explored and distilled the opinions of pharmacovigilance experts in an iterative process that generated 27 responses. Group members were requested to weigh the indicators based on whether they considered them "core" or "supplementary." The indicators chosen by the Delphi group were used to formulate relevant assessment questions and generate a body of expert opinion. The components of IPAT represent the elements of a functional pharmacovigilance system, including—

1. Policy, law, and regulation
2. Systems, structures, and stakeholder coordination
3. Signal generation and data management
4. Risk assessment and evaluation
5. Risk management and communication

IPAT indicators measure all the elements of a comprehensive post authorization surveillance system including previously known or unknown ADRs, medication errors, and product quality. For instance, the IPAT has several measures for product quality including indicators that measure the existence of a form for reporting suspected product quality issues (as a subset in the ADR form or as a separate form), pharmaceutical product quality survey conducted within the

last five years, and percentage of medicines sampled in the last year that passed product quality tests. The IPAT also for the identification and quantification of patients that experienced unexpected events. One of the indicators specifically measures the percent of patients in public health programmes for whom drug-related, serious "unexpected adverse drug events" were reported in the last year. The reporting of previously unknown and serious adverse events and the establishment of their association with the medicine the patient was exposed to provides safeguard that events that occur post approval will be documented. Lack of capacity for post approval reporting of serious events including medical occurrence that results in death, life threatening, hospitalization or prolongation of existing hospitalization, persistent or significant disability or incapacity, or in a congenital anomaly or birth defect are required to be reported by pharmacovigilance regulations in most countries.

Another significant indicator that impacts the deployment of new medical products is the average time lag between identification of safety signal of a serious ADR or significant medicine safety issue and communication to health care workers and the public. Signal refers to the 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 verificatory and, when necessary, remedial actions. Best practices in pharmacovigilance require that new signals of serious ADR to be communicated to healthcare providers and the public as soon as the signals are generated. Signals can be generated either locally or through scanning the global literature for safety reports. Once these reports are obtained, locally relevant

ones that are significant to in-country clinical practice and public health are immediately communicated to health workers and the public. We studied the availability of quality assurance fields in phase IV clinical trials of approved medicines used as Investigational Medicinal Products (IMPs). Our study showed that none of the clinical trial registries including CTRs of ICMJE and WHO platforms has adequate fields to establish that the source of the IMPs is quality assured. In our work on quality assurance and UHC, we showed that the reported prevalence of substandard and falsified medicines is negatively associated with both an indicator for coverage of essential services ($p = 0.05$) and with an indicator for government effectiveness ($p = 0.04$). We estimated that investing in improving the quality of antimalarials by 10% would result in annual savings of $8.3 million in Zambia, $14 million in Uganda, $79 million in two DRC regions, and $598 million in Nigeria, and was more impactful compared to other potential investments we examined.

2.12. Surveillance systems in action

For generic medicines, the issues with post marketing surveillance are compounded by diametrical viewpoints: that unexpected adverse reactions are unlikely for well-established medicines even from generic formulations versus the position that quality issues from generic manufacturers may account for a significant number of adverse events. Major drug safety mishaps have occurred from contamination and stability issues related to well-established generic medicines. Examples include the mass poisoning from diethylene glycol that resulted in more than 800 deaths across 12 countries from the US index case in 1937 to the recent 2020 case in India's Jammu and Kashmir territory, the 2012 death of 125 Pakistan patients from cardia drug contamination with an antimalarial, the contamination of sartan containing products by

NDMA impurities, and the contamination of heparin with oversulfated chondroitin sulphate (OSCS). Those cases point to lack of quality control in manufacturing as the origin of important safety issues. For environmentally sensitive products, the lack of compliance to good manufacturing practices can combine with storage conditions to raise the issues of poor-quality medicines. The study Quality medicines in maternal health: results of oxytocin, misoprostol, magnesium sulfate and calcium gluconate quality audits[52] involved the conduct of compendial analysis on the quality of oxytocin injection, misoprostol tablets, magnesium sulfate, and calcium gluconate injections in Nigeria. Oxytocin and misoprostol recorded 74.2% and 33.7% percentage failure respectively. Most of the oxytocin used in Nigeria are imported, some from unreliable sources with poor manufacturing practices. Oxytocin is temperature sensitive. The high failure rate was attributed to degradation due to inadequate storage conditions. Nigeria accounts for about 19% of all global maternal deaths. The high failure of these products used for the management of post-partum hemorrhage contributes to that high maternal mortality as seen in the descriptive study of healthcare-providers' experiences with the use and quality of oxytocin for the prevention of post-partum hemorrhage in Nigeria.[53]

CHAPTER 3: MODEL INTEGRATED QUALITY AND SAFETY REVIEW SYSTEM FOR REGULATORY RELIANCE AND POST MARKETING SURVEILLANCE

3.1. Introduction

Given the experiences from the past 3 decades of strengthening LMICs regulatory systems to support the introduction of new medical products as documented in chapter 1 and in the literature review in chapter 2, this chapter's objective is to provide models and best practices for improvements. How can regulatory reliance be operationalised to ensure that resource-constrained agencies obtain high quality summaries for their decisions? What is required for post marketing surveillance systems that can support safe and accelerated introduction of new products? This chapter attempts to answer those questions by proposing model review system and tools.

3.2. Reforming a disparate and time-consuming process

A major weakness of the current system for pre-approval review of medical products is that the review processes are disparate and time consuming. It does not synthesise data from all sources to come to timely decision. Also, the lack of robust post approval surveillance (PMS) system that can comprehensively track product performance and patient experience disincentives early access. Inadequate post approval systems forfeit opportunity for expanding product knowledge so regulators opt to delay approval decisions preferring to learn more on the quality and safety of the product before approval. These shortcomings may result in delayed drug approval for stringent agencies. Consequently, there is an even much more extended delays in LMICs who

should take advantage of prior reviews from stringent agencies as highlighted in our study on the registration timelines of antiretroviral medicines in Ghana and Kenya.[54] In collaboration with other authors, we have also contended that many LMICs where new products are intended to be introduced need pharmacovigilance systems to effectively monitor their post-market safety.[55] In a safety and surveillance Working Group publication, we specifically recommended for focus on pharmacovigilance for novel or newly introduced drugs and vaccines that will be launched in developing countries through global health programmes, such as the GAVI Alliance and Global Fund to Fight AIDS, Tuberculosis, and Malaria.[45] Regulatory reforms in the US and Europe over the past three decades has targeted reform of the review process and post-approval safety monitoring, the two areas of weakness, and developed systems for addressing them. Many developed countries have established policies and regulations to ensure that medical products for serious conditions are available to patients in a timely manner. Those expedited pathways or facilitated regulatory pathways (FRPs) provide alternatives to the standard medicines development and registration by accelerating the development, submission, or regulatory review of important medicines for unmet medical conditions. The US expedited programmes and the EU early access programmes were designed to address these issues. Specifically, the EMA's adaptive pathways encourages for medicine development and data generation which allows for early and progressive patient access. Integrated review of data from multiple sources, for example the Integrated Summaries of Safety and Effectiveness is now a routine practice in the US FDA and the EMA. Lastly, they both have developed strong and functional pharmacovigilance system to monitor the products once in the market. Those experiences have shown that where regulations for expedited programmes exist, integrated pre-approval review and robust pharmacovigilance systems can ensure timely access to life saving medical products.

Successful PMS generates data for timely decision making to keep the product in the market, expand or restrict indication, refine manufacturing process, or remove product from the market before it leads to harm.

This chapter discusses changes needed in the review process to facilitate review products that are useful for LMICs. To operationalise regulatory reliance, stringent agencies review products should be available as integrated summaries and assessment reports. Integrated summary reports from well-resourced agencies have the potential to benefit less resourced countries. In implementing good review and reliance practices during abridged and full reviews, developing countries can base their authorization of new products on secondary review of integrated summaries of safety and quality. Hence, improvements to the review process of well-resourced agencies consequently improves the value and quality of secondary reviews for LMICs. Also, from the experiences of regional harmonization initiatives, the operationalization of reliance requires a functional regulatory information management system.

3.3 Drug review process and benefit-risk evaluation

The primary objective of the review process is to determine that a product works as it claims and that its benefits outweigh the known risks. The regulatory review process can be a burden to both the health authorities charged with new drug approval as well as to the pharmaceutical industry. In some instances, the current regulatory process for approving new drugs does not work very well for patients. Hence, several initiatives have been developed to facilitate the review process and encourage the adoption of efficiency mechanisms like work-sharing, reliance, and mutual recognition to ensure timely access. That also includes initiatives for timely access to medical

products that have recently shown promise in managing life threatening diseases. These medicines are usually new chemical entity in phase II/III clinical trials for the serious conditions and are awaiting filing by the sponsor. Patients who have not received those products through participation in the clinical trials and who may have failed other existing therapies look forward to these new drugs as their only hope. Such patients fervently hope that the drug development and approval process should be accelerated so they can obtain promising treatment on time. Yet, the regulatory agency must balance the benefit and risks of the products before granting market approval and extensive use in the population. The most important challenge for the regulators is therefore to find the right balance between timely access and risk to the patient. For most products with proof of efficacy for the indication they are being studied for, additional delays in approval are usually attributed to safety concerns. Due to the limitations of clinical trials, it is not possible to fully characterise all the safety issues that could be related to the use of the product particularly long-term adverse events. Similarly, real-time stability data, manufacturing variation, impurities, and other product quality issues may not be completely understood at the point of approval. After approval, gaps may remain in knowledge due to lack of completeness of ascertainment, inadequate characterization of safety, and quality issues that may occur during storage and distribution. These late-phase drug development and review challenges can constitute an impediment to access. Alternatively, a streamlined review process can integrate findings from the evaluation of the quality overall summary (QOS) and summary of clinical safety (SCS) presented in the common technical document (CTD) to project the post marketing quality and safety requirements for the product. Unfortunately, that is not the case for most regulatory agencies, particularly in low- and middle-income countries. Product sponsors use the clinical summaries on efficacy (SCE) and summary of clinical safety (SCS) provided in module

2 of the CTD to discuss study design and to present general efficacy and safety results. The FDA requires that the integrated summary of effectiveness and safety (ISE/ISS) be presented in Module 5. ISS which is presented in module 5.3.5.3 is meant for the purposes of summarizing safety information from all clinical trials.[56] Sponsors use the result for the final assessment of the benefit risk of the product. Formal assessment and quantitation of the benefits and risks of new products is critical for informing approval decisions and justifying risk management plans. Unfortunately, this practice is not consistent across jurisdictions and regions. Additionally, the requirements for post marketing commitments (PMC), periodic safety update reports (PSUR), annual product quality reports (APQR), manufacturing variation, and other post approval changes vary across jurisdictions and regions. The recent release of ICH Q12 guidelines on Technical and Regulatory Considerations for Pharmaceutical Product Lifecycle Management provides a globally harmonised approach for the management of post approval manufacturing quality changes. Robust review process and benefit-risk evaluation can provide guarantee that unresolved safety issues during expedited approval can be sufficiently monitored post approval and hence allows timely access to new medicines.

Whereas early access may mean that the new product can be provided to limited number of patients, unfortunately, there are no globally harmonised guideline for the determining the extent to which the pharmacovigilance system aligns with each countries regulation. Real world data and evidence collected post-approval provides tremendous opportunity for more insights into the safety and effectiveness of the new product, but unfortunately that opportunity is not being fully utilised. The systems to safeguard patient safety in early and expedited access to medical products for serious diseases are disjointed and pose threat to patients. The assessment of the

safety of medical products throughout the life cycle is fragmented. Only until recently, the information obtained during the product development and pre-marketing application are often not utilised for proactive determination of post approval safety objectives and plans.[57,58] With respect to quality, products being considered for expedited programme and early access may require manufacturing at a faster timeline than for products approved using standard timelines. That was the case in the large-scale manufacturing of COVID-19 vaccine.

3.4. Model design elements

At the point of approval or conditional use authorization, the regulator lacks data on the details of commercial manufacturing, lacks long-term stability data that helps to inform shelf-life determination, lacks understanding on the comparability of the clinical batch to the commercial batch, and the ability of manufacturer to supply timely. When standards and tools for testing and stability data are not being readily available, it impacts the conduct of clinical trials and can delay use of product in EUA programmes. Accelerated stability assessment and predictive modeling could be valuable in those situations as well as models that can predict tolerable temperature excursion. In the absence of real-time stability data, regulators may have to rely on accelerated stability studies and request product developer to produce additional data post-authorization of the product as well as to submit annual product quality reports. Post approval data gathered during the real-world use of the product helps to further enrich data gathered during pre-approval review and evaluation. It helps to address uncertainties and may suggest ways for more effective and safer use of the product. A system that combines pre and post approval information and integrates them into one unit for decision making is therefore a necessity. It is akin to a proactive safety surveillance system that can predict and prevent safety

issues. Such a system will provide critical information for LMICs reliance-based secondary review particularly when built on a robust regulatory information management system. The development of such a system starts with the identification of the elements of a model quality and safety system that are currently not used in the day-to-day activities of regulatory authorities. Below, we have provided examples in Table 7 to illustrate what could constitute the model systems design for the integrated analyses of quality and safety data from pre- and post-approval. The model system identifies 'design elements' (shaded gray), that will complement the existing safety and quality programmes.

Table 3.1: Model system design elements

	Safety programmes	***Model system design elements - Safety***	***Quality programmes***	***Model system design elements - Quality***
Pre-approval	Integrated Summaries of Safety and Efficacy (ISS and ISE)	Computational predictive drug safety	Stability summary and conclusions	Predictive stability modeling
	Development safety update reports	Quantitative Benefit Risk Assessments	Characterization of impurities	In Silico models for predicting impurities
Post-approval	Passive reporting – FAERS, VAERS	Drug Disease interaction models	Product quality complaints handling	Active surveillance for product complaints handling programmes
	Active surveillance, Sentinel surveillance, Exposure Registries, Phase IV clinical trial, PASS, PAS	Use of RWD/RWE for safety and effectiveness regulatory decision-making	Annual product quality report	Post-approval stability protocol and commitment
	PSURs and Annual Reports, PMR/PMC	Pre-authorization safety benchmarked to treatment outcomes	Post approval surveillance inspections programme	Post approval bioequivalence studies
	Vaccines safety surveillance, VSD, Biologics safety surveillance, BEST	Adverse events register that combines clinical trials events to those seen during post approval use.	Drug quality reporting system	Product quality events register that combines clinical trials events to those seen during post approval use.

Key: **FAERS** - FDA Adverse Event Reporting System, **VAERS** - CDC Vaccine Adverse Event Reporting System, **PASS** – Post authorization safety studies e.g., EMA ENCePP,[59] **PAS** - FDA Post approval studies,[60] **PSURs** – Periodic safety update reports, **PMR/PMC** – Post marketing requirement/Post marketing commitment,[61] **VSD** – Vaccine Safety Datalink, **BEST** - Biologics Effectiveness and Safety Initiative,[62] **RWD/RWE** – Real world data/Real world evidence.

Below, we present in a tabular format, case studies from 3 small molecules - Ibrutinib (BTK inhibitor), Remdesivir (COVID-19 viral RNA inhibitor), and Rifapentine (antiTb); 2 monoclonal

antibodies – Adalimumab (rheumatoid arthritis) and Ibalizumab (MDR HIV-1 infection); and a vaccine - Ervebo (ebola). For each of the products, we identify safety and quality concerns pre-approval, and then list the current post-approval issues. We hypothesise that a greater knowledge of preapproval safety issues encountered during the review of the product and their anticipation can enable safer use of the product and maximise the benefit risk profile. Each of the examples below can be further developed into a case study for how an integrated and proactive safety surveillance system can facilitate the prediction and prevention of adverse events. Since 1960, nearly 200 drugs have been withdrawn from the market. The adverse events that resulted in the withdrawal were in most cases seen or suspected during the pre-approval period but was not fully described. The occurrence of those events in early clinical use was also not picked up due to weak post approval systems. The model as described can help to identify sentinel issue for closer observation and recording. When such system that consolidates relevant data in one place is in operation, it may help to quicken the regulatory decision to allow products into the market early.

Data for Table 8 below was obtained through the review of several databases including public assessment reports from FDA drug approval package, EMA and TGA public assessment reports, clinical trial registries like Clinicaltrrials.gov, drug safety databases like FAERS and European database of suspected adverse drug reaction reports, and drug information databases like DrugBank and PubChem.

Table 3.2: Analysis of approval decision, safety, and quality issues for select drugs

Product	First Regulatory Approval	Type of approval Programme	Mode of Action and (Indications)	Safety concerns		Quality concerns	
				Pre-approval	Post-approval	Pre-approval	Post-approval
Ibrutinib	FDA approved November 2013, EMA Oct 2014	Early access, Expedited, Accelerated approval for Mantle cell lymphoma (MCL)	Potent irreversible BTK inhibitor for B cell malignancies. (MCL, CLL/SLL with 17p deletion, Waldenström's macroglobulinemia (WM), Marginal zone lymphoma (MZL) Chronic graft versus host disease (cGVHD) after failure of one or more lines of systemic therapy)	Neutropenia, pneumonia, thrombocytopenia, fatigue, diarrhea, anemia, musculoskeletal pain, lymphocytosis, and high blood pressure (MCL and MZL confirmatory trial required)	Thrombocytopenia, diarrhea, fatigue, musculoskeletal pain, neutropenia, rash, anemia, and bruising; Ongoing monitoring for cardiac, infectious, bleeding and secondary malignancies. Active pharmacovigilance plan includes cardiac arrhythmias and hepatotoxicity.	Solubility 0.003 mg/ml almost insoluble in water; No PMC and PMRC	Enhance bioavailability and drug release profile for improved antitumor activity
Remdesivir	FDA approved October 22, 2020, EMA conditional marketing authorization July 3, 2020	EUA, early access (EAP)	Broad spectrum antiviral activity against RNA viruses, COVID-19 viral RNA inhibitor	Uncertainties - use in pediatrics, pregnancy, renal or hepatic impairment, optimal duration of treatment. Required PMR and PMC.	Safety signal for acute Kidney injury;	None	Nasal formulation
Rifapentine	FDA approved 1998 for active Tb in combination with one or more antiTb drugs	Accelerated approval, Priority review, Regular approval pathway	AntiTb that inhibits DNA-dependent RNA polymerase, indicated for active Tb in combination with other drugs and latent Tb with isoniazid	Elevation of liver enzymes	Nitrosamine impurities (1-cyclopentyl-4-nitrosopiperazine, CPNP).	None	Manufacturers to report if acceptable intake limit is above 0.1PPM for CPNP
Adalimumab	FDA approved December 31, 2002, EMA September 8, 2003	Accelerated approval, Priority review,	Monoclonal antibody TNF blocker for rheumatoid arthritis and 9 other immune mediated diseases	Fungal infections, malignancy	Case report of progressive multifocal leukoencephalopathy	Stability	Shelf-life stability studies
Ibalizumab	FDA approved March 6, 2018; EMA September 26, 2019	Fast track, Priority review, Breakthrough therapy, orphan drug	Monoclonal antibody for MDR HIV-1 infection	HIV-associated immune reconstitution inflammatory syndrome	Back pain, seizures, rash, hepatitis B reactivation	Drug product stability	Bulk drug substance container closure system, shipping study
Ervebo	EMA 11th November 2019; WHO PQ 12th November 2019; FDA 19th December 2019	Priority Review, Tropical Disease Priority Review Voucher, and Breakthrough Therapy designation.	Vaccine for active immunization against Ebola virus Disease	Safety and immunogenicity in Pediatrics 12 months to 17 years.	Routine pharmacovigilance for data on arthritis and safety and reduced efficacy in immunocompromised hosts	Final stability study results;	Storage condition - 70±10°C, post-licensure stability data

The ISS provides overall analysis of adverse events from clinical studies. Often the percent of occurrence of those events are listed. However, in post approval use, the incidence and frequency of occurrence of some of the noted adverse events are not available. In Table 9, we reviewed the FDA Adverse Events Reporting System (FAERS) Public Dashboard[63] for data on the select products in our case studies from 2017 till 06/30/2020 (except for Remdesivir 2020 data and Ervebo 2019 data). These are reported cases without confirmation that the drugs caused the events.

Table 3.3: FDA adverse events reporting system (FAERS) public dashboard

Products	***Serious cases***	***Deaths (selected reported cases)***
Ibrutinib	19,790	3,610 (80 from fatigue, 74 drug ineffective, and 26 peripheral oedema
Remdesivir	1,025	302 (12 from multiple organ dysfunction syndrome, 40 pulmonary embolism, and 32 hypoxia)
Rifapentine	132	3 (1 hemorrhage in 2018, and 2 cases of drug induced liver injury in 2019 and 2020)
Adalimumab	111,361	6,845 (117 deaths from dyspnea, 29 Tb, 19 from Staph, and 17 from fungal infections[64]
Ibalizumab*	1	0
Ervebo (Ebola vaccine)	1	0

*Ibalizumab (Trogarzo) – cases of hepatitis B reactivation, dysphagia, and oesophageal pain has been reported in the EU.

3.5. Reforms for timely access in LMICs

COVID-19 facilitated the use of emergency use authorization in some LMICs.[65] It also helped countries acknowledge the need for reliance for timely access to medical products during health emergencies. Notwithstanding, most LMICs still lack formal processes, procedures, and tools for expedited reviews. To accomplish timely access to innovative medicines in LMICs will require the deployment of new regulatory tools. We propose that for LMICs to achieve timely access to innovative medicines, they need to create policies and regulations for expedited pathways and

emergency authorization, strengthen the regulatory review process, and consolidate quality and safety surveillance throughout the product lifecycle. Review reports from the integrated quality and safety systems described in the previous section can for the basis for secondary review of reference agencies work. When developed countries review reports are integrated, include benefit-risk evaluation, and define infrastructure for addressing data gaps, as described in the Model system design elements, it facilitates the secondary review by LMICs.

3.6. Proposed model

The framework for the model Integrated Quality and Safety Review (IQSR) system describes the bridging of disparate pre- and post-approval review systems, pooling of data on quality and safety of products from all sources to produce summarised information that facilitates early access and safeguard patient safety. We have proposed an IQSR framework that consolidates and integrates pre-approval review with the post-approval surveillance system to identify and address product critical attributes from a quality and safety perspective. The framework excludes efficacy. However, information on efficacy that impacts on the safety of the product as well as the effectiveness may be relevant and could be included in the framework as needed. From a quality perspective, the framework relied on the contents of the CTD Quality Overall Summary (QOS) and the principles for the Pharmaceutical Quality System (ICH Q10) as effective quality management system for the development and manufacture of drug substances and drug products. Regulatory agencies around the world require dossier submission in the CTD format and use QOS in the review process. Both the CTD and ICH Q10 have been implemented by mature agencies like the US FDA and EMA. For safety, the framework identified the Summary of Clinical Safety (SCS) which is contained in the CTD Module 2.7.4 and lists all clinical studies

with safety information, analysis of adverse events, summary of treatment-related serious adverse reaction, and the safety conclusions. The SCS can be used to integrate safety findings from all studies. Together with the Integrated Summaries of Safety (ISS), as is the case for US FDA, they describe the comprehensive safety profile and the risks to be included on the product label. However, what is lacking is the use of the SCS to identify potential risk of the product and plan for a robust post marketing surveillance action. That gap is addressed through the ICH guidelines E2A to E2F which cover topics from the design, planning, reporting, and evaluation of pre- and post-authorization safety data and the conduct of pharmacovigilance systems. In several publications, the author and collaborators have argued for comprehensive health product safety surveillance system throughout the product lifecycle using epidemiological methods including active surveillance and large simple studies to complement passive surveillance.[66,67,68] Such a system covers topics in safety surveillance (spontaneous reporting and adverse event notification systems, active surveillance), quality surveillance, risk management, and benefit-risk assessment. The framework denotes the Benefit-Risk Assessment as the centerpiece for the decision for the authorization of the product. Post marketing quality and safety surveillance systems that is integrated and encompassing can address all issues related to safety and quality of medical products including safety reporting systems, post approval safety studies, post approval inspections and stability commitments. Together with ongoing benefit-risk assessment and implementation of risk management plans, the framework provides the bridge for continuous evaluation of the extent to which the product meets its target profile.

3.7. Basic elements of the Framework

Given the above, the IQSR framework (Figure 6) defines the following basic elements of the pre-approval system to include the Summary of Clinical Safety, Quality Overall Summaries, and Benefit Risk Assessment. The sub-basic elements include the Integrated Summary of Safety, ICH Q10 Pharmaceutical Quality System and ICH E2A – E2F. From a product quality perspective, the QOS will enable reviewers identify risk in the manufacturing process and define mitigation strategies for both post approval commercial manufacturing and anticipated variations. When review process is well developed and reviewers are well trained, they can use the QOS to identify known and unknown product quality risks and their potential impact on the patient.

In accepting uncertainties, regulators want to be sure that there is a robust system in place going forward to uncover new information and use it to iterate the regulatory decision. The reference to the target product profile as noted in the framework enables the system to have a benchmark for the product. According to the WHO, target product profile states the intended use, target populations and other desired attributes of products, including safety and efficacy-related characteristics.[69] Specifically for quality review, the Quality Target Product Profile (QTTP) provides a prospective summary of the quality characteristics that ideally will be achieved to meet the desired quality and safe use of the product.

When these elements are well developed and combined with a robust integrated post-approval surveillance system, the opportunity for timely authorization of new products increases. This is because such a system has guarantees in place to monitor post approval how the products meet

the target profile. Also, regulatory actions can be taking promptly as the integrated post-approval surveillance programme can generate timely data on the products performance during actual use. PMS system that can provide guarantee to safeguard patients provides an impetus for timely access. When pre-approval review and post approval surveillance systems are robust, the framework posits that a new product can be approved for use timely. In the absence of such systems innovative new drugs experience delated access.

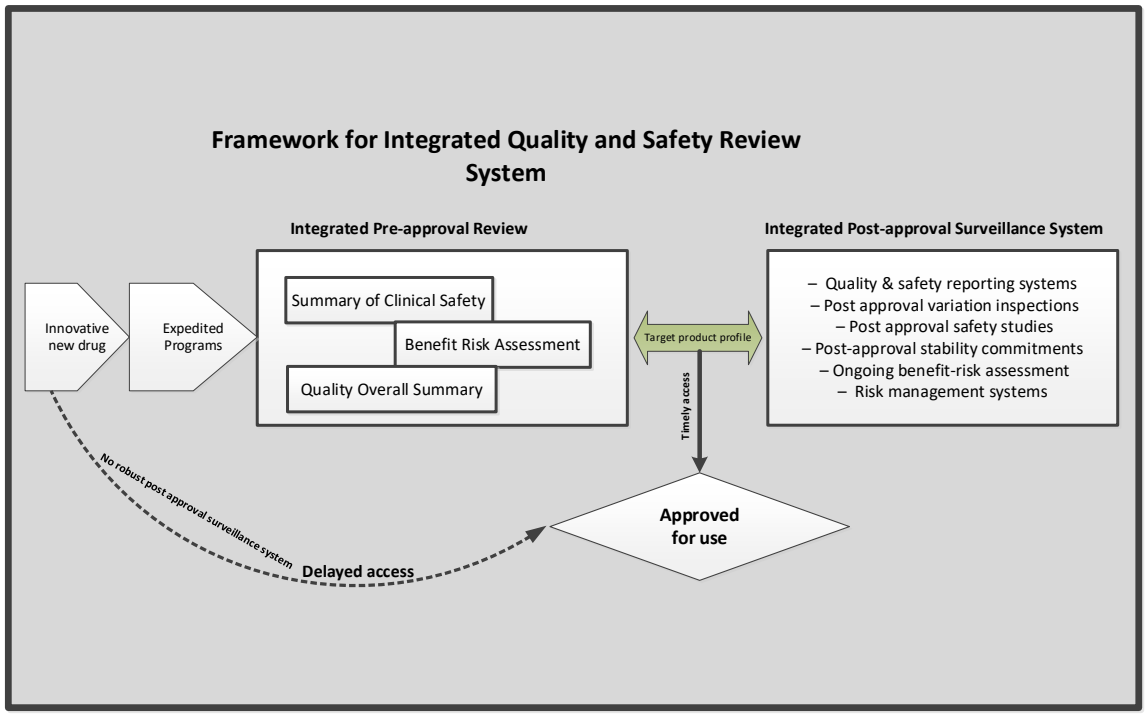


Figure 3.1: Graphic representation of the IQSR framework

3.8. Applying the Framework to LMICs

3.8.1. Integrated pre-approval review

Based on the above, we argue that developing countries can base their authorization of new products on the review of the SCS, QOS, and ISS. Such integrated summaries will be valuable

resources for the application of good review and reliance practices particularly during health emergencies. For instance, the QOS provides condensed summary on all quality-related information of the product and could substantially decrease the effort needed by developing country regulators to understand, summarise, collate, and interpret quality-related data in an application. The author and colleagues have proposed the basic elements critical for the operationalization of reliance practices.[70] Integrated summaries will be sufficient for LMICs to get to a decision to approve or not approve products. Such approval decision will also rely on the state of robustness of the post approval surveillance systems. During COVID-19 many LMICs did not review the dossier for the EUL granted by WHO. Such an approach can impinge on the statutory role of the agency. Conversely, it will be unwise to waste time in duplicative reviews during health emergency. The framework we have provided serves as ideal middle ground for timely review and approval of medical products during health emergencies as well as for the timely approval of products for life threatening conditions. The counterbalance for that expedited review is the safeguard that a robust comprehensive post-approval quality and safety surveillance system provides. We recommended leveraging new product entry to build pharmacovigilance systems.[71] This has been accomplished previously with some success using HIV/AIDS and malaria programmes to build post-market safety surveillance systems.

The IQSR can be a framework for operationalizing LMIC's reliance on mature agencies decisions to facilitate timely approval of new medicines notwithstanding the limited review competency and resources available to those countries. Adopting such a framework facilitates timely access to new drugs. Figure 7 show where the quality overall summary (QOS) and the Summary of Clinical Safety are located in the CTD.

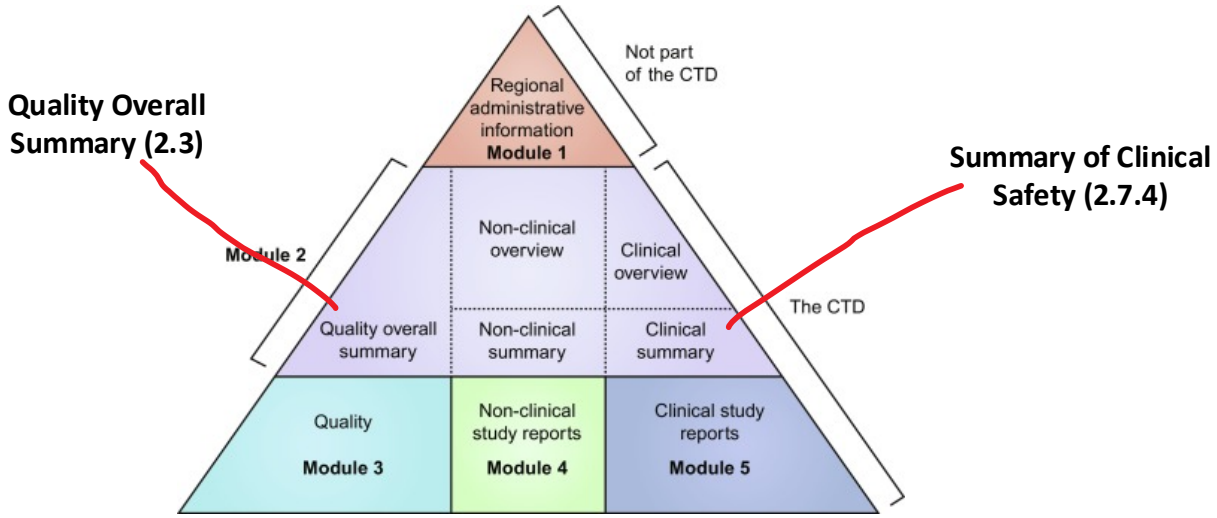


Figure 3.2: Location of the QOS and SCS in the CTD

3.8.2. IQSR checklist and tools

LMICs can use the following checklist to determine their progress towards the implementation of the IQSR. The existence of the functional systems is denoted by the items under "Tools/measures of success" which needs to be in place in that country to show that the 'Attribute' is functional and utilised for the management of pre and post approval quality and safety systems. Table 10. provides checklist of the "Measures of success" - policies, regulations, guidelines/guidance, and procedures that are required to exist and in use in the country's regulatory system. While the other measures are validated benchmarking tools like the requirement for countries to attain the WHO Global Benchmarking Tool (GBT) Maturity Level 3 in the Vigilance function or category 4 of the pharmacovigilance system when measured using the Indicator-based Pharmacovigilance Assessment Tool (IPAT) developed by this author.

Table 7: Checklist for measuring successful implementation of IQSR

Attribute	***Example***	***Tools/measures of success***
Expedited programmes	Accelerated approval Breakthrough therapy designation Fast track designation Priority Review	• Early access policies, regulations, and guidelines • Reliance regulations, reliance guidelines
Pre-approval		
Safety	Summary of Clinical Safety (SCS)	• Reviewers' guidance
	Integrated Summaries of Safety (ISS)	• Reviewers' guidance
Benefit Risk review	Benefit Risk Assessments	• Benefit risk assessment framework
Quality	Quality Overall Summary (QOS)	• CTD QOS, Reviewers' guidance
	GMP requirements, ICH Q10	• Pharmaceutical quality system regulation and guidance
Post-approval		
Quality and safety reporting systems	Passive and active reporting ICH E2A – E2F	• WHO Maturity Level 3 in Vigilance function or IPAT systems category 4 • Guidelines on Good Pharmacovigilance Practices
	Post approval variations	• Risk-based variation classification and management system. • Post approval change management protocols/comparability protocols
	Post approval safety studies	• Post marketing commitment regulations • Post approval safety study protocols
	Post approval stability studies	• Agency's stability guidance • Post approval stability commitments
Benefit risk evaluation	Ongoing benefit risk assessment	• Benefit risk guidance, assessment procedure • Conditional approvals
	Risk management systems	• Risk management plan guidelines • Drug safety advisory committee/Pharmacovigilance risk assessment committee

3.8.3. Reliance-based secondary review

The reliance guidelines which is part of the above checklist, should provide details for the secondary evaluation of the IQSR from stringent agencies. Irrespective of how and where it is presented in the stringent agency review package, the IQSR elements of Summary of Clinical Safety, Quality Overall Summaries, and Benefit Risk Assessment should form the basis for LMICs secondary review. Equally important that the reliance guidelines differentiate data

required for submission of standard review applications compared to emergency authorization applications. Table 11 below provides an example.

Table 3.5: EUA and standard approval CMC data needs

	EUA	Standard approval
API/FPP	Characterization, composition, specification, impurities, etc., intended changes on scale-up	Complete data on drug substance and drug product manufacturing quality and specifications.
Manufacturing	Company scales up production during clinical trials	Commercial production starts after approval
Stability	Short-term stability data available	Both short-term and long-term stability data considered
Inspection	May rely on previous GMP inspection report	Remote or onsite inspection
Post authorization variations	Variations in manufacturing and storage conditions	Variation requests streamlined

Other tools that could be beneficial for LMIC regulators from a reliance perspective include guidelines for biowaiver and bioequivalence, post- approval stability studies, and product specific guidelines. FDA recommends the use of product specific guidelines by generic drug manufacturers as they provide the agency's current thinking and expectations on how to develop generic drug products that will be therapeutically equivalent to specific reference listed drugs.[72]

3.8.4. Integrated post-marketing surveillance system

From literature we had defined the elements of a comprehensive pharmacovigilance or post marketing surveillance system and proposed the value of integrated quality and safety surveillance. The proposed model integrated quality and safety review system rests on the foundation of a strengthened post marketing surveillance system. Such a systems utilises pre-approval review data to anticipate problems as well as effectively survey the market for

emerging issues with the quality and safety of the product as it is used in the population. The figure 8 below illustrates how such an integrated system can work together.

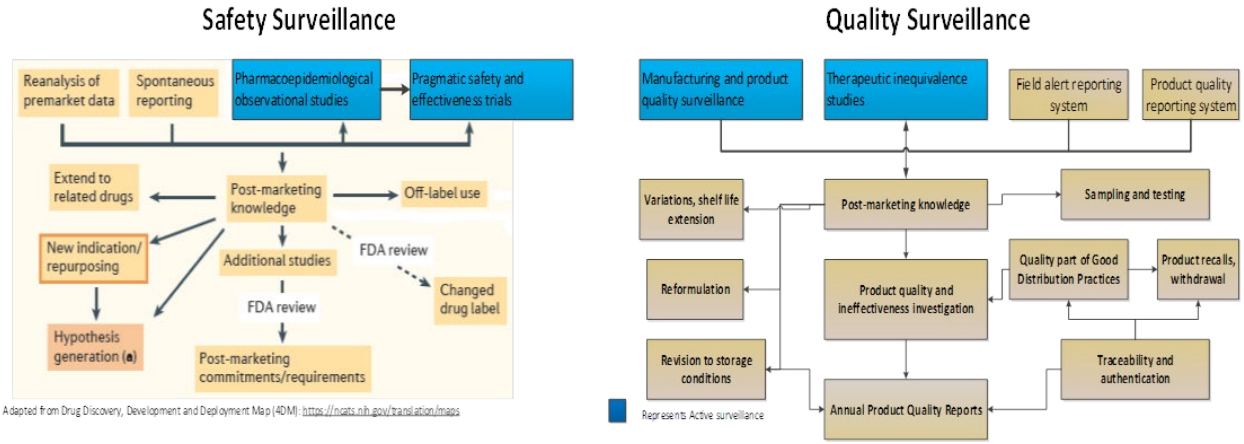


Figure 3.3: Integrated post approval quality and safety surveillance system

The integrated surveillance systems describe the interconnected nature of safety and quality surveillance. The safety surveillance part of the Figure was adapted from drug discovery, development, and deployment maps (4DM) which provides dynamic representations of the modern therapeutic development process for easy identification of inefficiencies and to integrate efforts to expedite new therapies for patients.[73] The quality surveillance equivalent was developed and juxtaposed with the 4DM. The Figure highlights the common and interconnected aspects of the areas of focus for medical products surveillance activities. Both safety and quality surveillance activities employ passive and active surveillance methodologies, from simple reporting to formal studies thereby providing opportunities for the use of similar tools and approaches. The efficiencies created is most valuable for LMICs. Passive reporting is an area very amenable for integration. Adverse events reporting form in many countries have fields for the reporting of quality issues. After reports are received, the investigation process can go in

different directions yet utilise similar toolkits. The Figure 9 below proposes an integrated model for investigating adverse events of pharmacological and physiochemical origins.

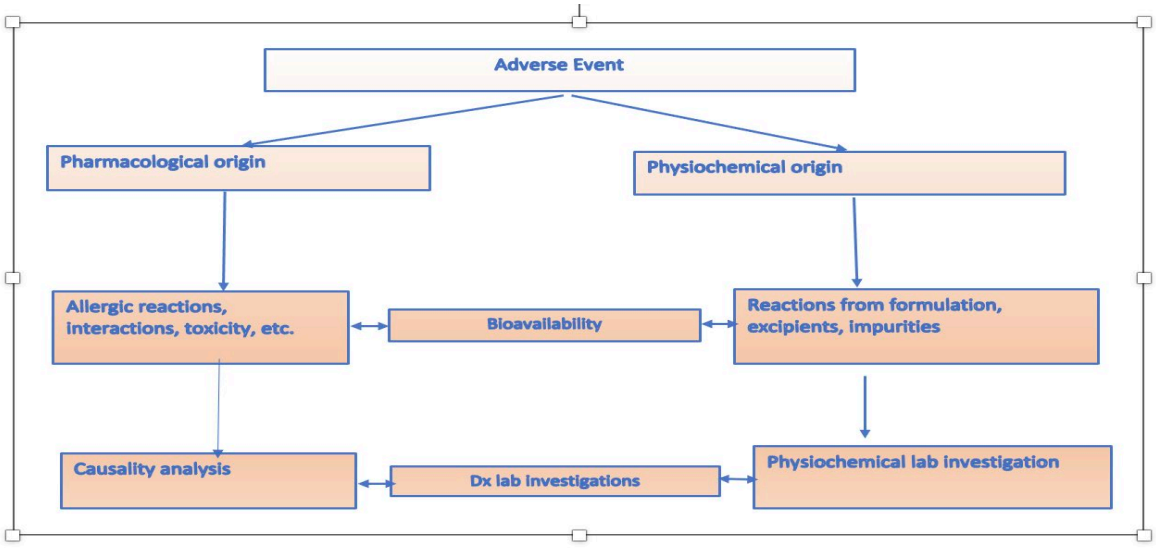


Figure 3.4: Investigating adverse events from pharmacological and physicochemical origins

An ideal post marketing surveillance system involves the reporting of adverse events and product quality complaints that trigger investigation and corrective actions. Missing out on the opportunity to use the adverse event reporting system for monitoring quality is a disservice to public health given that major medication mishaps in history were related to quality issues. Manufacturing issues related to inadequate quality control testing, assessment of impact of variations, control of quality defects, and impact of storage and distribution are important tasks for pharmacovigilance systems.[74]

3.8.5. Tools for integrated surveillance

It is important to emphasise that each of the factors listed in Table X "Measures of success" need to be formally established and routinely used for the IQSR model to serve the purpose of early access. Hence in completing the checklist LMICs must ensure great objectivity and accurate

responses to determine measures that are working and those that need strengthening. For instance, many LMICs may contend that their quality and safety reporting system, that is their pharmacovigilance system is functional. However, many of those countries lack essential elements of an ideal quality and safety reporting system. Often the factors that are missing in the system include lack of regulation and capacity for active surveillance or phase IV studies, regulatory agencies do not require or conduct pharmacovigilance inspections, lack of requirement for qualified persons; no procedure for managing product complaints to trigger investigation and corrective actions, non-harmonised requirements for post approval variations; and no formal tools for benefit risk evaluation.

Developed countries have legal requirements for mandatory industry reporting of serious adverse events. In some cases, stringent agencies make market authorization to be conditional on the industry conducting additional safety studies to address unresolved safety issues. Such studies are referred to as Phase IV studies and are used by the regulatory agency for decision-making on the safety of the product in the population or within special patient groups. Phase IV studies can be observational or randomised controlled trials (RCTs) and has specific objectives targeted at the safety concern in question. These types of studies are also regarded as active surveillance when they utilise observational epidemiological methods. Active surveillance take advantage of the wide deployment of electronic health records. Electronic health records (EHR) are currently the most important source of information to capture real-world data on safety of medicines, especially in populations that are not sufficiently included in clinical trials. Public health treatment programmes implement active surveillance including cohort event monitoring studies to enable them to understand the safety and tolerability of products used in the population.

3.8.6. Pharmacovigilance audits

pharmacovigilance audits are defined as systematic and independent process by which activities and documentations can be accessed and evaluated against agreed procedures to establish levels of compliance, competence, effectiveness, and probity. The objectives of pharmacovigilance audits may include anticipation of inspection by regulatory authority, to provide reassurance, benchmark, and identify areas of improvement. Whereas pharmacovigilance inspections is the official review of documents, facilities, conduct, pharmacovigilance systems, responsibilities, records, and any other resources that are considered by regulatory authority to be related to pharmacovigilance to verify compliance to regulations. Pharmacovigilance audits and inspections establish that systems requirements are in place for quality systems pharmacovigilance system master file (PSMF)[1]. LMICs should develop inspection systems that includes guidelines, procedures, and checklists. Specific guidelines and checklists for implementing best practices, examples include PSMF, qualified persons for pharmacovigilance (QPPV), reporting database, periodic safety update reports (PSUR), guidelines for post authorization safety studies (PASS), conduct of internal audits, and risk management plans (RMP).

3.8.7. Regulatory information management systems for enabling reliance

The necessity for regulatory information management system has been documented in most of the evaluation of work sharing and joint review activities of regulatory agencies and regional

harmonization initiatives. Information technology provides the greatest opportunity to transform, unify, and exchange standardised data to ensure safe, effective, and quality-assured medical products. However, regulatory Information management system in many LMICs is fragmented and not connected to other sectors of the health system. Figure 10 depicts an ideal link between the regulatory information management system and supply chain system for managing medical products as well as the electronic medical records for patient management. For information management system to serve regulatory agencies effectively, they should be aligned with the national eHealth policy and utilise relevant data standards.

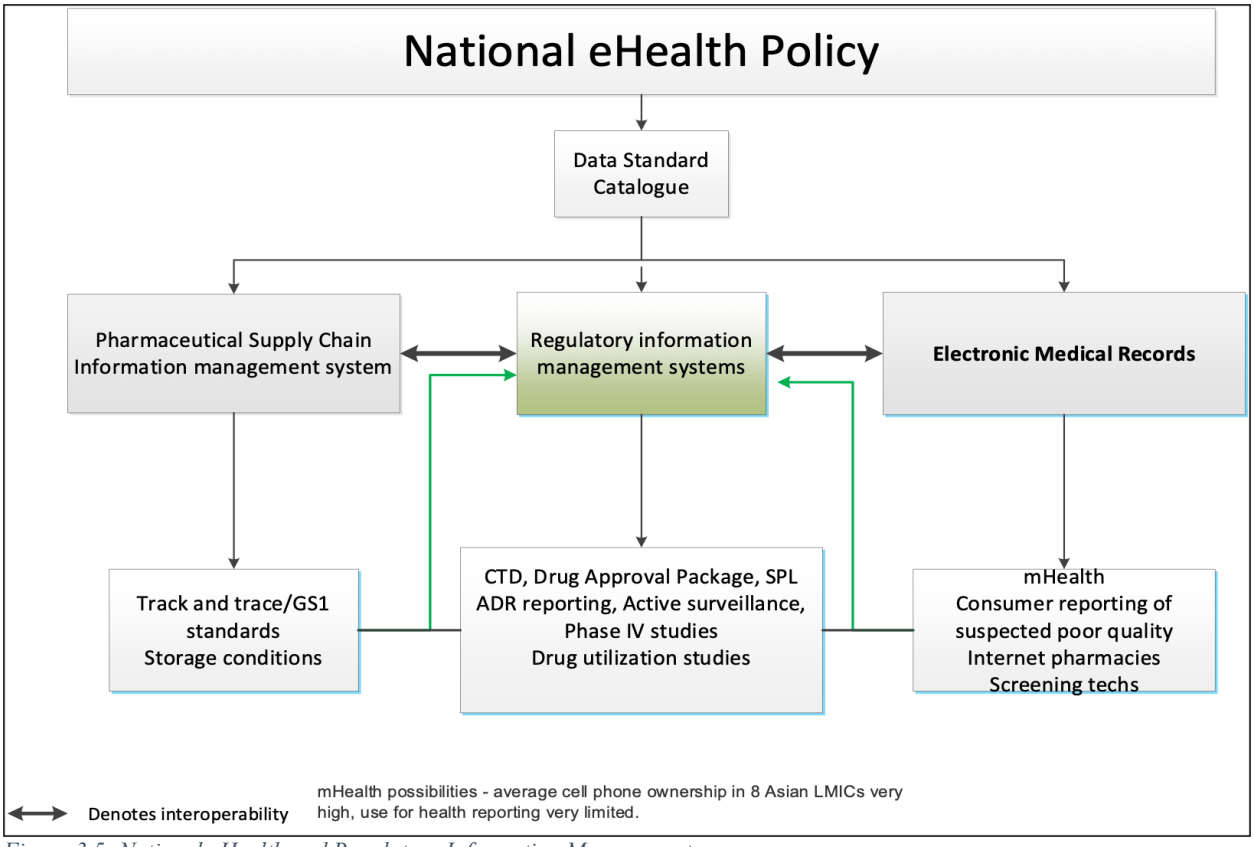


Figure 3.5: National eHealth and Regulatory Information Management

The idea regulatory information management systems should be integrated and cover all regulatory functions, it should be based on data standards, interface with existing computerised

instruments and network databases, and facilitate electronic transmission of regulatory information. The electronic regulatory submission system should have well defined submission format and structured contents. Data standards, dictionaries, and harmonised terminologies are key enabler of meaningful scientific discussions and exchange of regulatory information. The ideal information management system will enable the establishment of an automated standards-based information technology environment for the exchange, review, and management of data supporting regulatory processes throughout the product lifecycle.

Data standards facilitates regulatory reviews and communication with the applicant. It also facilitates exchange of regulatory information amongst regulatory authorities, creates enabling environment for reliance, and help set the foundation for exchange and use of regulatory information for clinical purposes and review of real-world data for regulatory actions. The common technical document format is typically in the top priority for LMICs in the adoption of data standards. Figure 11 provides a model for the progressive development of capacity for the adoption of eCTD standards in LMICs.

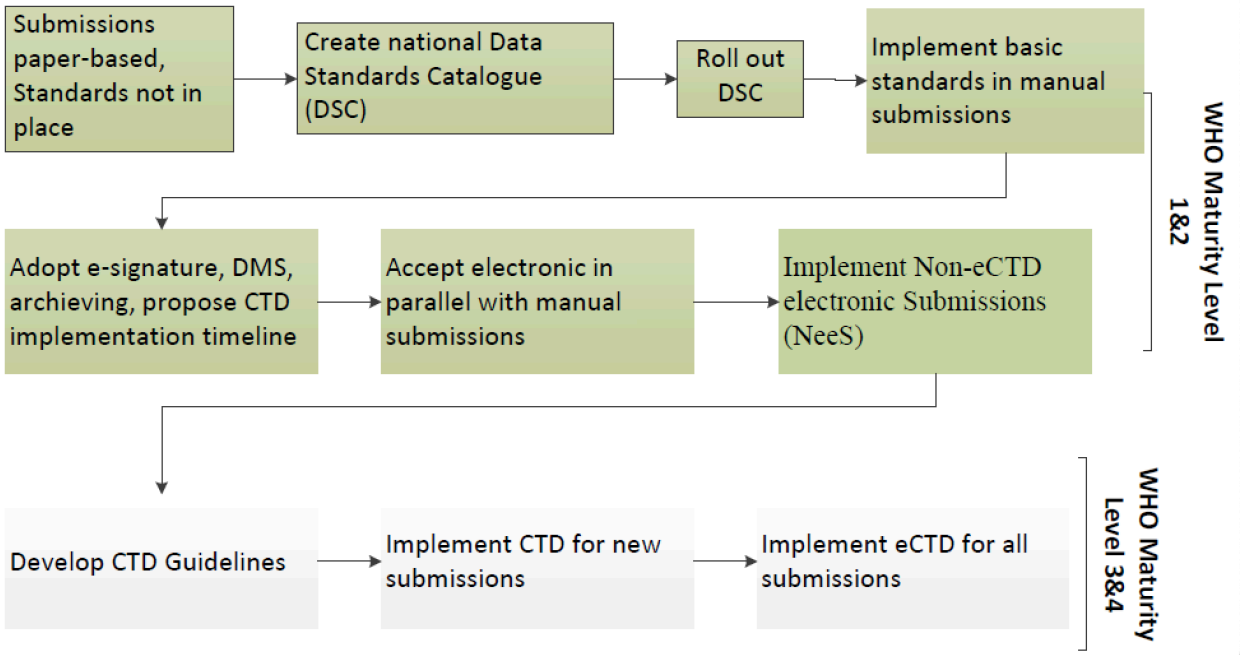


Figure 3.6: Progressive adoption of eCTD in LMICs

Electronic submission of dossiers and regulatory information using eCTD format facilitates online review. Exchange of regulatory information in eCTD is critical for reliance as the reference agencies that are typically the source of those information would have structure their information in that format. Table 12. below provides illustrative list of sources of information that LMICs can utilise for reliance purposes.

Table 3.6: Reliance information resources

Reliance resources	Available from
FDA Drug Approval Package, Orange Book, Purple Book, Drugs@FDA	https://www.accessdata.fda.gov/scripts/cder/daf/
FDA Risk Management Plan	https://www.fda.gov/animal-veterinary/animal-cloning/risk-management-plan
FDA Risk Evaluation and Mitigation Strategies (REMS)	https://www.accessdata.fda.gov/scripts/cder/rems/index.cfm
FDA Postmarketing Requirements and Commitments database	https://www.accessdata.fda.gov/scripts/cder/pmc/index.cfm
OpenFDA	https://open.fda.gov
Clinical Trials registers	https://clinicaltrials.gov
EMA Public Assessment Reports (Human medicines)	https://www.ema.europa.eu/en/medicines/what-we-publish-when/european-public-assessment-reports-background-context
EudraGMDP database	https://www.ema.europa.eu/en/human-regulatory/research-development/compliance/good-manufacturing-practice/eudragmdp-database
EMA Post Authorization Safety Studies	https://www.ema.europa.eu/en/human-regulatory/post-authorisation/pharmacovigilance/post-authorisation-safety-studies-pass-0
EMA Certification of medicinal products	https://www.ema.europa.eu/en/human-regulatory/post-authorisation/certification-medicinal-products
European Union electronic Register of Post-Authorisation Studies (EU PAS Register)	https://www.encepp.eu/encepp/studiesDatabase.jsp Full list of studies available from http://www.encepp.eu/encepp/studySearch.htm
Eudravigilance	https://www.ema.europa.eu/en/human-regulatory/research-development/pharmacovigilance/eudravigilance
EMA Periodic Safety Update Reports	https://www.ema.europa.eu/en/human-regulatory/post-authorisation/pharmacovigilance/periodic-safety-update-reports-psurs
EMA Post Authorization Safety Studies	https://www.ema.europa.eu/en/human-regulatory/post-authorisation/pharmacovigilance/post-authorisation-safety-studies-pass-0
WHO Public Assessment Reports (WHOPARs) Medicines	https://extranet.who.int/pqweb/medicines/prequalification-reports/whopars
WHO Public Inspection Reports (WHOPIRs) Medicines	https://extranet.who.int/pqweb/inspection-services/prequalification-reports/whopirs-medicines
WHO Public Inspection Reports (WHOPIRs) Vaccines	https://extranet.who.int/pqweb/inspection-services/prequalification-reports/whopirs-vaccines
WHO Public Inspection Reports (WHOPIRs) In Vitro Diagnostics	https://extranet.who.int/pqweb/inspection-services/prequalification-reports/whopirs-vitro-diagnostics
WHO Model certificate of a pharmaceutical product	https://www.who.int/teams/regulation-prequalification/regulation-and-safety/rss/certification-scheme/model-certificate-of-a-pharmaceutical-product
TGA Public Assessment Reports (AusPAR)	https://www.tga.gov.au/products/australian-register-therapeutic-goods-artg/australian-public-assessment-reports-prescription-medicines-auspars

A major shortfall of the information received from stringent agencies is that they are often extensively redacted thereby negating their value in reliance. Notwithstanding, when LMICs have a good understanding of how to source and use drug approval packages from agencies like the US FDA, they can use those resources to facilitate their own review efforts. Turner's article provides description on how to access and process FDA drug approval packages for use in

research.[75] Figure 12. shows a package that includes approval history, letters, reviews, and related documents for the Pfizer COVID-19 vaccine Comirnaty.

Source - https://www.fda.gov/vaccines-blood-biologics/comirnaty

Figure 3.7: Approval history, letters, reviews, and related documents for the Pfizer COVID-19 vaccine Comirnaty

CHAPTER 4: DISCUSSION AND CONCLUSIONS

The body of literature on safe and accelerated introduction of new medical products in low- and middle-income countries are diverse in focus and content. However, from our integrative review, common themes and concepts emerged. Those are that strong regulatory systems are critical, regulatory reliance facilitates timely access and improves efficiency, and that strong post marketing surveillance systems are required. Lessons have been learnt from the experiences of the introduction of antiretroviral drugs in the 2000s in Africa and Asia and the subsequent extensive use of new medical products for tuberculosis, malaria, SARS, H1N1, and new vaccines introduced through the national immunization programmes. More recently, the experiences from outbreak of viral diseases like Ebola, COVID-19, and Monkeypox has further highlighted the need for regulatory preparedness for health emergencies. Special measures are needed to ensure timely access wherever there are promising products that can address unmet medical needs. Well-resourced countries have therefore developed expedited regulatory pathways for such situations. The challenge that exists is that LMICs are not as prepared. They lack models for adopting best practices and implementable guidelines and procedures for early access regulatory pathways, reliance practices, models for integrated safety and quality surveillance, etc. They also lack adequate regulatory information management tools. To ensure that those best practices are implemented, practical tools should be developed particularly for the operationalization of reliance practices and post marketing surveillance systems. The model integrated Quality and Safety Review (IQSR) checklist, reliance-based review, and tools for integrated surveillance are major contributions worth consideration by LMICs. The value of the proposed integrated model and tools include –

- Serve as a resource for drug development and approval programmes. The model as described, and the elements can be translated into tools for use in late-stage drug development to aid review and approval decision-making.
- Reduces divergence and uncertainties in regulatory approval and post-marketing decision-making which result in improved patient safety.
- Enable the development of a proactive safety surveillance system that can predict and prevent safety issues.
- Facilitate regulator's ability to link strategies for pre- and post-marketing quality and safety assessment, understand their complementary roles, and opportunities for safeguarding patient safety.
- Complement existing guidance on safety during early access and emergency use.
- Identify unresolved quality and safety issues during review and highlight them for post approval surveillance.
- Support developing country regulators to identify resources and tools for implementing integrated quality and safety review systems.
- Define the complementary roles of several drug surveillance tools and facilitate understanding of their use in product lifecycle management.

Delayed access costs lives. We hope that this paper on *Regulatory Reliance and Post-Marketing Surveillance Systems for Safe and Accelerated Introduction of New Medical Products in Low- and Middle-Income Countries* will contribute to new knowledge and improve the understanding of the science and practice of new drug regulation, manufacturing quality assurance, and integrated safety and quality surveillance.

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APPENDIX 1: PAPER 1 – Comparative Analysis of Pharmacovigilance Systems in Five Asian Countries

COMPARATIVE ANALYSIS

Pharmacovigilance Systems in Five Asian Countries

USAID
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SIAPS
Systems for Improved Access to Pharmaceuticals and Services

Comparative Analysis of Pharmacovigilance Systems in Five Asian Countries

Jude Nwokike

Elisabeth Ludeman

Melissa Thumm

SEPTEMBER 2013

USAID
FROM THE AMERICAN PEOPLE

SIAPS
Systems for Improved Access to Pharmaceuticals and Services

This report is made possible through an interagency agreement between the US Food and Drug Administration (FDA) and the US Agency for International Development (USAID). The combined support enabled the Systems for Improved Access to Pharmaceuticals and Services Program to implement the study, under the terms of cooperative agreement number AID-OAA-A-11-00021. The opinion expressed in this report does not necessarily reflect the official position of the FDA, the USAID, or the US Government. The contents are the responsibility of Management Sciences for Health and do not necessarily reflect the views of USAID or the United States Government.

About SIAPS

The goal of the Systems for Improved Access to Pharmaceuticals and Services (SIAPS) Program is to assure the availability of quality pharmaceutical products and effective pharmaceutical services to achieve 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, medicine safety, post-marketing surveillance, quality control, quality assurance, medicine information, medication error, treatment failure, regulatory system

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Foreword

Bangladesh

Pharmacovigilance is not a new concept in Bangladesh. As known, it is not about the medicines but the value it places for health, welfare and safety of any patients in the healthcare systems; yet the importance and attention given to it by the authorities has not been significant over the years. We are thankful to MSH/SIAPS program for this assessment report which has provided us with important and valuable recommendations to identify areas and take initiatives. Taking from the recommendations; important measures have been taken to strengthen the Adverse Drug Reaction Monitoring (ADRM) cell and the Adverse Drug Reaction Advisory Committee (ADRAC), as a result of which now Bangladesh has launched the National Pharmacovigilance Program and the national regulatory authority, the Directorate General of Drug Administration (DGDA) has been recognized as the National Pharmacovigilance Center by the Ministry of Health and Family Welfare (MOHFW). This is just the beginning, we strive to learn from our experience and undertake corrective actions to improve. All these efforts could not be accomplished without the active technical assistance of MSH/SIAPS program and financial assistance from USAID.

Major General Md. Jahangir Hossain Mollik
Director General
23 SEP 2013
Directorate General of Drug Administration (DGDA)
Dhaka, Bangladesh

Cambodia

The practice of pharmacovigilance as a systematic method to ensure patient safety is relatively new for Cambodia in which most health professionals trained in Cambodia are not yet familiar with the subject and concept of PV. A national pharmacoviglance system was established in 2008, following establishment of the Cambodian PV Center in 2008, revision of the National Medicine Policy to include medicine safety statements in 2010, and introduction of the national PV guidelines in 2012 to improve medicine safety monitoring in Cambodia within both the public and private sectors, including formation of the Cambodian PV Center. This significant milestone represented an important first step to establishing a comprehensive PV system within the Cambodia health system to systematically monitor, record, and share adverse drug events (ADEs) and adverse drug reactions (ADRs) occurring in the country.

The assessment on pharmacovigilance system and its performance in Cambodia indicates that Cambodia has made important progress in introducing a system to achieve medicine safety monitoring and promote public health, but much works remain to be done. This assessment has provided important and valuable recommendations to address identified gaps and further enhance the existing PV system in Cambodia. As a result of the recommendation,

important step has been taken by the PV center to strengthen ADR reporting in both public and private health facilities and planning to revise regulation and guideline on medicinal product safety for pharmaceutical companies based on the recommendations provided. The experiences and lessons draw from other Asian countries participated in the assessment will further provide foundation and concepts of pharmacovigilance system that are useful for Cambodia to improve and strengthen our own system. This would not be possible without the support of USAID and FDA who sponsored the project.

Dr. Heng Bunkheit
Director of Department of Food and Drug
Ministry of Health, Cambodia

Philippines

We are thankful for this PV report entitled *Comparative Analysis of Pharmacovigilance Systems in Five Asian Countries*. As PV is an evolving discipline, in the Philippines, we strive to learn from our experience and undertake corrective measures to improve. After all, PV is not about the medicines but the value it places for the health, welfare and safety of any patients under the care of health systems. Yet, ironically, the attention and importance given to PV by most authorities is low.

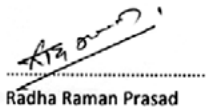
The key driver to improvement is in finding the champions willing to innovate and take initiative to evolve PV to the next level, and, finding the right mix of political support and administrative capacities to create a PV culture with technical proficiency.

KENNETH Y. HARTIGAN-GO, MD
Acting Director General
Food and Drug Administration

Nepal

In context of Nepal, we are already a member of WHO-UMC Collaborating Center for International Drug Monitoring and reporting ADR reports since 2006. Seven hospitals are participating in the system. Pharmacovigilance though a subject matter of global importance and the entire humanity, it is relatively new area even among its stakeholders so in the country. Assessment on Pharmacoviglance system and its performance has been undertaken by this department with the approval of Ministry of Health and Population. The assessment has clearly indicated the status of PV in the Asian region and the possibilities of learning from each other. Following this assessment study of PV in the country, we feel that the healthcare, medical, pharmaceuticals and other stakeholders are well sensitized. This study has created a conclusive environment for its system development in the Asian region including Nepal. I think this is the right time to strike to strengthen the PV system in the country with the solidarity of all stakeholders and the supporting agencies.

I would like to express my sincere thanks to SIAPS/MSH for supporting this study in Nepal. I take this opportunity to thank all the stakeholders involved in this study, Ms. Elisabeth Ludeman and Mr. Navin Prasad Shrestha for coordinating the study.



Radha Raman Prasad
Director General
Department of Drug Administration
Ministry of Health and Population,
Government of Nepal
July 2013

Thailand

Pharmacovigilance system in Thailand was given establishment in 1983. The national center was established under the Food and Drug Administration with ADR monitoring program as its main focus. Starting from 176 total reports by several tertiary hospitals during the first year, the number of reports is now more than 50,000 annually with pharmacists as a major reporter. Today the scope of work has been expanded to cover all health products and to involve various stakeholders in health system including consumers, market authorization holders, as well as, health facilities, i.e., drugs stores, physician clinics, private hospitals, and all levels of public hospitals, ranging from community hospitals to tertiary hospitals to academic and research hospitals.

Although the role of the national center has been well accepted, the extent of pharmacoviglance system and functions must now be extended beyond its initial responsibilities. Collaboration among stakeholders as well as supporting their demands on patient safety becomes vital challenges influencing system effectiveness. Influx of health information due to the advancing of information technology and health products from the free trade area is another challenge to the system. Enhancing system performance requires coordination and integration of all concerned parties not only nationally but also internationally.

Knowing where we are now is the initial reference to move our system forwards. Learning from certain Asian countries with comparable resources is the next advantage for us to cooperate as well as collaborate to strengthen each own pharmacovigilance system. Thanks to USAID for the initiative to assess the pharmacovigilance system in Thailand together with other Asian countries. The information and learning experience gained from the project not only benefits the countries being studied but could also provide foundation and concepts of pharmacoviglance system for others.

Dr. Boonchai Somboonsook
Secretary-General of the Food and Drug Administration
Ministry of Public Health, Thailand

Acronyms and Abbreviations

ADR	adverse drug reaction
AE	adverse event
AERS	adverse event reporting system
AHWP	Asian Harmonization Working Party
AIDS	acquired immunodeficiency syndrome
APEC	Asia Pacific Economic Collaboration
ASEAN	Association of Southeast Asian Nations
BCPNN	Bayesian confidence propagation neural network
CRO	Clinical Research Organization
DDF	Department of Drugs and Food [Cambodia]
DIC	Drug Information Center
DSUR	development safety updated report
DTC	Drug And Therapeutics Committee
EMA	European Medicines Agency
EU	European Union
FDA	US Food And Drug Administration
FDAAA	Food And Drug Administration Amendments Act
FP	family planning
Global Fund	Global Fund To Fight AIDS, Tuberculosis And Malaria
GMP	Good Manufacturing Practice
HIV	human immunodeficiency virus
HPVC	Health Product Vigilance Center (Thailand)
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
ICSR	individual case safety report
IOM	Institute of Medicine [United States]
IPAT	Indicator-Based Pharmacovigilance Assessment Tool
ISO	International Standards Organization
MAH	Marketing Authorization Holder
MedDRA	Medical Dictionary for Regulatory Activities
MSH	Management Sciences For Health
NDP	National Drug Policy

NML	National Medicines Laboratory
NMP	National Medicines Policy
NRA	National Regulatory Authority
PHP	Public Health Program
PMA	post-marketing alert
PPWG	Pharmaceutical Product Working Group
PQM	Promoting the Quality of Medicines [USP]
PRAC	Pharmacovigilance Risk Assessment Committee [EMA]
PSUR	Periodic Safety Update Report
PV	pharmacovigilance
QA	quality assurance
QC	quality control
RH	reproductive health
RHI	regional harmonization initiatives
RMP	Risk Management Plan
SOP	Standard Operating Procedure
SIAPS	Systems for Improvised Access to Pharmaceuticals and Services Program [USAID]
SMP	Safety Monitoring Program [Thailand]
SOP	standard operating procedure
SPS	Strengthening Pharmaceutical Systems Program [USAID]
SRA	Stringent Regulatory Agency
STG	standard treatment guideline
TB	tuberculosis
UNICEF	United Nations Children's Fund
USAID	US Agency For International Development
USD	US dollars
USP	United States Pharmacopeia
VAERS	Vaccine Adverse Event Reporting System
WHO	World Health Organization

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Executive Summary

Access to medicine is improving in low- and middle-income countries (LMICs), thanks to the efforts of global health initiatives and also to the commitment of national governments. Medicines and other health commodities are required to be safe, effective, and of good quality to achieve their intended purpose. However recent history records several incidences of harm from poor quality or unsafe products. The increasing influx of these products into global supply chains can diminish the significant improvements in access and compromise the success of public health programs. The primary objective of pharmaceutical regulation is to safeguard the public from unsafe medical products. Countries can achieve that by establishing a comprehensive pharmacovigilance (PV) system. In many low and middle-income countries (LMICs), PV activities are fragmented, weak, and unable to protect the public adequately. Recognizing the importance of assisting countries protect the public from unsafe and poor quality medicines, the US Agency for International Development (USAID) and the Food and Drug Administration (FDA) funded the Systems for Improved Access to Pharmaceuticals and Services (SIAPS) Program through an interagency agreement to assess PV systems' performance in selected Asian countries. The objectives of the assessment are to benchmark national systems' performance, identify replicable and successful experiences, map the contributions of donor agencies, and recommend options for enhancing PV and post-market surveillance systems' capacity and performance.

All countries assessed have national medicine laws in place that include legal provisions for medicine safety, but their PV regulatory requirements vary greatly.

Study Methods

We conducted a review of the regulatory and PV systems literature with a focus on the Asia region. A comprehensive assessment of the PV system in Bangladesh, Cambodia, Nepal, Philippines, and Thailand was conducted by teams of local consultants and data collectors and detailed report developed for each country. Using primary data from the individual country assessments, we conducted comparative analysis of the five components of the PV system including Governance and Policy, Law, and Regulation; Systems, Structure, and Stakeholder Coordination; Signal Generation and Data Management; Risk Assessment and Evaluation; and Risk Management and Communication

Current State of Pharmaceutical Market in Asia

The Asian pharmaceutical market size is estimated at 140 billion US dollars (USD), with China and Japan accounting for about 70% of the total value. Most of the market is dominated by generic medicines. Of the countries studied, Thailand has the largest pharmaceutical market size with over USD 4.4 billion and Nepal has the smallest with USD 1.4 million.

Results

Pharmacovigilance at the National Level

Governance, Policy, Law, and Regulation

Of the five Asian countries studied, Bangladesh, Philippines, Thailand have regulatory frameworks, regulatory registers and governance structures. All countries have registers for approved medical products, licensed pharmaceutical premises, and licensed pharmaceutical personnel in place. All countries assessed have national medicine laws in place that include legal provisions related to medicine safety but their PV regulatory requirements vary greatly. Cambodia and the Philippines have legal provisions mandating industry to report adverse events but only the Philippines mandates industry to conduct post-marketing surveillance of specified products based on stringent regulatory authority requirements. Generally risk assessment and evaluation and also risk management practices are not explicitly required in the countries legislations.

Although all countries have a national PV center and an adverse events form, less than half of the health facilities surveyed have the form available to them.

Systems, Structures, and Stakeholder Coordination

All countries have a national PV center. Thailand has a dedicated annual budget for PV-related activities. Cambodia and Thailand have national PV guidelines in place. Cambodia, Nepal, and Thailand have Medicines Safety Advisory Committees that meet regularly (at least once within the past year) and have documented decision-making processes, however only Thailand's Advisory Committee has policies that address conflict of interest. Although all the five countries address elements of product quality assurance within their National Regulatory Authorities (NRAs), only the Philippines has a formal quality management system in place and only Thailand has a WHO pre-qualified quality control laboratory. Cambodia, Nepal, Philippines, and Thailand are official members of the WHO International Drug Monitoring Programme. During this assessment Bangladesh initiated plans to join the WHO program.

Signal Generation and Data Management

All countries have a standardized national adverse events (AE) form. Thailand AE forms is for all health products and collect data on suspected ADRs, product quality issues, medication error, and treatment failure. Thailand and Philippines implement consumer reporting. Availability of the AE reporting forms within service delivery points was found to be limited. Only 41% of health facilities and 21% of pharmacies sampled across five countries reported existence of AE forms within their facility. Significant underreporting was observed in all countries, with the exception of Thailand.

Risk Assessment and Evaluation

Risk assessment and evaluation was identified by the assessment as the weakest component of the PV system across all the countries. Only the NRA in Thailand reported conducting active surveillance activity in the last five years.

Risk Management and Communication

Thailand and the Philippines have medicine information processes that are functioning with a minimum of one information request received and responded to per month. Nepal and Thailand regularly publish medicines safety bulletins. All countries reported use of prequalification schemes for procurement decisions related to at least some medical products. Nepal, the Philippines, and Thailand estimated the levels of unregistered medicines in their respective markets to be less than one percent, while Cambodia estimates the levels

of unregistered medicines at 30%. Bangladesh also estimates high levels of unregistered medicines within its market. All countries studied reported that medical products were both sampled and analyzed for quality in national medicines laboratories in 2011. Encouragingly, Cambodia, Philippines, and Thailand reported alerting healthcare workers and the public within three weeks of the detection of a medicine safety concern. The ASEAN post-marketing alert (PMA) mechanism for sharing information relating to defective or unsafe medicinal products seems to provide an underutilized opportunity for collaboration to safeguard the supply chain in the member countries.

Pharmacovigilance in Public Health Programs

The assessment included interviews with representatives from 19 national HIV and AIDS, malaria, and TB immunization programs. Among PHPs assessed, 84% reported having a policy document that mentions PV and product quality assurance. Thirty seven percent were found to have a PV point of contact assigned responsibility for monitoring medicine safety within the program. Forty two percent reported keeping a log or database of PV data collected. For all countries adverse events reporting in the public health programs (PHPs) were low and uncoordinated with the national PV system. However, the national immunization program in Bangladesh reported collecting 1,100 adverse events reports following immunization in 2011 against a patient population of 3.7 million children vaccinated. A review of Global Fund to Fight AIDS, Tuberculosis and Malaria (Global Fund) grants for round 10 shows that Cambodia and Thailand included activities or interventions related to PV in their disease specific or health systems strengthening grants. Though disease surveillance activities are in place, active safety surveillance of medical products was very limited. Other components of the PV system including risk management and communication were minimal or lacking in all five countries.

For all countries, adverse events reporting in the PHPs was low and uncoordinated with the national PV system.

Pharmacovigilance at the Service Delivery Level

A total of 86 health facilities and 62 pharmacies were surveyed across the five countries. Only a quarter of the private or community pharmacies surveyed are aware that a national PV center exists in their country. Nearly half of the community pharmacies were aware of a national policy for monitoring and reporting adverse events. However, less than half of the health facilities surveyed have adverse events reporting form available. In Nepal, Thailand, and the Philippines a quarter of facilities surveyed reported that they had received medicines safety bulletins from their national PV centers.

Pharmacovigilance in the Pharmaceutical Industry

The assessment included five clinical research organizations (CROs), seven medical device companies, and 38 pharmaceutical companies, including multinational innovator, multinational generic and local innovator and generic manufacturers. Sixty-six percent of pharmaceutical companies, 57% of medical device companies, and 80% of CROs have a PV or medicine safety unit. The pharmaceutical industry PV performance is below expectation in an already weak regulatory environment. More than one third of pharmaceuticals, biotechnology and medical device companies do not submit adverse events reports in national standard forms or in E2B compliant formats. Among the companies included in the assessment, it was found that less than half of pharmaceutical companies (42%) and just more than half of medical device companies (57%) collected spontaneous adverse events reports, put them in a database, and transmitted to the local NRA. In 2011, causality was determined for only a third of the reports. Risk assessment and evaluation and risk management practices are not being implemented presumably since they are not explicitly required in country laws.

Pharmacovigilance at the Civil Society Level

Ten consumer groups, 22 professional organizations, and 21 medical and pharmacy academic institutions were surveyed in this group, members from three (30%) and eight (36%) respectively serve on the national safety advisory committee in Bangladesh, Cambodia, and the Philippines. Few respondents (20% in consumer group and 27% in professional associations) reported that consumers and members of their association were aware of the existence of a national policy for monitoring and reporting adverse events. About half of the professional associations reported having a member who is aware of the national PV center while only 20% of consumer groups reported that this knowledge exists among patients and consumers.

The pharmaceutical industry's PV performance is below expectation in an already weak regulatory environment.

Capacity and Performance of PV Systems in the Studied Countries

Countries were grouped based on the systems classification; of the five countries, Bangladesh and Nepal are in group 1 with minimal organizational structures and capacity for PV, Cambodia is in group 2 with policy and legal frameworks, basic organizational structures including guidelines, SOPs, and a safety advisory committee. Philippines is in group 3 which are countries that have capacity to collect and evaluate safety data on the basis of legal and organizational structure and Thailand is in group 4 for countries that have performing PV systems to detect, evaluate, and prevent medicine safety issues.

Selected Recommendations and Options for Enhancing PV Systems

National Level

Strengthen Regulatory Policies and Framework

Based on the level of development of regulatory and PV systems, countries can develop new regulatory policies and frameworks to ensure that regulations are effective and in the public interest or revise and consolidate the existing ones. Alternatively they can review sections of existing legislation that deal with aspects of medicines quality, safety, and post-marketing surveillance, ensure that legislations are congruent with other relevant local laws.

Ensure Convergent Regional and International Regulations

Options for countries for developing regulations convergent within the Asian region—map differences and provide guidance on regulations that the country considers as equivalent to regional and international standards or develop guidance to industry to explicitly document regional equivalencies or countries can completely revise their PV legislation to make them convergent with that of stringent regulatory authorities and also consistent with the regional harmonization guidelines within the Asia Pacific region and other international guidelines.

Improve Information Sharing and Participation in Regional Harmonization Initiatives

Asian regional harmonization initiatives should consider strengthening collaboration and information sharing about product safety and security of the supply chain by ensuring active participation of the all countries in the region.

Reform Organizational Structure to Achieve Integrated Safety Surveillance

Countries can create a single vigilance center that can facilitate the integration of adverse events reporting for all health products or consolidate post-marketing surveillance department that brings together PV, product quality surveillance, routine inspections, and control of advert and promotion into a single unit.

Improve Funding for PV

Countries should consider reviewing resource allocation for regulatory activities and determine an evidence-based approach for allocating adequate resources for post-marketing surveillance activities. Alternatively new sources of funding can be explored including donor funding, user fees and percentage of sales turnover.

Strengthen Spontaneous Reporting

Countries should adopt international reporting standards and explore opportunities for the use of information technologies for improving adverse events reporting. Countries should also explore opportunities to consolidate or streamline reporting forms for all health products (drugs, biologics, vaccines, and medical devices) and for reporting on all safety and quality issues.

Confront Falsified and Substandard Medicines

Donors and technical assistance providers should consolidate their support to expand WHO and regional harmonization initiatives rapid alert system as major instruments for addressing the issues of falsified and substandard products. Countries should be supported to improve their regulatory systems and enforcement capabilities for addressing fake products.

Public Health Programs Level

Strengthen Routine Collection of Information on the Tolerability of Medicines

Countries should encourage routine documentation of the reasons for treatment switches in the patient's case file which will provide data for studying the frequency of switches and tolerability treatment regimens.

Develop Sustainable Risk Assessment and Evaluation Activities

Countries should explore opportunities for establishing sentinel sites for active surveillance by working closely with ART, TB, malaria, vaccines, and mass drug administration programs.

Include PV in Donation Programs

Donors who donate medicines and health technologies should require their programs to conduct spontaneous reporting, active surveillance, and risk management, particularly for newer medicines, vaccines, and medical devices.

Health Facilities and Services Delivery Level

Inform Health Workers on the Value of PV

Countries should expand training on PV to enable health workers appreciate the contributions of adverse events reporting in safeguarding patients and improving treatment outcomes.

Streamline Adverse Events Reporting

The current adverse events reporting system is burdensome for the busy clinicians and the system does not motivate the reporter. Countries should consult with stakeholders in open forums to discuss on the best approaches for improving the roles of health workers, the health facilities, private pharmacies, consumers, and pharmaceutical industry in adverse events reporting.

Medicine safety systems within and across national borders need to be strengthened.

Pharmaceutical Industry

Strengthen Industry Commitment to PV

The pharmaceutical industry is not doing enough to support PV activities in the countries studied. In the absence of adequate legislation and enforcement in developing countries, due diligence and product stewardship should drive the industry to meet safety monitoring requirements locally as they do in better regulated markets.

Collaborate on Device Regulation and Vigilance

Medical device industry should collaborate with national regulatory authorities and regional harmonization initiatives to develop device vigilance systems.

Civil Societies

Improve the Visibility of PV as a Public Health Priority

Civil society's active involvement in PV systems depends not only on awareness of the legal mandate, structures and systems for PV in the country but also on the society's understanding of its importance and how drug safety affects their members. Civil societies should motivate their members interest in PV as part of its role as the watchdog for good governance in the pharmaceutical sector.

Conclusion

Strengthening the regulatory and PV system of the studied countries is a global imperative for preventing harm and improving outcomes in treatment and prevention programs and for protecting the global supply chain from falsified and substandard medicines. There is a strong and urgent need to strengthen medicine safety systems both within and across national borders of countries in the Asia region. Developing and developed countries are both suppliers and recipients within an increasingly complex global medical product supply chain. Public health programs, global health initiatives, and indeed, entire health systems rely on safe, effective, and good quality medicines. However, fully functional PV and regulatory systems are not yet in place in many LMICs. This report calls for concerted efforts to build regional and global coalition and leverage ongoing efforts in a consolidated manner to improve the systems and capacities required to assure patient safety and to improve health outcomes in Asia.

Introduction

Background on Asian Pharmaceutical Market

Asia has an estimated 4.2 billion inhabitants, representing nearly 60% of the world's total population. China and India together account for 37% of the world population and 61% of Asian population, with the remaining being dispersed among the other 46 countries that make up the continent. Southern Asia and Southeast Asia constitute about 54% of the Asia population. The 5 countries in this report belong to the two regions and have a total population of 359.7 million, about 16% of the regions' population. Asia region is characterized by vast discrepancies in wealth and development. The gross domestic product (GDP) per capita of the continent's poorest country, Nepal, is equivalent to just 2% of Singapore's, the continent's wealthiest country. In the Human Development Index ratings, four Asian countries are among the top 25 countries with "very high human development" while five others are among those with "low human development." The pharmaceutical market profiles of the five countries included in the present assessment—Bangladesh, Cambodia, Nepal, the Philippines and Thailand—reflect some of the same diversity seen throughout the region (table 1). The populations range from 150.5 million in Bangladesh to just 14.3 million in Cambodia. All of them are considered low- or middle-income countries with Nepal on the low end with a GDP per capita of 619 US dollars (USD) as compared to Thailand, an upper middle income country, with a GDP per capita of USD 4,972.

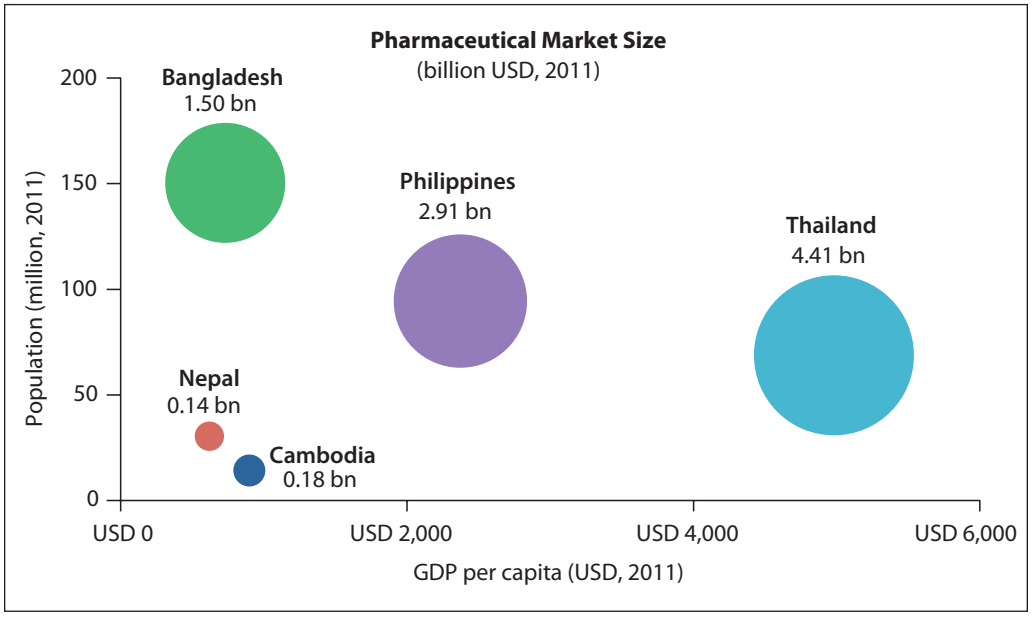
Figure 1. Map of Asian Countries Included in Assessment

Table 1. Summary of Pharmaceutical Market in Studied Countries

Pharmaceutical market	Bangladesh	Cambodia	Nepal	Philippines	Thailand
Population (million; 2012)*	154.7	14.9	27.5	96.7	66.8
Gross domestic product per capita (USD)*	744	900	619	2,370	4,972
Market size: pharmaceuticals (USD, 2011)†	1.5 billion	178 million	Not available	2.91 billion	4 billion
Market size: medical devices (USD, 2011)†	174 million	27 million	Not available	297 million	1.11 billion
Number of medicines registered (2011)‡	32,245	10,000 (est.)	10,316	32,069	24,087
Number of medical devices registered (2011)	Not available				2410
Total expenditure on healthcare per capita (USD, 2010)§	19	29	29	77	179
Total pharmaceutical expenditure (TPE) per capita (USD, 2006)§	5.7	9.3	4.7	21.3	70
Public expenditure on pharmaceuticals per capita (USD, 2006)§	Not available	1.3	0.9	2.1	42.5
TPE as % total expenditure on healthcare per capita (2006)§	31	21	16	28	39
Health workforce per 10,000 population‖	0.21	10.8	16.1	10.2 physicians; 53.1 nurses/ midwives; 5.4 licensed pharmacists; 11.0 pharmaceutical personnel	3 physicians; 15.2 nurses/ midwives; 1.2 pharmaceutical personnel
Financing mechanisms for pharmaceuticals§	Public (11%), Private/Other (89%)	Public (14%), Private/ Other (86%)	Public (19%); Private/Other (81%)	Public (10%), Public/ Other (90%)	Public (88%), Private/Other (12%)

* World Bank Database: http://data.worldbank.org
† Business Monitor International: Bangladesh Q1 2013 (January 1, 2013), Cambodia Q4 2012 (October 1, 2012), Philippines Q1 2013 (January 1, 2013), Thailand Q1 2013 (January 1, 2013)
‡ Directorate General of Drug Administration (Bangladesh); Cambodia MOH DDF; WHO Nepal Pharmaceutical Market (http://apps.who.int/medicinedocs/en/m/abstract/Js19096en/); Directorate General of Drug Administration (Philippines); Thai FDA, 2011;
§ Estimates derived from several WHO sources including World Medicines Situation 2011 Annex, Pharmaceutical Sector Country Profiles Data and Reports, and National Health Accounts.
‖ WHO World Health Statistics 2012

Figure 2. Pharmaceutical Market Size of Asian Countries in Assessment



The Asian pharmaceutical market size is estimated at USD 140 billion, with China and Japan accounting for about 70 percent of the total value. Most of the market is dominated by generic medicines, although Japan and Singapore have a strong patented medicine market, especially for chronic diseases. Of the countries studied, Thailand has the largest pharmaceutical market size with over USD 4.4 billion and Nepal has the smallest with USD 1.4 million. Vietnam has the fastest growing healthcare market in Southeast Asia, with more than 200 pharmaceutical companies registered that produce mostly generic medicines.1 In the Philippines, foreign drug companies account for 70 percent of the market. There are over 3500 pharmaceutical brands marketed with the main therapeutic categories including anti-infectives, antihypertensives, and analgesics.[1]

Regarding burden of disease, the Southeast Asian region accounts for about 30% of the global disease burden (Dhillon et al. 2012). In Asia and the Pacific, an estimated 6.1 million people were living with the human immunodeficiency virus (HIV) in 2009, 5.9 million of whom were adults. Although the epidemic is decreasing overall, the burden of HIV and AIDS remains high, especially in some countries like Thailand, which has the highest rates of HIV and AIDS in the Asia region (UNAIDS 2010). Tuberculosis (TB) also represents a major health problem in Asia. In fact, 60% of incident cases of TB globally in 2011 were in Asia (WHO 2012a). Although the incidence of malaria has decreased in the region over the last decade, there are still an estimated 30 million cases in Asia each year. This burden is further exasperated by increasing evidence in Southeast Asia of emerging resistance to artemisinin-based combination therapy, the recommended treatment for malaria (WHO 2012b).

Definition and Scope of Pharmacovigilance

The World Health Organization (WHO) defines PV as the science and activities relating to the detection, assessment, understanding, and prevention of adverse effects or any other possible drug-related problems (WHO 2004). PV systems should include all entities and

1 http://www.pacificbridgemedical.com/business-services/pharmaceutical-consulting/

resources that protect the public from medicines-related harm (adverse reactions, poor product quality, medication errors, and therapeutic ineffectiveness), whether in personal healthcare or public health services. The PV system safeguards the public through efficient and timely identification, collection, and assessment of medicine-related adverse events and by communicating risks and benefits to support decision making about medicines at various levels of the healthcare system. A comprehensive systems approach addresses the need for both active and passive approaches to identify medicines-related problems, effective mechanisms to communicate medicine safety information to healthcare professionals and the public, collaboration among a wide range of partners and organizations, and incorporation of PV activities at all levels of the health system (Strengthening Pharmaceutical Systems (SPS) Program 2011). Several multinational organizations and initiatives work on defining the standards of PV.

The WHO has provided technical and normative leadership on PV since the development of the first voluntary notification scheme in 1961. The WHO International Drug Monitoring program has more than 111 countries participating as of January 2013. WHO has defined norms and guidelines for PV and allow for information sharing among the participating countries. Another WHO PV-related activity is the work of the Council for International Organizations of Medical Sciences (CIOMS) which was established jointly by WHO and UNESCO in 1949. Starting with the publication of the Suspect Adverse Reaction Report Form (CIOMS Form I) by the CIOMS working group II, other CIOMS publications have greatly shaped the direction of PV.[2] CIOMS publications have also greatly influenced the development of International Conference on Harmonization of Technical requirements for Registration of Pharmaceuticals for Human Use (ICH) E2A-E2F guidelines in drug safety. The standards for the electronic transmission of regulatory information regarding the individual case safety report (ICSR) has been changing over the last decade. The ICH adopted the E2B(R2) in February 2001 and since 2005 the E2B(R3) is being developed as the proposed harmonized international standards for health products safety reporting. This effort led by International Standards Organization (ISO) and Health Level Seven International (HL7) has led to the development of ISO/HL7 27953-1:2011. These ICH guidelines have facilitated the adoption of harmonized standards for PV activities.

In 1999, the ICH formed the Global Cooperation Group (GCG) to promote a mutual understanding of regional harmonization initiatives to harmonization process related to ICH guidelines regionally and globally, and to facilitate the capacity of drug regulatory authorities and industry to use them. Part of the result of the work of the GCG and the open availability of harmonized guidelines from the ICH, is the increasing adaptation of ICH standards in non-ICH countries.

With regards to medical devices vigilance, the Global Harmonization Task Force (GHTF) use to set the standards for their regulation. However, the GHTF activities have been taken over by the International Medical Device Regulators Forum (IMDRF) formed in 2011. The GHTF SG2 guidelines on Medical Devices Post Market Surveillance: Global Guidance for Adverse Event Reporting for Medical Devices provides harmonized standards for monitoring safety of medical devices (European Commission 2013). The EU guidelines on reporting adverse

2 Including CIOMS II on periodic safety update reports (PSUR), CIOMS III core data sheets, CIOMS IV on benefit-risk assessments, CIOMS V on Current Challenges in Pharmacovigilance: Pragmatic Approaches, CIOMS VI on clinical trials safety data, CIOMS VII on development safety update reports (DSUR), and CIOMS VIII on Practical Aspects of Signal Detection in Pharmacovigilance.

events related to medical devices is set out by MEDDEV 2.12/1 rev.8 (European Commission 2013) and by MEDDEV 2.12/2 rev.2 (European Commission 2012) which promote a standard approach consistent with the SG2 guidelines. Table 2 below summarizes the functions of these various initiatives.

Table 2. Functions of Select PV Initiatives

Organization	Initiative/Program	Function
WHO	International drug monitoring program	▪ Defines norms and guidelines for PV and facilitates information sharing among participating countries ▪ WHO Collaborating Centre for International Drug Monitoring runs the international monitoring program
CIOMS	Safety requirements for the use of drugs	▪ Through 8 Working Groups CIOMS has defined technical standards in drug safety
ICH, GCG	Pharmaceutical standards harmonization and guidelines development	▪ Facilitates harmonization process related to ICH guidelines regionally and globally
GHTF, IMDRF	International medical device regulatory harmonization and convergence	▪ Harmonizes the standards for monitoring the safety of medical devices

Study Objectives and Methods

Objectives

This study contributes to filling the gap in the understanding of the PV systems capacity in Bangladesh, Cambodia, Nepal, the Philippines and Thailand by addressing the following objectives—

Assess and analyze systems capacity and performances for PV and post-marketing 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 performances

Study Methods

The following methods were used to conduct the study—

1. Review of regulatory and PV systems
2. Individual country assessments
3. Comparative analysis of results from individual country studies

1. Review of Regulatory and PV Systems

We conducted a detailed review of regulatory and PV systems literature using key search terms in drug regulation and PV. We also reviewed databases from WHO, ICH, and searched commercial regulatory intelligence databases from Thomson Reuters. We searched the websites of regional harmonization initiatives, and also reviewed websites of regulatory authorities from the United States, Europe, Japan, Australia, Canada, China, South Korea, Saudi Arabia, India, Malaysia, Singapore, and Indonesia, and all the five countries studied.

2. Individual Country Assessments

Local consultants led individual country assessments using the indicator-based PV assessment tool (IPAT) developed by the USAID-funded Strengthening Pharmaceutical Systems (SPS) Program. The IPAT allows for the systematic and longitudinal monitoring of country capacity and performance in ensuring the safety and effectiveness of health products registered in a country (Strengthening Pharmaceutical Systems (SPS) Program 2009a). The local consultants were identified by the national regulatory authorities. Working with a team of data collectors, the local consultants conducted in depth data collection in each country between April and November 2012.

Selection of Study Countries

Not much is known about PV systems in South Asia and Southeast Asian countries and there is scant literature that compares countries' PV systems from a regional perspective. This study included countries from the two regions. The countries were selected based on several factors including economic status, the existence of global and regional public health initiatives (i.e., the President's Emergency Plan for AIDS Relief [PEPFAR], the President's Malaria Initiative [PMI], and the Global Fund), manufacturing capacity, the size of the pharmaceutical industry, and the existence of a National Drug Regulatory authority. Other selection criteria included the existence of WHO prequalified quality control (QC) laboratories, WHO international drug monitoring program membership, participation in initiatives to combat counterfeit and substandard products, and Management Sciences for Health presence. Using these criteria, several countries qualified for the study. From the South Asia region we excluded India since the study did not have the resources to cover a country of that size. Several countries in the two regions presented logistical challenges that could not be overcome by the available funding for the study. Five countries were eventually chosen for the study—Bangladesh, Cambodia, Nepal, the Philippines, and Thailand and in-depth assessment of the PV systems was conducted in those countries

The summarized version of the description of the study method is included in annex E in this document. Further details on the selection of study sites within each country, recruitment of consultants and data collectors, data entry, limitations, and results of the study are in the individual country reports (Stergachis A, Rahman Md M 2012; Men C 2012; Shresta NP 2012; Marcelo J 2013; Sakulbumrungsil R 2013).

3. Comparative Analysis of Results from Individual Country Studies

The data from the individual country assessment was collated and entered into a database developed for the purposes of the study based on the five PV components namely Governance and Policy, Law, and Regulation; Systems, Structure, Stakeholder Coordination; Signal Generation and Data Management; Risk Assessment and Evaluation; and Risk Management and Communication. A rating scale was applied to classify the performance of each component area within the study countries' PV systems. Based on the scoring of the five components of the PV system in the data collection tool, specific strengths and gaps in each component were identified. Tables and bar charts were used to compare performance of indicators within the same component. Radar charts were used to illustrate the performance in each component. Qualitative information from the literature reviews were used to supplement the quantitative data collected through the individual country assessments.

Review of Regulatory and Pharmacovigilance Systems

As access to medicines improves, the value of strengthening PV systems is becoming increasingly recognized. However, PV systems in many countries are not well described. Most Asian drug safety literature focuses only on adverse event reporting. Books on Asian regulatory systems mainly address PV regulations in China, India, Japan, and Singapore (Klincewicz S, Yap Y 2009; Gillespie J 2009) and do not discuss the medicines safety systems in any depth. Also there is no documentation of how PV systems contribute to improved treatment outcomes. The review discusses significant medication safety events that have impacted on regulatory reforms, the importance of PV, and recent efforts at international cooperation and harmonization for sharing safety information.

The reason for pharmaceutical regulation is to ensure the safety of health products and protect public health.

Medication Mishaps Have Catalyzed Medicines Regulation

Historically, development of medicines regulation has been catalyzed by medication mishaps. Harm from the use of medicines can be a consequence of manufacturing error, product falsification, intrinsic toxicity of the product, and unsafe use (by prescribers, dispensers, and patients). The death of 107 people in 1937 from elixir of sulfanilamide contaminated with diethylene glycol, and the severe malformations, primarily phocomelia, in about 10,000 children which occurred from 1956 to 1962 in mothers who were exposed to thalidomide during pregnancy, were defining drug safety events that spurred regulatory actions. The diethylene glycol case led to the enactment of the Federal Food, Drug, and Cosmetic Act (1938) and in reaction to the thalidomide cases, the WHO developed the voluntary notification scheme in 1961. The fundamental reason for pharmaceutical regulation is to ensure the safety of health products and protect public health.

In Asia, medication mishaps have led to public concerns and calls for strengthening regulations. In 2005, a sophisticated investigation into fake artesunate suggested that the fake antimalarial drugs were killing millions (WHO estimates 20% of the one million malaria deaths per year is from fake products). The investigators identified two trafficking networks, one from the Thai-Myanmar border and northern Laos and the other from southern Laos, Vietnam, and Cambodia. Three people were arrested for trafficking 240,000 blister packs of fake artesunate into Myanmar (Newton et al. 2008) containing no or subtherapeutic amounts of the active antimalarial ingredient, which has led to deaths from untreated malaria, reduced confidence in this vital drug, large economic losses for legitimate manufacturers, and concerns that artemisinin resistance might be engendered.

The 2008 heparin related deaths and allergic reactions in the United States were attributed to economically-motivated adulteration of heparin with over-sulphated chondroitin sulphate from Baxter's Chinese heparin supplier. A total of 131 heparin-related deaths were reported to US Food and Drug Administration (FDA) between January 1, 2007 and April 13, 2008. In 2012, the then Chinese State Food and Drug Administration shut down more than 80 manufacturing lines in Zhejiang, seized more than 77 million capsules, and arrested 22 people

in connection with chromium-laced capsules of medicines, including many antibiotics. Medication mishaps and corruption coupled with a vision to strengthen local industry has resulted in several changes in the Chinese regulatory systems leading to the reorganization and consolidation of the powers of the State Food and Drug Administration into a ministerial-level agency, the China Food and Drug Administration (CFDA). Similarly, in India a parliamentary committee audit of the Central Drugs Standard Control Organization (CDSCO) argued that the organization is facilitating the development of the drug industry to the detriment of public health. The committee found that the CDSCO approved marketing of 13 drugs including dipyrone which did not have permission for sale in any of the major developed countries and also approved clinical trial for fixed-dose combination of aceclofenac with drotaverine, a combination not in use in developed countries (Parliament of India 2012). Subsequently another committee recommended that a Special Expert Committee should be set up that should be independent of the Drug Technical Advisory Board to review all drug formulations in the market and identify drugs which are potentially hazardous and/or of doubtful therapeutic efficacy (Chaudhury expert committee 2013). In Pakistan, the death of 125 patients in 2012 who received a cardiac drug contaminated with an antimalarial medicine lead to the Pakistani government quickly establishing a central Drug Regulatory Authority in 2012. This case underlined the need to address the jurisdictional confusion created by the passage of the amendment that decentralized public health.

Recognition of Importance and Practice of Pharmacovigilance

Adverse reactions, poor product quality, medication errors, and therapeutic ineffectiveness waste resources and have devastating impact on the health systems by leading to treatment failure, drug resistance, loss of confidence in the health system, and increased morbidity and mortality. Adverse drug reactions are the fourth–sixth leading cause of death (Lazarou 1998) and patients who experienced adverse drug events (ADEs) were hospitalized an average of 8 to 12 days longer than patients who did not suffer from ADEs and their hospitalization cost USD 16,000 to USD 24,000 more.

The overall objective of a NRA for medicinal products is to ensure that all medicines, medical devices, vaccines, blood products, and other biologicals are of assured quality, safety and efficacy and are accompanied by appropriate information to promote their safe use. Regulatory authorities are responsible for making decisions regarding label changes (dose, indication, etc.) or variation in marketing authorization, drug safety alerts, control of unapproved claims, prescription to over-the-counter status switch and vice versa, and product withdrawal or recalls. Though the enactment of new regulations has been the main tool by governments and the regulators to prevent subsequent harmful occurrences and protect public health, the understanding of how to protect the public health is still evolving. From recognizing the need to demand safety, quality, and efficacy before medicines are introduced in the market, national regulatory authorities also developed surveillance and enforcement units to monitor the market and ensure that products maintain their quality and safety after approval. However, efforts to secure the market have not been completely successful with the continued availability of substandard and falsified medicines in the supply chain of most countries. The development of PV and post-marketing surveillance systems is a strategy that could be used to supplement information gathered prior to market authorization. According to the US Institute of Medicine (IOM), preapproval clinical trials do not obviate continuing formal evaluation after approval (IOM 2007). Clinical trials for the authorization of new medicines usually focus on determining efficacy of the product in limited number of persons, typically with narrowly defined characteristics, for a short duration of time. Like in developed countries the importance

of PV is well recognized amongst the regulatory authorities in the Asia region. Most of the countries regulatory organizations have maintained a post-marketing surveillance or PV unit as a part of their agency's structure. Countries in the region are participating in the WHO international drug monitoring program. The table below shows the current membership status for Asia.

Table 3. WHO-UMC Membership Status

Official member	Associate member	Non-member
Brunei Darussalam (2005) Cambodia (2012) China (1998) India (1998) Indonesia (1990) Japan (1972) Korea, Rep. (1992) Malaysia (1990) Nepal (2006) Philippines (1995) Singapore (1993) Sri Lanka (2000) Thailand (1984) Vietnam (1999)	Bhutan Mongolia Pakistan	Afghanistan Bangladesh Korea, Dem. Republic Lao PDR Myanmar

Early members of the WHO drug monitoring program like Japan, Thailand, Indonesia, and Korea have well developed spontaneous reporting systems. Korea and Thailand are in the top 10 countries in the WHO Global ICSR database (Uppsala Monitoring Center 2013). Many of the official members have more developed regulatory systems with surveillance and enforcement units, newer members and non-member countries are beginning to put these structures in place. Notwithstanding PV practices in the region vary tremendously. A review of the regulatory requirements shows different reporting timelines and different reporting forms and requirements for electronic submission, PV inspections and audits, etc. Sharing of information on regulatory decisions vary as well. While many NRAs in the region barely communicate their regulatory action, Singapore HSA in 2011 issued more than 280 decisions related to safety of medicines and Indonesia Badan Pom and Malaysia National Pharmaceutical Control Bureau provides opportunities for consumers to report health products complaints online. In their quest to protect the public and also answer tough questions on the products they allow on the market, regulators are challenged to develop strategies for improving the safety of products. Several strategies additional to spontaneous reporting systems have been incorporated including requirements for the conduct of risk management, post-authorization studies, and review of the benefit-risk throughout the product life-cycle. These practices are not very common among regulatory authorities in the region.

International Collaboration and Harmonization

Securing the supply chain from unsafe products in any country is a challenge no regulatory authority can now confront alone. To help PV achieve its intended purpose, international collaboration and information sharing is required. International collaboration in regulatory activities can help to reduce duplicative testing of products, clinical trials, and inspections. Timely information sharing between regulatory authorities can be helpful in addressing outbreaks of substandard, falsified, and unsafe medicines, and is a condition for securing

the global supply chain. With growing globalization of drug development, complexity of the products, and global economic challenges, the need for harmonization or at least some convergence of standards and requirements is increasingly being recognized. Thus, the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) was launched in 1990 to develop technical guidelines for product registration to harmonize standards and reduce duplication. The ICH has developed over 50 guidelines including the guidelines that cover the reporting and evaluation of data on safety and efficacy of pharmaceutical products in pre- and post-approval periods (drug safety guidelines E2A to E2F). Also supporting ICH work are the M2 guidelines that facilitate the electronic standards for the transfer of regulatory information (ESTRI), the Medical Dictionary for Regulatory Activities (MedDRA) terminology, and the Common Technical Document. Besides Japan, a founding member of the ICH, Asia regulators are at different stages of adoption of international standards and guidelines developed by the ICH. The need for sharing of regulatory information is recognized and the adoption of common standards is improving.

Comparison of Pharmacovigilance Practices of Stringent Regulatory Authorities and Asia Reference Authorities

The European Medicines Authority (EMA) is the authority responsible for coordinating PV systems in the European Union (EU). Regulation EC 726/2004 calls for intensive supervision of undesirable effects of medicinal products within the framework of community PV activities and rapid withdrawal of products presenting a negative risk-benefit balance under normal conditions of use. In the United States, the reporting of adverse events is mandated by law for the product sponsors. The regulations governing drug safety are covered by Title 21 of the Code of Federal Regulations. Title IX of the Food and Drug Administration Amendments Act (FDAAA) of 2007 provided FDA with enhanced authorities regarding post-market safety of drugs.

PV activities in the EU and United States have continued to change and evolve as the public asks for greater transparency and protection (Health Action International 2008; Wolfe 2006). The EMA posts the European Public Assessment Report (EPAR) in their website, the FDA posts the products approval package on its website Drugs@FDA, and the Japan PMDA posts the review reports for approved products on its website. Provided in the table 4 below is some comparison of key features of the drug safety system across the stringent regulatory authorities (SRAs) of EU, United States, and Japan alongside the practices in China, India, and Singapore.

Regional Harmonization Initiatives in Asia

The Asia Pacific Economic Collaboration (APEC) set up the Regulatory Harmonization Steering Committee (RHSC) with the aim to promote a more strategic, effective, and sustainable approach to regulatory convergence by proactively identifying and prioritizing projects of greatest value to regulators and the regulated industry. One of RHSC's harmonization topics is on PV—the Korea FDA is the lead agency. Through this work group, the steering committee strives to address regulatory harmonization in PV. The roadmap for strengthening PV systems is currently being developed. The Asian Harmonization Working Party (AHWP) activities are focused on the medical devices. The AHWP was established to study and recommend ways to harmonize medical device regulations in Asia and other regions and to work in coordination with the Global Harmonization Task Force, APEC, and other related international organizations (Asian Harmonization Working Party 2010).

Table 4. Comparison of Drug Safety Systems Across SRAs

Regulatory requirements	Stringent NRAs			Asian competent/reference NRAs		
	EMA	US FDA	Japan	China	India	Singapore
PV regulations	Regulation EC 726/2004; Directive 2010/84/EU; Regulation (EU) 1235/2010; EU Vol. 9A	FD&C Act 1938; FDA Modernization Act 1997; FDAAA 2007; FDASIA 2012; 21 CFR	Pharmaceutical Affairs Law; MHLW Ordinance No.135 of 2004; GVP and Good Post-Marketing Study Practice (GPSP)	Drug Administrate-tion Law 1984; Regulations for Implementation of Drug Administration Law 2002	Drugs and Cosmetics Act 1940; Drugs and Cosmetics Rules 1945 (Schedule Y)	Medicine Act Chapter 176, 1977
Mandatory industry reporting of serious ADRs	Yes					
Clinical trials register exists?	Yes (EudraCT)	Yes (clinicaltrials. gov)	Yes (JapicCTI)	Yes (ChiCTR)	Yes (CTRI)	Yes (HSACTR)
Monitoring period for new drugs required	Yes (5 years)*	Yes (5 years)	Yes (4–10 years)	Yes (5 years)	No	
Expedited reporting of serious ADRs for marketed drugs required	Yes (15 days)					
PV Inspections and audits required	Yes			No		
Risk management plans (RMP) mandated	Yes (RMP)	Yes (REMS)	Yes (GPSP)	No		No (however applications should include RMP or REMS)
Spontaneous reporting database exists	Eudra-Vigilance	FDA Adverse Event Reporting System (FAERS), VAERS database	ADR information management system	National ADR Monitoring System	Vigiflow provided by UMC is used under Pharmaco-vigilance Program of India (PvPI)	No
Periodic safety update reports required (frequency)	Yes (every 6 months for the first 2 years)	Yes (every 3 months for first 3 years)	Yes (every 6 months for the first 2 years)	Yes (annually for the first 5 years)	Yes (every 6 months for the first 2 years and then annually thereafter, but applicable only to "new drugs, until 4 years after launch")	Yes (every 6 months for the first 2 years)
Active surveillance initiative	EU-ADR project, ENCePP, PROTECT	Sentinel system	MIHARI project	No		
Identified person responsible for PV mandated†	Yes (QPPV)	No	Yes (Safety Control Manager, SCM)	Yes (PMR rules)	No	Yes

* The EMA has a black triangle scheme that will come into effect in the last quarter of 2013. The scheme requires that black inverted triangle should be displayed in the package leaflet of new medicines and denotes that the medicine is under intense additional monitoring.

† Industry is mandated to have someone responsible for PV. An example is the Qualified Person for Pharmacovigilance (QPPV) in Europe.

ENCePP- European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
MIHARI - Medical Information for Risk Assessment Initiative
PMR- Administrative measures for monitoring and reporting of ADRs, 2004
QPPV- Qualified Person in Pharmacovigilance
PROTECT- Pharmacoepidemiological Research on Outcomes of Therapeutics by a European Consortium

Seventeen member economies including Cambodia, Philippines, and Thailand are AHWP members. Recently, the AHWP was accepted as a member of the International Medical Devices Regulators Forum.

Cambodia, Philippines, and Thailand are also members of the Association of Southeast Asian Nations (ASEAN). The ASEAN Economic Community (AEC) Blueprint identifies standards and conformance as one of the technical areas for harmonization. The blueprint includes the objective to strengthen post market surveillance systems to ensure the successful implementation of the harmonized technical regulations (AEC 2008). One of ASEAN's working groups is the Pharmaceutical Product Working Group that serves as the regional harmonization initiative. The initiative aims to develop ASEAN member countries harmonization schemes of pharmaceutical regulations to complement and facilitate the objectives of the ASEAN Free Trade Area (AFTA), particularly the elimination of technical barriers to trade posed by regulations without compromising product quality, efficacy, and safety. To facilitate this regional harmonization effort, the Pharmaceutical Product Working Group has identified mutual technical areas including GMP inspection, bioavailability and bioequivalence standards, and post-marketing surveillance. ASEAN countries participate in a post-marketing alert (PMA) system. The objective of the PMA system is for ASEAN member countries to share information relating to defective or unsafe cosmetics, health supplements, traditional medicines, and pharmaceutical medicinal products. In the event of a major safety concern that results in a recall or withdrawal, the PMA system can be used to notify the various regulatory agencies in a timely manner (Rahman E 2008).

A similar PMA framework has also been developed for medical devices. Some of the region's countries have limited capacity for medical device regulation. In the absence of adequate regulation, adverse events are not reported and when products cause harm, there is little in the way of corrective action and product recalls. So implementing the PMA for medical devices can help address some of these gaps in those countries that have limited device regulatory capacity. Under the PMA arrangement, the countries are harmonizing terminologies, standards, and reporting timelines; they also are developing systems for the use of common reporting forms and the sharing of information on quality and safety of products in the ASEAN market. In a report on the activities of the system it was identified that non-steroidal anti-inflammatory agents were the most commonly reported adulterants (45.8%). Most of the anti-inflammatory agents could have been manufactured by countries within the region or members of the regional harmonization initiative thereby providing an opportunity to deal with the problem from a regional level. An analysis of the Cambodia national medicines register showed that 89% of registered products (table 5) are manufactured in countries from the region.

Table 5. Countries of Manufacture of Cambodia Registered Products

Total # of products in the Cambodia national register 10,636		
Country of manufacture of products	**# of products**	**Registered products, %**
India	6,163	58
Thailand	1,604	15
Bangladesh	573	5
Philippines	197	2
Others	2099	20
Total	**10,636**	**100**

Bangladesh and Nepal are members of the eight member group, the South Asia Association for Regional Cooperation (SAARC). Working on strategies for the establishment of common standards or harmonization of regulatory requirements for pharmaceuticals has not been discussed by this group. However, during the 2005 SAARC Third Ministerial Conference on Health, attendees requested the Technical Committee on Health and Population to prepare a plan of action in the areas of medical expertise and pharmaceuticals, harmonization of standards and certification procedures; and increased production of affordable medicines as well as traditional medicines. It is not clear how things have progressed in the work of this technical committee since then.

SAARC members established the South Asian Regional Standards Organization to develop harmonized standards to facilitate intra-regional trade and to have access to the global market. Its Sectoral Technical Committee collaborates on harmonization in the areas of food and agricultural products, textiles, and quality management (Spanta RD, Chowdhury IH, Tshering U, Mukherjee P, Shahid A, Mahat RS, Qureshi MSM 2008). Pharmaceutical-related issues have never been addressed and could be a potential area to bring the members together to set standards on medicines regulatory harmonization. The lessons learned from the other regional harmonization groups like APEC and ASEAN in building the infrastructure for achieving convergence of standards, mutual recognitions, and sharing of regulatory information are important for the SAARC as well. Table 6 provides the regional harmonization initiatives, whether they work on pharmaceuticals and medical devices or not, and the countries that are members.

Table 6. Regional Harmonization Initiatives Member Countries

	Regulatory harmonization initiatives (RHI)			
Acronym of the RHI	**APEC**	**APEC**	**ASEAN**	**SAARC**
Working group/committee	RHSC	AHWP	PPWG	SARSO
Pharmaceuticals/medical devices part of harmonization	✓	✓	✓	
Participates in GCG	✓		✓	
Country membership				
Bangladesh				✓
Cambodia		✓	✓	
Nepal				✓
Philippines		✓	✓	
Thailand	✓	✓	✓	

Poor Quality Products

Poor quality products constitute major public health concern in the Asia region. Of 1437 samples of drugs in five classes from seven countries in Southeast Asia, 497 (35%) failed chemical analysis, 423 (46%) of 919 failed packaging analysis, and 450 (36%) of 1260 were classified as falsified (Nayyar et al. 2012). When substandard, adulterated, or falsified medicines are used treatments fail, drug resistance can occur (in the case of anti-infectives), and patients can be directly harmed from the products toxic effects. In many low and middle-income countries the need to protect the public from the adverse events associated with sub-

standard and falsified products by eliminating them from the supply chain is a major concern among health officials as well as consumers. Detection of product quality problems, harm from the use of unsafe products and actions taken by governments to extract substandard and falsified products from the market and punish offenders have been reported in developing countries across all regions (Promoting the Quality of Medicines Program 2013; Dorlo et al. 2012). In the region China and India have been mentioned as sources of poor quality products, though a government sponsored report in 2009 put the level of spurious drug in retail pharmacy in India at only 0.046% (CDSCO 2009). An IOM report suggests that information such as the number of doctor's appointments repeated because of falsified and substandard drugs, the number of hospital beds occupied by victims of pharmaceutical crimes, premature deaths from untreated disease, and productive years lost to society from medicine poisoning can be generated by PV. When PV systems detect problems related to the safety, efficacy and quality of medicines, the opportunity exists for these signals to be followed up more thoroughly. In-depth investigations can eventually produce data on the specific consequences, including magnitude and cost, of falsified and substandard medicines (Institute of Medicine 2013).

A comprehensive and sustainable QA system is needed to prevent, detect, and respond to substandard pharmaceutical products.

Countries need a comprehensive and sustainable quality assurance system that prevents, detects, and responds to the presence of substandard pharmaceutical products in circulation. A quality assurance system is comprised of the structures, functions and processes, including both managerial and technical activities that monitor the quality of pharmaceuticals throughout all stages of the product cycle, from production to use. PV is part of such a system, but alone is not sufficient. Quality assurance includes inspections for compliance with GMP, assessment of documentation on product quality submitted by manufacturers for registration as well as procurement, sampling and testing of pharmaceutical products from the market and other entry points and systematic evaluation of reported product quality problems through the PV system (Alghabban 2004). Many international, regional and national efforts have been launched to address the issue of substandard and falsified products through improved information sharing and are yielding good results for the benefit of patients. On the international level, WHO-UMC regularly publishes a document called *SIGNAL,* which contains medicine safety signals representing varying levels of suspicions, including suspected product quality concerns, based on the Center's analysis of the data submitted by countries worldwide into the WHO Global Individual Case Safety Reports database. Another initiative that can advance product quality information sharing in the region is the WHO Western Pacific Region (WPRO) rapid alert system as a vehicle for addressing the issues of falsified and substandard products. Regionally in Southeast Asia, the use of the PMA system by the ASEAN pharmaceutical product working group has been noted above. Individual countries can benefit greatly from information sharing on product quality issues at the international and regional levels, if they use information that is deemed relevant and applicable to the pharmaceuticals in their market to make regulatory decisions and take appropriate actions. Through information sharing, problems can be prevented or detected early, which not only saves money but also has the potential to save lives.

Challenges for Pharmacovigilance Systems in Asia

The lack of harmonized regulatory approach and differences in safety reporting requirements in the region is one of the major obstacles to PV in Asia. Another challenge is the inability of the current regulatory system to safeguard public health from incidences of falsified and substandard products in the market in the region. When the functions and operations of the regulatory authorities are reviewed or audited by government accountability offices, often the

central question is to determine the regulatory impact and effectiveness of the strategies in place for safeguarding public health. Other challenges for regulatory and PV systems in the region include how to generate and share reliable data that can be used for timely benefit and risk decision making. The ability to collect data on real-life effectiveness will contribute to efforts to understand the benefits and risks of medicines. Inability to take timely regulatory decisions to protect public health is a challenge across developing countries. Products that are withdrawn by SRAs are available in the region. In most cases the NRAs have not reviewed the continued usefulness of the products nor provided reasons lack of regulatory action. Advocates for improved access to medicines in LMICs countries use a metric called drug lag—to indicate how long it takes before an essential medicine licensed by SRAs is introduced by developing countries (Wardell 1973, Andersson 1992, Olson 2013). At the other end of the drug lag is the safety lag—how long it takes for developing countries to react to a regulatory action taken by SRAs for a product that is also marketed in their country. One of the new challenges of PV is to reduce safety lag globally. The harmonization of standards, use of common terminologies, and sharing information can help reduce safety lag and reduce continued exposure to harmful products. PV in the Asia region has to prove its utility and return on investment, for instance, reduction in medicines-related mortality and morbidity. Asia can also use PV data to determine therapeutic gaps and define goals for new medicines. Using data on real-life safety and effectiveness will make it possible to define the limitations of existing medicines in terms of therapeutic failure, toxicities, adherence challenges, inconvenient formulations, and abuse potential, and use this information to define what is required of the ideal medicine for that indication.

The lack of a harmonized regulatory approach and differences in safety reporting requirements is one of the major obstacles to PV in Asia.

Comparative Analysis of Results of Assessment of Pharmacovigilance Systems

Pharmacovigilance at the National Level

The comparative analysis of the results of the PV systems in Bangladesh, Cambodia, Nepal, the Philippines and Thailand is presented in this section of the report. At each of the five key stakeholder groupings — national level (including the ministry of health and NRAs); public health programs (HIV and AIDS, TB, malaria, vaccine and immunization program, and mass drug administration); health facilities and service delivery level; pharmaceutical industry; and civil societies level, we reviewed and compared countries performance using the relevant indicators from the five components of a comprehensive PV system (1. Governance, Policy, Law, and Regulation, 2. System, Structure, and Stakeholder Coordination, 3. Signal Generation and Data Management, 4. Risk Assessment and Evaluation, and 5. Risk Management and Communication).

Governance, Policy, Law, and Regulation

Governance

Countries were regarded as performing well in the area of governance if the following indicators were addressed—

- Existence of regulatory framework
- Existence of regulatory registries
- Governance structures mandated by the legislation/regulations and in practice

Existence of Regulatory Framework

All countries assessed were found to have at least some description of their regulatory framework. These were either defined by the national pharmaceutical policies or the pharmaceuticals sector strategic plans. The frameworks typically describe means for achieving objectives mandated by pharmaceutical legislation and regulations. For Cambodia and Nepal, the regulatory framework is not explicitly described.

Existence of Regulatory Registries

All countries have registers for products, licensed pharmaceutical premises, and licensed pharmaceutical personnel in place. Bangladesh, Cambodia, Nepal, Philippines, and Thailand have their product registers readily available through the NRA website, though some of these were only available in the local language, outdated, or only available in a database format that cannot be easily downloaded or tabulated. Investing in maintenance of record-keeping systems allows regulatory authorities to streamline workload and improve governance and transparency by making up-to-date information on medical products and regulatory activities more readily accessible to stakeholders.

Governance Structures Mandated by Regulations and in Practice

According to WHO, governance is a process of decision making and the process by which decisions are implemented (or not implemented); it involves ensuring that there is a strategic policy framework, effective oversight, coalition-building, regulation, attention to system-design, and accountability and the recognition that governments should operate in a transparent and accountable manner with high regard for rule of law (Anello 2008; WHO 2009). All countries have at least some governance structures within the pharmaceutical system that were mandated by legislation and regulations, including systems for accountability, transparency, and legislative enforcement. The assessment measured the extent to which these governance structures were implemented and in practice as mandated. Bangladesh, the Philippines, and Thailand reported having had an evaluation of regulatory systems within the past five years and a government accountability audit conducted within the last one year. Both Nepal and Cambodia reported existence of governance structures; however, neither has had an audit or evaluation to determine the extent to which they are

implemented and enforced. Of the five Asian countries, three (Bangladesh, Philippines, and Thailand) were found to have key attributes of a functioning governance system in place, including the existence of a regulatory framework, regulatory registries, and governance structures (table 7).

Table 7. PV Governance at the National Level

	Bangladesh	Cambodia	Nepal	Philippines	Thailand
Regulatory framework	✓	*	*	✓	✓
Regulatory register	✓	✓	✓	✓	✓
Governance structures mandated and in practice	✓	*	*	✓	✓

* Exists but not assessed or fully in place

Policy, Law, and Regulation

Essential Statements on PV or Medicines Safety in National Policy

All countries surveyed have a National Medicines Policy (NMP) that address medicine safety. The NMPs contain requirements for ensuring product quality assurance (QA) (at a minimum Good Manufacturing Practices [GMP] inspection) and provisions for the control of medical product advertising and promotion. The Philippines has a specific national PV policy.

Legal Provision for PV in the National Medicines Legislation

All countries assessed have national medicine laws in place that include legal provisions broadly related to medicine safety. However, the regulatory requirements for pre- and post-marketing surveillance activities are found in different laws and are not always aligned with each other. The Philippines has a detailed inventory of its food and drug laws and regulations including the National Policy and Program on Pharmacovigilance ("Food and Drug Administration Philippines"). Cambodia specifically mentions PV in the legislation. Laws and regulations provide the legal basis for conducting medicines safety activities in a country, with regulations guiding implementation and enforcement of the law.

Provisions That Mandate Market Authorization Holders to Conduct Post-Marketing Surveillance

Cambodia, the Philippines, and Thailand, were found to have legal provisions mandating pharmaceutical industry to report suspected adverse events to the National PV Center. However, the PV requirements, where they exist, are not always consistent with international standards and vary greatly across the countries. Only the Philippines mandates that industry conduct post-marketing surveillance of specified products based on stringent regulatory authority requirements. The Philippines also requires a three-year initial registration prior to being eligible for application and approval for general use. This program is regarded as monitored release of a new medicine. In Thailand, the Safety Monitoring Program (SMP) mandates that the industry monitor the safety of new medicines for two years.

Table 8. Content Analysis of PV Regulatory Requirements for the Pharmaceutical Industry in Two Countries

Regulation	Philippines	Thailand
Sections of laws and regulations related to safety of medicines†	Republic Act section2 l of 3720; Republic Act No. 7394; FDA Circular No. 201 3-003	Drug Act B.E. 2510 (1967) Section 86, 91
Industry reporting of serious ADEs mandated (expedited reporting required)	✓	✓
▪ Reporting timelines for marketed products (serious)	7 days	24 hours (for fatal outcomes), 7 days (unexpected with fatal outcome) and 15 days (other serious AEFI/ADR)
▪ Reporting timelines for marketed products (non-serious)	Quarterly, 30th of first month	60 days
Periodic safety update reports required ▪ Reporting timelines	✓ every 6 months	✓ (for selected products)
▪ Reporting timelines for clinical trials (SUSAR)	7 days	7/15 days
- Fatal/life threatening		24 hours
Monitoring period for new medicines required	✓ 3 years	✓ 2 years

✓ Checkmark denotes that the regulation is required in the country
† For Philippines, this is specified in the FDA Circular No. 201 3-003, not specified for Thailand

Legal Provision for Product Quality Assurance

All countries were found to have at least minimum legal provisions for the quality assurance of medicines in their national laws and regulations (table 9). To ensure the quality of products, legal provisions in a country should address product quality standards relating to manufacturing, importing, exporting, wholesale, distribution, storage, dispensing, and retail sales.

Table 9. Content Analysis of Pharmaceutical Legislation

Legal provisions for product quality assurance	Bangladesh	Cambodia	Nepal	Philippines	Thailand
Laws/regulations that require GMP inspection	✓	✓	✓ (imports)	✓	✓
WHO prequalification and Certificate of Pharmaceutical Product (CPP) referenced during the registration	Not mandatory	n/a	✓	✓	✓
Requirement that a GMP certificate is issued to manufacturers of pharmaceutical products	✓	No	✓	Not mandatory	✓
Laws/regulations to ensure that donated products are registered and inspected	✓	✓	✓	✓	✓
Guidelines for Good Distribution Practices in place	✓	✓	No	Drafting	Drafting

Case Study 1. The Safety Monitoring Program (SMP) in Thailand

Post-marketing surveillance is particularly relevant for medicines identified as high-risk or with unknown or incomplete safety profiles among the general population or in certain high-risk groups such as pregnant women, children, the immune-compromised, and the elderly. The safety profile of new medicines at the point of market introduction is incomplete. In 1991, Thailand's Food and Drug Administration (FDA) began implementing the Safety Monitoring Program (SMP) to monitor the safety of new medicines. SMP is intended to confirm the safety of new medicines in Thai patients by generating earlier safety signals and gathering more safety information before granting unconditional registration approval. It monitors all new medicines, including products with new chemical entities, new indications, new combinations, and new delivery systems. Under SMP, the Thai FDA grants conditional approval for registration of new medicines for a period of two years. Products with conditional status must have a blue triangular emblem displayed on the product packaging and can only be distributed through hospitals or healthcare facilities under the close supervision of physicians. During the two-year safety monitoring period, reporting of adverse drug reactions is mandatory for the pharmaceutical companies seeking full marketing authorization (Wibulpolprasert 1999). At the end of the two years, pharmaceutical companies must submit comprehensive summary reports to the Thai FDA, which may include reports of adverse drug reactions (ADRs), drug consumption, and detailed drug experiences from other countries where the product has been used. Drug products with no evidence of serious adverse events or with benefits that outweigh its risks will receive unconditional approval. The market authorization holders are then allowed to distribute the approved products through regular channels (Amrumpai et al. 2007).

Legal Provision for Control of Promotion and Advertisement

All countries in the assessment were found to have laws in place controlling the promotion and advertisement of medicines (table 10). The actual content of the legislation or the degree of their enforcement was not determined, however. NRAs should have legal provisions and guidelines to ensure that statements made about medical products through advertising and promotional activities are accurate and correspond to approve product information, including clinical indication and use. NRAs are responsible for providing independent, non-promotional information on medicines to the public and healthcare providers. Authority should be granted to NRAs to take regulatory action against industry found to be in violation of the legal provisions, recognizing the risk to patient safety posed by incomplete or misleading information and the potential for such information to strongly influence the way that medicines are purchased and used. NRAs should have ethical guidelines in place that adhere to the WHO Ethical Criteria for Medicinal Drug Promotion guidelines and serve as authoritative sources (HAI Global 2010).

Discussion

Governance involves ensuring that there is a strategic policy framework, effective oversight, coalition-building, regulation, attention to system design, and accountability and the recognition that governments should operate in a transparent and responsible manner with high regard for rule of law (Anello 2008; WHO 2009). The existence of governance systems and structures that promote transparency and accountability within national regulatory authorities, including policies, laws and regulations, provide a fundamental platform for effectively regulating the safety, quality, and effectiveness of health products, safeguarding public health, and promoting pharmaceutical sector trade and economic growth. Regulatory

Table 10. Summary of Policy, Law, and Regulation

	Bangladesh	Cambodia	Nepal	Philippines	Thailand
PV or medicines safety policy	✓	✓	✓	✓	✓
PV or medicine safety in national medicines legislation	✓	✓	✓	✓	✓
MAH mandated by law to report serious adverse drug reactions to NRA		✓		✓	✓*
MAH required to conduct post-market surveillance per stringent regulatory authority standards				✓	
Legal provision for product quality assurance	✓	✓	✓	✓	✓
Legal provision for promotion and advertisement	✓	✓	✓	✓	✓

* SMP mandatorily requires the industry to monitor the safety of new medicines for 2 years

frameworks define countries' pharmaceutical regulation and governance, and include legislation, policies, guidance documents, and other governance instruments that collectively define how pharmaceuticals are regulated. Establishing regulatory registers is the first step in the process to define what is allowed in the market. The registers, depending on type (product register or list of registered pharmacies, premises, etc.) should contain minimum sets of information. For instance, WHO recommends that minimum information should include generic name, dosage form, strength, trade name, marketing authorization holder, authorization number, indications, status (new chemical entity [NCE] or non-NCE [WHO 2011]). Registers can facilitate information sharing and increases transparency if publically available (WHO 2010a).

One of the most important elements in the regulatory framework is pharmaceutical legislation, which includes statutory laws and regulations to guide enforcement activities. The framework for most countries also defines and delineates the mission and strategic objectives of the regulating authorities, their functions, the scope of products they regulate, and the outcome of their activities, typically measured in terms of promoting access and protecting public health. Many regulatory bodies have challenges in meeting the public expectations and defining stakeholders' roles in advancing access while avoiding medical mishaps. For instance, the legal requirements for the industry should be clearly stated in the law. International standards, such as the ICH guidelines (International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use) and practices of stringent regulatory authorities including the European Medicines Agency (European Medicines Agency 2012) and US FDA, require MAH to report serious adverse events wherever their products are marketed. They also may require post-marketing surveillance or risk mitigation activities for products with significant unresolved safety concerns or for high-risk medicines. Without the necessary legal provisions in place, the safety of medicines cannot be adequately monitored; laws and regulations provide the

legal foundation for conducting and enforcing a country's medicines safety activities with regulations guiding how laws are implemented.

According to WHO, NMP should contain several elements relating to medicine safety, including requirements for establishing PV systems and developing legislation and regulations for monitoring the safety of medicines (WHO 2004). Additionally, NMPs should include provisions related to product quality assurance and control of promotion and advertising. Such essential statements on PV may also appear in other documents, including public health program (PHP) policies or treatment guidelines. An approved national PV or medicines safety policy is the guiding document that provides the authority and mandate to monitor medicine safety and take appropriate regulatory action. To complement the policy, PV guidelines provide operational direction and standards for implementing activities, such as spontaneous reporting of adverse drug reactions (ADRs), active surveillance, provision of medicine information, and delineation and coordination of stakeholder roles and responsibilities.

Systems, Structure, and Stakeholder Coordination

PV Center or Unit with a Clear Mandate, Structure, Roles, and Responsibilities

All countries had a national PV center or unit in place operating under the Ministry of Health's medicines regulatory authority and a staff member dedicated to PV within their centers. The national PV centers in Cambodia, Philippines, and Thailand had clear and documented mandates, structures, and scopes of work in terms of roles and responsibilities; whereas in Bangladesh and Nepal, the mission, vision, and function were not explicitly documented. Nepal has plans to update its NRA organizational structure to include the national and regional PV centers. Further review of the structure of the PV centers showed that the mandate, structure, and scope of activities varies across the countries and opportunities for leveraging expertise and resources throughout the NRA for safety monitoring are not exploited. The Thailand Health Product Vigilance Center (HPVC) has expanded its mandate to monitor the safety of all health products.

Budget for PV

Thailand reported having a dedicated annual budget for PV-related activities (table 11) and receives dedicated annual funding to cover its operations.

Table 11. Funding for PV Activities in Five Countries

Dedicated budget available for PV-related activities	Bangladesh	Cambodia	Nepal	Philippines	Thailand
Annual budgetary allocation for PV activities or PV center			Limited*		✓
Funds provided by MoH or donors toward PV activities in 2011	✓	✓	Limited*	✓	

* WHO-UMC dues only

Part of the PV funding that is available for countries is from the Global Fund. A review of Global Fund grants for round 10 shows that Cambodia and Thailand, have included activities or interventions related to PV in their disease specific or health systems strengthening (HSS) grants (table 12).

Table 12. Grants to Support PV

Country	Global Fund grants for PV
Bangladesh	No
Cambodia	Yes
Nepal	No
Philippines	No
Thailand	Yes

Quality Control Lab (or Unit) with Clear Mandate, Structure, and Functions

All five countries have quality control laboratories; however, only Thailand (WHO 2013a) has WHO pre-qualified quality control laboratory facilities (table 13).

Table 13. Availability of Quality Control Lab Services in Five Asian Countries

Existence of quality control lab (or unit) with clear mandate, structure and functions	Bangladesh	Cambodia	Nepal	Philippines	Thailand†
QC lab (or unit) under the NRA or affiliated with the NRA	✓	✓	✓	✓	✓
Functions of QC lab include?	a, b, c, d, e	a, c, d, e	a, c, d, e	a, b, c, d, e	a, b, c, e
QC lab have a documented quality management system*	✓	✓	Drafted	✓	✓
QC lab is prequalified by the WHO					✓
QC lab has been audited in the past five years	✓			✓	✓

a. Testing of pharmaceuticals (non-biological products)
b. Testing of biological products such as vaccines
c. Participation in registration activities
d. Inspection of industry quality control labs
e. Collaboration with the Inspectorate to test collected samples
* based on ISO 17025
† Accessed the WHO Public Inspection Report of the BDN http://apps.who.int/prequal/WHOPIR/pq_whopir.htm

National PV Guideline/National Standard Operating Procedures for PV and QC

Cambodia and Thailand have national PV guidelines in place. In the Philippines, the national PV policy also serves as the guidelines. The Philippines and Thailand both reported existence of standard operating procedures (SOPs) for PV and QC, though a document was not available for verification. Bangladesh and Nepal had neither guidelines nor SOPs for PV or QC. Further content review showed that national guidelines are limited to the notification system for passive reporting of suspected adverse drug reactions. Typically, the existing guidelines did not cover other PV methods like active surveillance and did not address other PMS activities like product quality surveillance, risk management, and control of advertisement and promotion.

Medicines Safety Advisory Committee and Quality Control Advisory Committee

All but one of the countries, Thailand, reported the existence of a Medicines Safety Advisory committee that meets regularly (at least once within the past year) and has a documented decision-making process. The Philippines' 2011 PV policy calls for an advisory committee; however, the committee has not yet been formed. Only Thailand has a Medicines Safety Advisory Committee with policies addressing conflict of interest and a mandate for reviewing safety concerns associated with clinical trials. Both Thailand and Cambodia reported existence of fully functional Quality Control Committees that have met at least once in the last year.

PV Medicines Information Service

All countries report that the PV center addresses medicines safety inquiries.

Core Communication Technologies for PV/Core PV Reference Material in PV Unit/Drug Information Center

The assessment found that with the exception of Bangladesh, all countries reported the presence of basic communication technologies for medicine safety including phone, fax, internet, e-mail, computers, and software for databases that record regulatory activities like information requests received and addressed, safety alerts released, and newsletters planned and published. Except for Bangladesh and Cambodia other countries have basic medicine safety reference materials on hand within the national PV center to address medicine safety requests.

Core PV Topics in Pre-Service Training Curricula

The assessment found that, within each of the countries studied, at least one of the academic institutions sampled is providing instruction on PV topics.

PV Stakeholder Coordination Mechanism

All countries listed the national PV center as the recognized and established mechanism responsible for coordinating PV stakeholders in their country, except for Bangladesh where the PV center had been established but has limited capacity to coordinate. The assessment found that the PV centers had limited success connecting with all relevant stakeholders and engaging them to participate fully in medicine safety and prevention activities, as evidenced by the absence of adequate representation in committees; relatively low rates of AE reporting by healthcare providers, industry and consumers; and, the limited reach of medicine information communication strategies.

WHO International Drug Monitoring Programme Membership

Cambodia, Nepal, the Philippines, and Thailand are official members of the WHO International Drug Monitoring Programme. Thailand joined as an official member in 1984, followed by the Philippines in 1995, Nepal in 2006, and Cambodia in 2012 (WHO 2013b). Bangladesh intends to apply for associate membership to the Programme in 2013.[3]

3 Personal communication with the Bangladesh Directorate General of Drug Administration, November 2012.

Quality Management System for PV and Quality Assurance

The assessment found that, although all countries address quality management issues within their NRAs, only the Philippines have a formal quality management system in place addressing PV and quality assurance. The Philippines FDA also has an agency-wide quality management system (QMS). Inspectors conduct PV inspections and as of the time of assessment have conducted 41,030 audits. However, the QMS may not be adequate for performing PV and quality assurance activities. As noted previously, Thailand has a QMS based on ISO 17025 for their quality control laboratory.

Thailand introduced a Performance Management and Quality Assurance system within national-level agencies, including the Thai FDA that monitors quality through key performance indicators (World Bank 2012), though the assessment found that the system is not focused specifically on medicine safety and PV within the Thai FDA or Thailand's HPVC. Below is a summary of the country assessments for the PV component of systems, structure, and stakeholder coordination (table 14).

Discussion

National PV centers can serve as the coordination point for conducting PV activities in a country. However, the current structure of those centers fragments the related post-market surveillance and overall safety monitoring functions. Across all the countries assessed, the current system does not exploit opportunities for leveraging expertise and resources. PV centers function optimally with a dedicated budget, at least one full-time staff member (WHO recommends at least one part-time staff member (WHO)), a clear mandate and organizational structure, and well-articulated roles, responsibilities, and reporting requirements. Countries that lack PV center and basic infrastructure and capacity will not be able to reach timely informed decisions to protect their populations from the untoward and harmful effects of medications.

National quality control laboratories serve an important role in ensuring quality testing and detection of falsified and substandard medicines. Without these systems, patients and communities may be exposed to ineffective and toxic products that can lead to undesirable or even fatal consequences. However, countries do not seem to consider quality and safety issues in whole but rather across the different units of the regulatory authority and close collaboration between the regulatory units was not evident. Countries need medicine quality control laboratories in place to ensure appropriate testing and examination of products (Strengthening Pharmaceutical Systems (SPS) Program 2009b). Moreover, countries should aim at obtaining the WHO prequalification for their national labs, which means that the laboratory is in conformity with the standards recommended by the WHO for medicines quality control (Strengthening Pharmaceutical Systems (SPS) Program 2009b). Also for adequate functioning of national PV and quality assurance activities there is a need for guidelines and SOPs. National guidelines serve as the basis for structured and coordinated actions, according to established standards, by the various stakeholders within a PV system. They explain and support compliance with existing medicine safety laws, regulations, and policies in a country. In all the countries studied, the PV guidelines contain only basic information on the passive surveillance notification system and nothing on active surveillance. The guidelines addressed identification of spontaneously reported adverse drug reactions and do not include other sources of product-related harm, such as poor product quality, medication error, inappropriate advert and promotion. They also do not articulate the roles of all stakeholders and the need for collaborated efforts at addressing issues related

Table 14. System, Structure, and Stakeholder Coordination at the National Level

System, structure, and stakeholder coordination	Bangladesh	Cambodia	Nepal	Philippines	Thailand
PV center or unit	✓	✓	✓	✓	✓
PV center/unit has clear mandate, structure, function		✓		✓	✓
QC lab/unit with clear mandate, structure, function	✓	*	*	✓	✓
PV information service	✓	✓	✓	✓	✓
Dedicated staff for PV	✓	✓	✓	✓	✓
Budget for PV					✓
Up-to-date National Guidelines for PV		✓			✓
SOPs for PV and quality control			†	✓	✓
Medicine safety advisory committee		✓			✓
Quality control committee		✓			✓
Core communication technologies for PV		✓	✓	✓	✓
Core PV reference material in PV center/drug information center	✓		✓	✓	✓
Core PV topics present in the pre-service training curricula	✓	✓	✓	✓	✓
Healthcare workers trained on PV and medicine safety	✓	✓	✓	✓	✓
PV stakeholder coordination mechanism		✓	✓	✓	✓
WHO Programme for International Drug Monitoring Membership		✓	✓	✓	✓
Quality management system for PV and quality assurance				✓	✓

✓ Indicator is met by the country
* Exists but not assessed/audited or fully in place
† SOP for QC only,
Blank cells denote that the assessment was unable to confirm the status of the indicator

to product safety. SOPs help stakeholders to implement guidelines and to standardize medicine safety functions operations within the regulatory authority. Thus, it is crucial that all countries develop and implement comprehensive guidelines and SOPs for PV activities.

To support national PV centers in meeting their mandate, multidisciplinary advisory committees are required. WHO recommends that medicines advisory committees include members from related scientific disciplines, including general medicine, clinical pharmacology, toxicology, epidemiology, pathology, drug regulation and quality assurance, and drug information (WHO 2000). The committees support PV centers and NRAs with the collection and assessment of medicine safety data, evaluation of risk, and communication of medicine safety decisions and information. There is also movement to have consumers represented on advisory committees through inclusion of patient groups or civil societies active in promoting access and safe use of pharmaceuticals. Consumer representation on medicine safety advisory committees is advised as a means of fully addressing and engaging patients in the national PV system.

The responsibility for PV should be shared among multiple stakeholders within a country, including drug regulators, the pharmaceutical industry, PHPs, health service delivery providers, civil society, international technical institutions (such as WHO), regional cooperation bodies, donor organizations and the public. Many countries have had limited and fragmented interactions and coordination efforts among stakeholders. Yet, a coordination mechanism is needed to know exactly what is happening where and when and who is doing what. This will allow an efficient use of resources and avoid duplication. Regular mapping of stakeholders, meetings with representative stakeholders, and defining pathways of collaboration between parties involved can contribute to this coordination. The WHO Programme for International Drug Monitoring is a global network that provides a mechanism for members to collaborate and build their capacity in PV so that early signs of medicine safety issues can be identified, information about them can be effectively shared, and appropriate actions can be taken on a global level. Membership in the program gives countries access to a database of worldwide medicine safety information, early information about potential safety hazards, data tools, and technical resources for PV (support, trainings, and guidelines). The membership requires that country must be a WHO member state; country must have a program for collection of ICSRs in place; country must have a national PV center recognized by the MoH; country has to demonstrate that it is capable of submitting data in the required format; a sample of at least 20 ICSRs collected in the national PV program should be submitted to the UMC (WHO 2010b).

Except for Bangladesh, all countries studied reported that they have core communication technologies to support their PV activities. Investments in communication technology and medicine safety reference materials within NRAs is necessary for national PV centers to receive, collate, and disseminate locally relevant medicine information and safety reporting to healthcare providers, consumers, industry, and other stakeholders.

Basic medicine safety reference materials help ensure that national PV centers have access to and can make full use of current and accurate medicine safety information to address medicine safety inquiries or generate safety communication materials and alerts. Countries may use the list of recommended core reference material for PV to benchmark their medicine safety information resources (annex F). The assessed countries are all doing well in ensuring that core PV topics are taught in pre-service programs and that health worker are trained in PV. The integration of locally relevant and contextualized PV topics into pre-service and in-service education for healthcare providers is vital to prepare them and refresh their knowledge and skills.

Because PV is a cross-cutting issue that touches on many disciplines, components of PV can be integrated into various existing courses and training programs. Public education on responsible and informed medicine use and attention to medicine safety are equally vital for a comprehensive approach to supporting the medicine safety system. Countries may refer to the list of PV topics to develop training materials for current and future healthcare professionals (annex F).

Signal Generation and Data Management

Systems for Coordination and Collation of PV Data from all Sources within a Country

With the exception of Bangladesh, all countries surveyed have a national database in place for collating ADR data and transmitting data to the WHO International Drug Monitoring Programme (table 15).

Table 15. PV Data Management

Existence of a system for coordination and collation of PV data from all sources in the country	Bangladesh	Cambodia	Nepal	Philippines	Thailand
Local database system for collating PV data from all sources		✓	✓	✓	✓
Method by which reporting forms are typically collected and transmitted to PV center or unit	Post	Electronic	Electronic*	Post/in person, electronic	Post, electronic
PV data transmission comply with E2B format		✓*	✓*	✓*	✓
Standard dictionaries and terminologies used to transcribe reported events (i.e., WHO-ART, MedDRA)		✓*	✓*	✓*	✓

* Via VigiFLow, the WHO-UMC ICSR management system; blank cells denote that the indicator is not met in that country

The system for the collation of PV data should enable a country to review submitted reports, identify missing data, and generate basic aggregate reports. The assessment also reviewed the data mining methods used by the different countries (table 16).

Table 16. Data Mining Methods Used in the Study Countries

Country	Method used
Bangladesh	Not available
Cambodia	BCPNN*
Nepal	BCPNN
Philippines	BCPNN
Thailand	ROR†

* BCPNN: Bayesian confidence propagation neural network (this is the WHO method and countries rely on the analysis done by the WHO)
† ROR: reporting odds ratio

Though four countries have database systems for collating PV data from all sources, none had a centralized data warehouse for storing adverse events reports from all sources including spontaneous reports through the passive surveillance system, active surveillance data or reports, periodic safety update reports (PSURs), and development safety update reports (DSURs). Bangladesh has not fully adopted ICH E2B format or the CIOMS I form for the reporting of adverse events.

Existence of a Form for Reporting Suspected ADRs

All countries surveyed were found to have a standardized national AE or suspected ADR reporting form that is designed to collect basic adverse event information. However, these forms were limited in their availability within service delivery points. Only 35 of 86 health facilities (41%) and 13 of 62 pharmacies (21%) sampled across five countries reported existence of an ADR form within their facility. Availability of ADR forms within industry was also limited: the assessment found that 23 of 38 pharmaceutical companies (61%), 4 of 7 medical device companies (57%), and 2 of 5 clinical research organizations (40%) studied had an ADR form available.

Low rates of ADR reporting are a serious challenge in Nepal, Cambodia, and Bangladesh. The contents, format, and transmission requirement of the reporting forms vary greatly across the countries; some require the reporter to determine seriousness, causality, and electronic transmission

The assessment found that Thailand and Philippines both have national ADR reporting forms that collect data on product quality issues, and medication error, and treatment failure.

Table 17. Signal Generation and Data Management at the National Level

	Bangladesh	Cambodia	Nepal	Philippines	Thailand
National PV data collation system		✓	✓	✓	✓
Consumer reporting form				✓	✓
Suspected ADR reporting form	✓	✓	✓	✓	✓
Product quality reporting form				✓	✓
Medication error reporting form				✓	✓
Treatment failure reporting form				✓	✓

Thailand has a consolidated form for the reporting of all suspected adverse events and for all health products.

Both Thailand and the Philippines have a separate and simplified consumer reporting form for suspected ADRs. Dissemination of the consumer reporting form to the service delivery level remains a challenge, particularly in Thailand, where none of the health facilities and pharmacies sampled was found to have the reporting form available. In the Philippines, only 3 of the 20 pharmacies studied (15%) had the form available, although it was found in almost half of the health facilities (11 of 23, 48%).

Discussion

The generation of safety signals is critical to detecting potentially harmful medical products, and taking appropriate regulatory action. Detecting and reporting of adverse events is the first step in a comprehensive and continuous PV monitoring process. WHO defines a medicine safety signal as "reported information on a possible causal relationship between an adverse event and a drug, the relationship being unknown or incompletely documented previously" (WHO 2000). Managing data once it is generated is equally important to allow safety risks to be evaluated, causality to be determined, and regulatory action to be taken in a timely manner. When a signal arises from one or more sources, particularly a potential signal that has significant public health importance, it should be further investigated. This process is essential both to ensure that harmful medical products are avoided and that safe and effective products remain in use.

Although countries had reporting forms available for ADR, optimal safety data reporting was affected by the low availability of reporting forms in points of service, the lack of forms to report medication error, deficient product quality, and treatment failure, and underreporting of adverse events by health professionals. Except for Thailand, in the other countries the reporting system for ADRs and product quality are separated and so is the reporting system for medical devices and vaccines separated from those of other health products.

Case Study 2. One Form for All Events in Thailand

In Thailand, the HPVC has developed one reporting form for suspected adverse events to all health products including medicines, drug/narcotics and psychotropic substance, food, cosmetic, medical device, and hazardous substance. The scope of adverse events covered by the form is adverse reactions, product quality, medication error, and treatment failure. The form is also a very good example of using a single form for spontaneous, intensive, and clinical trial reporting. While being consistent with international ICH E2B standards, the form's checklist format promotes adverse events reporting by requiring minimal written information which facilitates easy reporting.

The use of a consolidated form for the reporting of all suspected adverse events of health products is an emerging idea at the international level. This effort led by ISO and HL7 has led to the development of ISO/HL7 27953-1:2011 as an ISO standard for data exchange and information sharing.[1]

The opportunities for the development of this consolidated form in Thailand may not be unconnected to the overarching mandate of its HPVC to monitor the safety of all health products.

1 Individual case safety reports (ICSRs) in pharmacovigilance. http://www.iso.org/iso/home/store/catalogue_tc/catalogue_detail.htm?csnumber=53824

Risk Assessment and Evaluation

Number of Spontaneous Reports

Significant underreporting was observed in all countries, with the exception of Thailand. Table 18 provides the number of reports received by country in 2011.

Table 18. Actual ADR Reporting versus Expected

Country	No. of ADR reports (2011)	Population (million, 2011)*	Expected (200 ADR reports per million population)†	% of Expected
Bangladesh	0	150.5	30,100	0
Cambodia	83	14.3	2,861	3
Nepal	35	30.5	6,097	1
Philippines	3,351	94.9	18,970	18
Thailand	57,573	69.5	13,904	414

* World Bank Database, Accessed September 10, 2012 http://data.worldbank.org/country http://data.worldbank.org/country
† The WHO Programme for International Drug Monitoring recommends that in relation to ADR reporting, the optimal National Pharmacovigilance Centre should send over 200 reports per million inhabitants per year http://who-umc.org/DynPage.aspx?id=108476&mn1=7347&mn2=7252&mn3=7322&mn4=7558

Only Thailand met and exceeded the WHO requirement for optimal National Pharmacovigilance Centre to produce 200 reports per million population (WHO). Practices that may have contributed to this success include the adoption of the number of ICSRs as a performance indicator for health facilities by the Thailand National Health Security Office, the PV promoting activities of the Adverse Drug Reaction's Community of Pharmacy Practice (ADCoPT) which have provided a platform for reinforcing the need for reporting among pharmacists, and the Thai FDA implementation of the SMP.

Cambodia and Thailand conducted causality assessments on more than half of the adverse events reports generated through passive surveillance activities. This allowed for the further assessment and evaluation of signals that were likely to have a causal link with the associated medicine.

Active surveillance activities were found to be particularly limited among study countries (table 19). Only the NRAs in Thailand reported conducting active medicine safety surveillance in the last five years. Academia, including higher education institutions and organizations, in all countries reported conducting active surveillance activities with the exception of Cambodia. The University of Science and Technology in Bangladesh reported conducting active surveillance studies for an anti-epileptic medication, diabetic medication, and oncology medication. Industry and health facilities also reported conducting active surveillance activities in Bangladesh, Philippines, and Thailand.

Bangladesh, Cambodia, and Thailand reported conduct of product quality surveys and inspections by the NRA. None of the countries conducted studies in 2011 to quantify medication errors.

Table 19. Risk Assessment and Evaluation at the National Level

	Bangladesh	Cambodia	Nepal	Philippines	Thailand
Spontaneous reporting ≥ expected					✓
ICSRs with causality assessed (≥50%)		✓			✓
Product quality survey and inspections planned and conducted	✓	✓	Yes		✓
Medication errors studied				✓	✓
Medicine utilization studies	✓	✓		✓	✓
Active surveillance activities			✓		✓

Discussion

Medicine safety risks are typically identified within a country through signal generation activities, which require further investigation to protect patients and safeguard public health. The periodic review of suspected ADRs reported through passive surveillance and evaluation of potentially important safety signals detected through active surveillance are fundamental to any comprehensive PV and medicine safety system. A spontaneous report of a suspected ADR generates a qualitative safety signal that may warrant further investigation if the data is sufficiently complete and a causal relationship with a medical product is likely. In contrast, active surveillance generates quantitative information that provides information on the incidence (frequency) of safety events observed though various methods, including cohort event monitoring, product exposure registry, sentinel-site cohort studies, large simple trials, and other types of epidemiological studies (case-control study, cross-sectional study) (European Medicines Agency 2005; Meyboom et al. 1997). Active surveillance is particularly valuable for PHPs, such as HIV and AIDS, TB, immunization, and malaria control programs, and can provide useful information for making evidence-based decisions involving the selection of new medicines or revision of standard treatment guidelines. Study countries represent a range of capacity related to the assessment and evaluation of medical products safety signals. Risk assessment is essential in PV for it can provide the critical information needed for prompt decision making. Countries need to increase their capacities for causality assessment. Surveys on the quality of circulating medicines and related products as well as studies on medication errors are also informative PV interventions.

The five countries have their PV system as a distinct unit that does not have much interaction with the other units, particularly those involved in post-marketing surveillance for product quality, inspection, and enforcement. For example, the quality control laboratory relationship with the PV unit is weak and therefore opportunities for using the adverse events reporting form for product quality and medication error surveillance is not being exploited. Product quality surveillance generally occurs when the inspectors are out in the field to collect samples for testing. Control of advertising and promotion is also handled separately and complaints form for bogus promotional activities are nonexistent. Data collected from serious and unexpected adverse reactions during clinical trials of investigational drugs are not shared with the PV unit. Also, data from phase IV studies that have safety and effectiveness as outcome of interest is not in the national PV databases

Risk Management and Communication

Medicine Safety Information Requests Received and Addressed in the Last Year

The assessment found that Thailand and Philippines have medicine information processes that are in place and functioning with a minimum of one information request received and responded to per month. Medicine information offices are also in place in Nepal and recently established in Cambodia, although information requests are not yet routinely received or addressed.

The assessment found that Nepal and Thailand regularly publish medicines safety bulletins. However, the countries appear to still face challenges in the dissemination of medicine safety information, including bulletins, to PV stakeholders. In Thailand, 10 of 12 (83%) health facilities sampled reported receipt of the national medicines safety bulletin in 2011, but only 14 of 62 (23%) community pharmacies received the bulletin. In Nepal, 3 of 17 (18%) health facilities and 1 of 15 pharmacies (7%) sampled reported receipt of the national medicine safety bulletin in 2011.

All countries reported use of prequalification schemes, such as the WHO Prequalification Programme, for procurement decisions related to at least some medical products, most notably the national vaccine program. In the Philippines, for example, the government considers WHO Prequalification in vaccine procurement decisions, though conducts its own local prequalification practices for procurement of other medical products, such as generic medicines.

Nepal, the Philippines, and Thailand estimated the levels of unregistered medicines in their respective markets to be less than 1%. The assessment also found that Cambodia, which closely monitors the quality of its medicines in part to proactively combat the emergence of drug resistance, estimates the levels of unregistered medicines at 30%. Bangladesh also estimates high levels of unregistered medicines within its market (Business Monitor International 2013) and, as a result, its government has been vocal and proactive in recognizing the need to address this threat to medicines quality and public health.

All countries studied reported that medical products were both sampled and analyzed for quality in national medicines laboratories in 2011 (table 20).

NRAs in Cambodia, Philippines, and Thailand reported risk mitigation plans for high-risk medicines. The assessment found that of the 5 countries sampled, 10 of 19 (53%) national public health programs, 14 of 62 (23%) pharmacies, 17 of 86 (20%) health facilities, 8 of 38 (21%) pharmaceutical manufacturers, 0 of 7 medical device manufacturers, and 3 of 5 (60%) clinical research organizations have risk mitigation plans for high-risk products in place within their facilities. However, follow-up review indicated that countries have not adopted risk-based approaches as standard practice. Formal risk-based regulation is an efficient way

Table 20. Number of Medical Products Sampled and Analyzed for Quality

Country	Medicines sampled that were analyzed for product quality			
	No. sampled	No. analyzed	%	% failure
Bangladesh	3,720	2,687	69	0.04
Cambodia	1,837	1,837	100	4.6
Nepal	80	67	83	27
Philippines	4,298	4,185	97	
Thailand	2,000	2,000	100	10

Blank denotes no data

to focus limited resources on high-risk products and reduce regulatory burden on low-risk medicines. None of the countries have international risk management standards similar to the ISO 31000:2009 (ISO).

The Philippines and Thailand reported identification of medicine safety issues from outside sources such as other regulatory authorities including the US FDA, the EMA, and WHO. All countries reported taking at least one medicine safety action other than ADR reporting, such as issuance of safety alerts, recall of products, or withdraw of licenses within the last year. National PV centers reported that at the health facilities level, medicine safety action may be initiated by Drug and Therapeutic Committees (DTCs). All countries, with the exception of Bangladesh, were found to have at least one DTC in place that took medicine safety action to protect patient safety in 2011.

The assessment found some evidence of rapid communication methods for dissemination of medicine safety information, including posting of medicines safety alerts on NRA websites in Nepal, the Philippines, and Thailand. In Cambodia, the PV unit has an organized reporting system whereby PV focal point persons in each provincial health department and operational department are notified immediately by e-mail. Safety signals are then transmitted to health workers and the public by phone, fax, and official MoH correspondence. Encouragingly, Cambodia, the Philippines and Thailand reported alerting healthcare workers and the public of medicine safety alerts within three weeks of the detection. Through a literature review we identified that opportunities for regional information sharing on the safety and quality of products are available through the countries participation in the regional harmonization initiatives (RHIs). The PMA system of the ASEAN member countries can be used to notify the various regulatory agencies in a timely manner about defective or unsafe health products. However, at the time of the study, none of the ASEAN member countries studied was actively sharing information through the PMA system.

Table 21. Public Communication Activities

Country	Public or community education activities related to medicine safety carried out in the last year
Bangladesh	None through NRA; training and communication through pharmacist association.
Cambodia	None
Nepal	Media spots in newspaper; publication of drug bulletin; training on Good Dispensing Practice through Nepal Pharmacist association.
Philippines	Publicly available trainings through Philippines FDA Academy; training and communication through professional associations
Thailand	Public meeting on GMP; BE/BA 3-5 times per year; training and communication through professional associations

The PV centers in Nepal, Philippines, and Thailand reported conducting patient education activities related to medicine safety monitoring in 2011. In those three countries, as well as Bangladesh, professional associations were also involved in education activities, namely training and communication (table 21).

The assessment found that all of the countries surveyed had taken regulatory actions of some kind in addition to ADR reporting in 2011 (tables 22 and 23). The most common actions taken were changes to the EML, medicine formulary, or STGs; and issuances of safety alerts (or Dear Doctor letter/Dear Healthcare Professional letter). In only a few countries were products recalled, product licenses withdrawn, or marketing authorizations suspended—actions generally only taken in extreme cases. In comparison, Singapore Health Sciences Authority in 2011 issued 229 label changes, 23 product safety alerts, 6 product recalls, and 29 Dear Healthcare Professional letters.

Table 22. Other Medicine Safety Regulatory Actions Taken Besides ADR Reporting in 2011

NRA action taken	Bangladesh	Cambodia	Nepal	Philippines	Thailand
Label or package insert changes/boxed warning				✓	✓
Treatment guidelines, medicine formulary, or EML changes		✓	✓	✓	✓
MoH memo or circular referencing safety data			✓	✓	
Product recalls			✓	✓	✓
Withdrawal of product license	✓		✓	✓	
Suspension of marketing authorization	✓	✓		✓	
Risk management activities recommended due to safety data					✓
Dear Dr. Letters or safety alerts issued				✓	✓

Blank cell denotes that no action was taken.

Table 23. Risk Management and Communication

	Bangladesh	Cambodia	Nepal	Philippines	Thailand
Medicine safety information requests addressed				✓	✓
Regularly published medicines safety bulletins			✓		✓
Prequalification schemes used in procurement decisions	✓	✓	✓	✓	✓
Unregistered medicines in pharmaceutical market <3%		✓	✓	✓	✓
Medicines sampled and analyzed for product quality >95%		✓		✓	✓
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 healthcare workers and public <3 weeks		✓		✓	✓
Public or community education activities on PV	✓	✓	✓	✓	✓
Medicine safety action taken other than ADR reporting	✓	✓	✓	✓	✓
Drug and therapeutic committees addressed medicine safety issues		✓	✓	✓	✓

Blank denotes that the indicator is not achieved.

Product Quality Surveillance

This section consolidates the findings and analysis of the situation with monitoring the quality of products at the national level. There are opportunities for addressing product quality at each stage of the pharmaceutical management cycle. At the procurement stage, the use of prequalified suppliers, including medicines prequalified under the WHO Prequalification of Medicines Programme, and mandatory product registration help to prevent substandard and falsified products from entering the supply system. The study found that all five of the countries used prequalification schemes in some capacity in medicine procurement decisions. With respect to product registration, all of the countries required product registration with three of the five reporting that unregistered products represented less than 3% of the products in the pharmaceutical market. During distribution and storage, product quality surveillance monitoring includes shipment inspections, facility inspections and routine sampling and testing. Only 2 countries have good distribution practices (GDP) guidelines, while 2 others say the GDP is in draft. The study found that Bangladesh, Cambodia and Thailand reported both planning and conducting product quality surveys and inspections.

Although active quality surveillance activities can effectively prevent many unsafe medicines from making their way through the various levels of the supply chain to the service delivery points and the patients themselves, a comprehensive quality assurance system must also have mechanisms in place to detect problems at the point of use through the voluntary reporting of healthcare workers, patients and consumers. A voluntary reporting system, which represents the passive approach to product quality surveillance, can empower health workers and consumers to report products of suspected poor quality (Strengthening Pharmaceutical Systems (SPS) Program 2011). It is especially important for countries to implement, and maximize the benefits of the passive approach to product quality surveillance, particularly when their active quality surveillance activities are weak or limited in scope. The study found that only two of the countries—the Philippines and Thailand—have a standardized product quality reporting form, which health workers and consumers can use to report directly to the national PV program. Although some health facilities surveyed in all of the countries responded that they have a product quality reporting form for health workers, it was not confirmed if those reports were submitted to the national PV program or remained within the facility. Product quality reporting forms from pharmaceutical companies, which presumably are submitted directly to the companies rather than to the national PV program, are reportedly more common in the five countries. Although the results of the study suggest product quality reporting to the national PV programs in the five countries needs to be improved across all groups, consumer reporting appears to be the weakest. Reports of outbreaks of serious adverse events, which are suspected of being related to product quality, will typically require an investigation of causality and attribution of the adverse events to the suspected product. These investigations include product quality analysis by national medicines quality control

laboratories and other qualified laboratories—at times working in collaboration with technical partners, such as the USP/PQM program—that have the capacity to conduct the necessary tests. All five of the countries in the study have a national quality control laboratory or unit for product quality testing; however, only two of the countries' labs had verifiable capacity and performance: the Philippines and Thailand. The labs in those two countries reportedly have quality management systems in place for QA/QC and have been audited within the past five years. They also reported analyzing more than 95% of the samples they received, as did Cambodia's national lab. The labs in Bangladesh and Nepal analyzed 69% and 83% of samples, respectively.

After a quality problem is confirmed by a qualified laboratory, safety concerns related to the product quality still need to be evaluated using epidemiological studies to confirm attribution, quantify incidence and establish possible risk factors. Functional medicine safety systems need to have the capacity and resources to conduct, or outsource, both laboratory and epidemiological investigations in order to fully understand signals generated from adverse events so that the necessary alerts can be communicated and shared. In developing countries, where the national PV systems and regulatory authorities may not be adequately staffed and resources are limited, academic or research institutions in the country with the relevant skills and expertise may be enlisted to conduct the epidemiological studies. In developing countries a majority of ADRs are in fact related to product quality issue. It is important that coordination between PV centers and QC labs should be strong and both should share information. In reality in countries with good PV systems, it's often the PV center who should that communicates information to QC lab which is responsible for analyzing the quality of products. The QC labs usually receive medicines from different sources; usually – Pre-market authorization, post-market surveillance, routine inspections, and complains. Many health programs such also run quality monitoring programs (e.g., those receiving support from donors like USAID, or under obligation from the Global Fund), so in reality quality monitoring is not only limited to post-market surveillance, so the reporting mechanism between PV center and QC lab should be going both ways. This is also to say that without having quality control capacity in developing countries, most AEs will not be assessed effectively because a big majority of AEs are linked to product quality. PV should be considered as part of quality assurance pillars in developing countries. Select indicators related to product quality assurance in the five countries assessed are provided in the table below.

Discussion

Regulatory authorities are expected to receive and respond to medicine information requests from the PV stakeholders in their country. Half of the countries assessed had functioning drug information systems. NRAs should be equipped and staffed accordingly to provide medicine information to the public. It is also important for the NRA to publicize the availability of medicine information service to ensure its optimal use by the public. A key tool for medicine safety communication is the regular publication and distribution of medicine safety alerts and newsletters, particularly medicine safety information and alerts of local relevance. The alerts may be detected within the country through safety surveillance, published in the WHO Pharmaceuticals Newsletter or released by regional regulatory authorities and stringent regulatory authorities, such as the EMA and US FDA. Newsletters should be regularly published in print as well as electronically and distributed via the NRA or PV Center's website; electronic methods, such as e-mail list serves; and, more traditional methods, such as mailings. The assessment findings suggest that current efforts to publish

Table 24. Summary of Indicators related to Product Quality Assurance

	Bangladesh	Cambodia	Nepal	Philippines	Thailand
Legal provisions for product quality assurance	✓	✓	✓	✓	✓
Prequalification schemes used in medicine procurement decisions	✓	✓	✓	✓	✓
Unregistered medicines in pharmaceutical market < 3%			✓	✓	✓
Product quality reporting form				✓	✓
Existence of a quality control laboratory (or unit) with clear mandate, structure and functions	✓	✓	✓	✓	✓
Quality Control Advisory Committee		✓			✓
Quality management system for QA/QC				✓	✓
Guidelines for Good Distribution Practices in place	✓	✓		Drafting	Drafting
Product quality survey and inspections planned and conducted	✓	✓			✓
Medicines sampled and analyzed for product quality (>95%)		✓		✓	✓
Medicine safety issues identified from external sources and acted on		✓			✓

Blank cell denotes that no action was taken.

and disseminate the national medicines safety bulletins are reaching some stakeholders within the PV system but not all, representing missed opportunities to communicate medicine safety information to the point of care, particularly within community pharmacies.

Countries should safeguard their market by ensuring that unregistered medicines are not in circulation and that registered medicines in the country's supply chain are analyzed and are of good quality. Measuring the volume of products analyzed together with the percentage of analyzed samples that failed quality standards can indicate the extent of product quality problems among the medicines circulating in the country. When tracked longitudinally, countries can determine whether the problem has increased or decreased over time. National medicines laboratories should not only test medicines submitted for analysis but also actively sample medicines from the market for testing.

Medicine safety events can be either minimized or prevented when clear plans exist for avoiding serious known risks of medicines, at both the NRA and health facility level. Some medicines are considered high risk because they are known to cause significant adverse events when prescribed incorrectly or used in error (Institute for Safe Medication Practices).

Risk mitigation plans are used to prevent and manage ADRs by averting serious known risks of medicines. Such plans allow for targeted, resource-efficient approaches to managing known risks associated with medicines in which therapeutic benefit outweighs known risks, such as certain oncology medications. Using limited PV resources for high-risk medicines can improve the ability of the countries to efficiently safeguard public health.

Tracking external safety alerts from stringent PV systems such as US FDA and EMA is a cost-effective approach to reach life-saving regulatory decisions. Equally important is the rapid communication of relevant safety information to stakeholders from the national PV centers, which should be established as an authoritative source of information. Medicine safety information is only effective in safeguarding the public's health if appropriate regulatory actions are taken in response to safety threats. Regulatory actions, other than ADR reporting, may include label or package insert changes; revisions to the EML, medicine formulary, or standard treatment guidelines; circulation of MOH memos referencing safety data; product recalls; withdrawals of product licenses; suspension of marketing authorizations; adoption of risk management activities; and, dissemination of safety alerts.

Case Study 3.
Cambodia's Success in Containing Unregistered Medicines

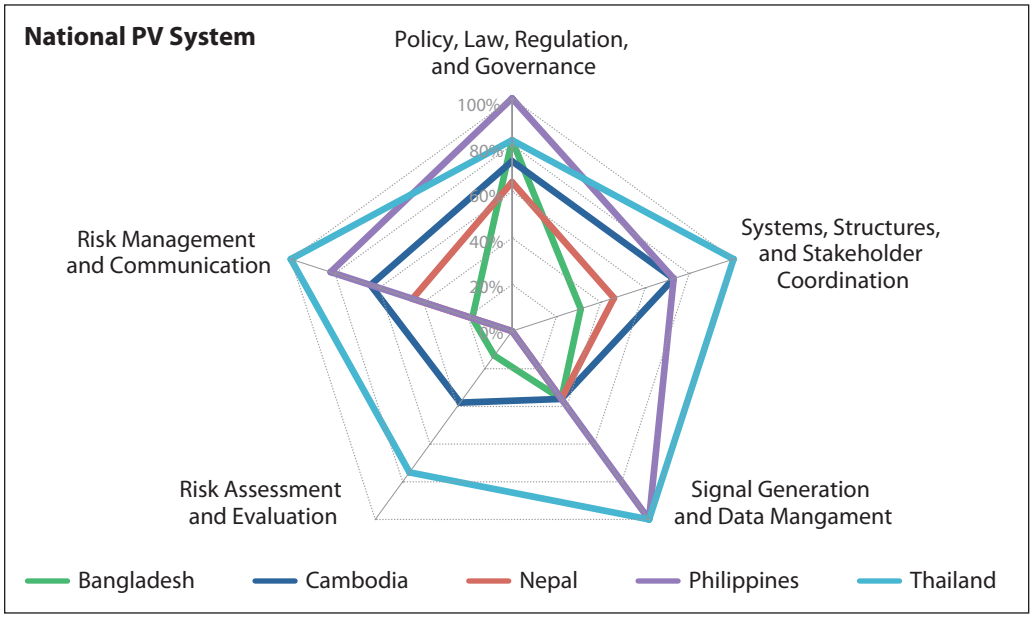
Controlling the sale of unregistered drugs on the market is a challenge for all countries, particularly those operating in resource-constrained settings. In Cambodia, the Department of Drugs and Food reports having capacity to identify the number of unregistered medicine in retail outlets, pharmacies and drug stores. Faced with the emergence of resistance to drugs such as antimalarials, the country has been proactive in closely monitoring the quality of medicines. Thanks to these efforts, the proportion of unregistered drugs has fallen sharply from 30%* to 3%.**

* Pharmaceutical Sector Strategic Plan 2005-2015, DDF, Ministry of Health, 2005)
** MoH, DDF 2012

PV Capacity at the National Level

Figure 3 represents the current situation and capacity of the PV systems at the national level by countries as demonstrated by the assessment findings, which measured the degree to which the countries had the key elements of a comprehensive PV system within each of the five main components. Stronger capacity is depicted by distance further from the center of the diagram, on a scale of 0 to 100%. As illustrated in the chart, Thailand has the greatest capacity, achieving 100% in three of the five PV components and over three-quarters in the other two. The Philippines also demonstrates strong capacity in four of the five areas; however, its capacity in risk assessment and evaluation is negligible, pointing to a suggested priority for their future efforts to strengthen the overall system. Although Bangladesh scores low in four of the five PV components, the strength of its capacity in policy, law, regulation, and governance provides a foundation and starting point for building up the other components of its PV system.

Figure 3. National PV Systems Capacity in Five Asian Countries



Options for Strengthening Pharmacovigilance at the National Level

Based on the findings from the individual country assessments and the review of the PV systems in the Asia region, we have provided options to be considered for addressing the limitations across the studied countries and in the region. In determining the most appropriate options, the level of development of the regulatory and PV system in the country should be considered.

Strengthening Regulatory Policies and Framework

Regulatory policy should articulate government's vision, principles, and practices for ensuring quality and safety of products. It should include governance clauses to ensure improved transparency of the functioning of the advisory committees, the participation of civil societies, protection for adverse event reporters, performance metrics for the regulatory authority to be held accountable, and evaluation of the impact of regulations. The regulatory frameworks of the countries studied were not explicitly stated by the NRAs. The Philippines has a National Policy and Program on Pharmacovigilance, which is a place to start but an overarching pharmaceutical regulatory policy may still be needed. With regards to the legislation, some aspects of the regulatory requirements for pre- and post-marketing surveillance activities are either very dated or nonexistent. These findings are consistent with the view expressed by a recent IOM report that some resource-constrained countries have no laws governing product safety; others have laws that are confusing and contradictory (Institute of Medicine 2012).

The studied countries have the following options based on the level of development of their regulatory and PV systems for strengthening their regulatory policy and framework—

- Develop new pharmaceutical regulatory policies and frameworks to ensure that regulations are effective and in the public interest or revise and consolidate the existing ones.
- Streamline sections of existing legislation that deal with aspects of medicines quality, safety, and post-marketing surveillance. Ensure that legislations are congruent with other relevant local laws or embark on regulatory reform and the development of entirely new legislations that will address emerging challenges for ensuring safety of health products.

Ensuring Convergent Regional and International Regulations

PV regulatory requirements among the countries vary a great deal. For instance, countries do not consistently require industry reporting of serious adverse events and the timelines for reporting these varies. Requirements for the submission of periodic safety update reports are

also varied. PV regulations that are not similar with those of stringent regulatory authorities (SRAs) or other competent regulatory authorities and are too demanding to meet can be an impediment to access to medicines. Conversely regulations that are too lax can expose patients to harm (Lebega O, Nwokike J 2012).

Options for countries for developing regulations convergent within the Asian region—

- Map differences and provide guidance on regulations that the country considers as equivalent to regional and international standards or develop guidance to industry to explicitly document regional equivalencies.
- Alternatively, countries can completely revise their PV legislation to make them convergent with that of stringent regulatory authorities and also consistent with the regional harmonization guidelines within the Asia Pacific region and other international guidelines. Some requirements countries could consider for convergence with SRA requirements and consistency within the region include timelines for reporting serious adverse events, PSURs, safety reporting during clinical trials , medical device vigilance regulations, use of the common technical document for registration application, requirements for PV plans and risk management plans, requirement for industry to conduct post-authorization studies, PV inspections and audits, and methods for benefit and risk assessments.

Improving Information Sharing and Participation in Regional Harmonization Initiatives

The globalization of pharmaceutical production and distribution activities and the increasing complexities of the products make the need for collaboration among regulatory authorities critical. When individual regulatory authorities repeatedly inspect manufacturers already inspected by others and fail to learn from the experiences of other regulators, there is duplication and lost resources. Mutual recognition, criteria-based prescreening or prequalification, and confidentiality agreements for regulatory information sharing are efficient strategies to avoid duplicative activities. These strategies are part of the objectives of regional harmonization initiatives. The ASEAN pharmaceutical product working group allows participants to coordinate their regulatory requirements and information sharing on the safety and quality of pharmaceutical products. However, countries seem to only participate in these initiatives including the mutual recognition agreement on GMP inspections and PMA system on a limited basis. The PMA presents an excellent opportunity for collaboration to safeguard the supply chain in the member countries. When safety concern that results in a recall or withdrawal happens, the system is used to notify the various regulatory agencies through the focal persons appointed by each country.

Options for improving participation in regional harmonization initiatives—

- The ASEAN pharmaceutical product working group should consider strengthening the PMA for collaboration and information sharing about product security in the supply chain by ensuring active participation and/or expand the program to cover the entire Southeast Asia region. The PMA should review its current functions, identifying opportunities for improvement and the participation of member countries. The review will help in setting up procedures and protocols. To improve its system, the ASEAN working group can review the functioning of the pharmaceutical Inspection Co-Operation Scheme Procedure for Handling Rapid Alerts and Recalls Arising from Quality Defects (PIC/S 2011) the WHO drug safety alert system, and the United

Kingdom MHRA defective medicines alert system (Medicines and Healthcare Products Regulatory Agency).

- The APEC AHWP should consider providing support to countries to begin the development of their regulatory pathway for medical devices and/or actively support countries efforts at capacity development for medical devices regulation.
- Since the SAARC and its standards organization South Asian Regional Standards Organization currently do not have any initiative with regards to harmonization of requirements for pharmaceuticals, an option can be to develop such initiatives. Another option would be for Bangladesh and Nepal to consider opportunities for information sharing with other regional harmonization groups in the region including the ASEAN working group and the APEC AHWP.

Reforming Organizational Structure to Achieve Integrated Safety Surveillance

Regulatory efficiency can be gained by restructuring the current operations of the post-marketing surveillance activities within the regulatory system. Countries should explore opportunities to review the structure for post-marketing regulatory activities. Across all the countries assessed, the current system is fragmented and opportunities for leveraging expertise and resources are not exploited.

Options for countries may include—

- Create a single vigilance center that can facilitate the integration of adverse events reporting for all health products. This has been implemented by Thailand through its HPVC. Also the Singapore Health Sciences Authority in 2009 renamed the Pharmacovigilance Branch as the Vigilance Branch. The Singapore authority said that this was important because the Vigilance Branch has expanded scope of safety monitoring of all health products since the same underlying principles of safety monitoring and risk management/mitigation applied to drugs are also applied to the other health products (Health Sciences Authority). This option, however, does not guarantee that all units involved in post-marketing monitoring will collaborate.
- Consolidate post-marketing surveillance department that brings together PV, product quality surveillance, routine inspections, and control of advert and promotion into a single unit. This will ensure that the different regulatory units dealing with these issues are placed under the same department.
- Enhance safety information sharing that may ensure that all regulatory units have systems in place to share databases and regulatory intelligence. Whichever option is preferred, restructuring should aim at developing an integrated surveillance system that is efficient and that supports the consolidation of all information about the safety of a product.

Ensuring Efficient Safety Surveillance and Reduction of Regulatory Burden

Some of the assessed countries' laws are redundant or too overreaching and the countries do not have the capacity to enforce them. When regulations are not enforced, it weakens the motivation for compliance. Countries can reduce regulatory burden and achieve efficiency through risk-based and risk proportionate regulations by adapting international risk

management standards like the ISO 31000:2009. In an effort to reduce administrative burden, the United Kingdom MHRA introduced a system of self-certification by the industry for low-risk medicines license variations (National Audit Office 2008). The authority also has a risk-based approach to PV inspections (Medicines and Healthcare Products Regulatory Authority 2013). The Australian Therapeutic Goods Administration introduced a risk based approach for regulating over-the-counter medicines. Countries should also reform their systems to consolidate reporting requirements on the industry. Fewer forms lead to a reduction in administrative and regulatory burden.

Possible options for countries to ensure efficient safety surveillance include—

- Explore opportunities for incorporating regulatory impact analysis as part of their regulatory system. This will ensure that the economic impact of new regulations and the determination of the cost-benefit of regulatory requirements are made part of the regulatory practice.
- Identify the most efficient ways to protect the population from unsafe products with minimal regulatory burden and using the limited resources available.
- Develop systems to ensure that PV regulations and enforcement efforts are risk proportionate or implement risk-based approaches using relevant criteria which may include the country of manufacture, falsification profile, storage and stability of the product, inspection history, and regulatory intelligence from other NRAs.

Improving Funding for PV

The assessment found that funding for PV is very limited. With limited budgets, regulatory authorities should revisit how they use the existing resources to achieve their mission to safeguard the public. Many countries have lopsided way of allocating their resources favoring registration over enforcement and post-marketing surveillance activities. In the United States, The US IOM committee on assessment of the US drug safety system found an imbalance in the regulatory attention and resources available before and after approval. Staff and resources devoted to pre-approval functions are substantially greater.[4] Less than 10% of products many regulatory authorities in LMICs register are new medicines that have never been registered elsewhere and therefore require full reviews. If countries reduce the need for duplicative reviews and inspections, they may have more resources for monitoring the safety and effectiveness of the products and enforcing regulatory actions.

Typically this is seen in terms of lack of dedicated budget for PV or the lack of staff dedicated to drug safety. Only Thailand confirmed that they have dedicated budgets available for PV activities. However, the consensus is that there is the need to develop innovative and rational means for funding regulatory and drug safety activities.

Options to countries for improving funding for PV include—

- Review resource allocation and use to determine the value for money for regulation and determine an evidence-based approach to resource allocation to regulatory function.
- Consider improving allocation to PMS including in-country product quality surveillance, licensing, in-country inspection, and enforcement activities.

4 Burke S. Chair, IOM Committee on the assessment of the US drug safety system. Statement before the committee on Health, Education, Labor and Pensions, US Senate. Nov 16, 2006.

- Identify other sources of funding. Options that exist include full public funding of PV or user fees charged to the industry, or some blending of these approaches. Germany and France use the full public funding option for all their regulatory activities, France case may be related to the benfluorex case of increased risk of heart valve diseases. In the EU, the introduction of the new legislations Directive 2010/84/EU and Regulation 1235/2010 requires the EMA to charge user fees for its PV services. The proposed fees include yearly service fee per product; fees for PSUR and post authorization safety studies (PASS), and referrals assessments. From the third reauthorization of the US Prescription Drug User Fee Act in 2002, the FDA is empowered to spend part of the fee on drug safety activities. The act versions IV and V have expanded the FDA's drug safety responsibilities and also the resources allocated. Funding PV through user fees charged on the industry is controversial because of concerns about potential conflicts of interest (HAI Europe 2012).
- Use of percentage of sales turnover. This method has been used in drug relief funds in Taiwan and Japan. To address the issue of additional funding for PV activities, a first step could be for governments in the studied countries to meet with stakeholders and discuss options.

Developing Comprehensive PV Guidelines

Countries should revise their PV national guidelines to make them more encompassing and address all issues related to safety and quality of medical products. Comprehensive national PV guidelines should address therapeutic ineffectiveness, medication errors, medical device vigilance, monitoring safety of blood products, control of promotional activities, and other emerging issues. The guidelines should also provide for the use of other epidemiological methods including active surveillance and large simple studies to complement passive surveillance. The national guidelines discuss the role of civil societies, conflict of interest, declaration of assets, and confidential financial disclosure by safety advisory committee members. The guidelines should also, prescribe procedures for meetings and contacts between the NRA and the regulated industries, dissemination of NRA deliberations/freedom of information, ombudsman, and existence of transparency measures and indicators.

Options for developing the guidelines may include—countries could revise existing guidelines or develop government circulars to address areas not included in the current guidelines. Alternatively, new comprehensive national PV guidelines could be developed by engaging the participation of all stakeholders and ensuring adequate buy-in from the regulated industry and government commitment to safeguard the safety of everyone exposed to all health products.

Strengthening Spontaneous Reporting

The assessment found that countries have approved national ADR forms, but their availability at the health facilities is limited. Only Thailand achieved the number of reports recommended by WHO. Several strategies can be used to strengthen reporting to facilitates signal generation and evaluation. Generated signals allow risk management to prevent further harm from the product. With the increasing diffusion of modern information technology it is clearly within reach to set up integrated health products surveillance system that will help improve understanding of medicines' safety and effectiveness during real-life use and also monitor quality of products in the supply chain.

Possible options for strengthening spontaneous reporting include—

- Use of information technologies for improving reporting include the adoption of online reporting forms, interactive PDF forms, reporting through electronic medical records, and cell phone text messaging. Cell phones are widely deployed in the countries studied, measured in terms of mobile cellular subscriptions per 100 inhabitants in 2010, except for Nepal (30.69). Philippines (85.7), and Thailand (100.8), have high cell phone diffusion that can be a good tool for post-marketing safety surveillance activities. Consumers can send reports of adverse events they think are related to medicines they used or report products with suspicious quality. These reports can be sent through prepaid lines. This type of system is currently being implemented in other countries (mPedigree).
- Adopt international standards for reporting. Assessed countries have not fully adopted ICH E2B format or the CIOMS I forms for the reporting of adverse events. The international safety reporting standard used by the SRAs and WHO for ICSRs is the ICH E2B standard.
- Explore opportunities to consolidate or streamline reporting forms for all health products (drugs, biologics, vaccines, and medical devices) and for reporting on safety and quality issues. The Thai FDA HPVC has a single form for reporting events related to all health products. Countries should also strengthen their data management capabilities to be able to consolidate or at least have easy access to pre- and post-authorization safety data on key products. This will allow for the construction of a more comprehensive safety profile for those medicines. Data from development safety update reports, spontaneous reporting system, and PSURs should be made easily available for review for taking regulatory decisions. A pre-registration clinical trial safety database can be a useful reference for flagging safety concerns that should be prioritized for post-marketing studies, thereby using the complementary roles of the pre-market and post-market safety data (O'Neill 1998). The HPVC single form for all events is also used for adverse events reporting in clinical trials.
- Develop online database for managing reports. The EMA has the EudraVigilance which is a data processing network and management system for reporting and evaluating suspected adverse reactions (EudraVigilance). The EU recently launched the European database of suspected ADR reports. The database is in most of the EU languages and provides immediate reports on reported suspected ADRs of medicines and several other reports that can be viewed through an interactive online PDF.
- Develop regional PV centers. Adverse events reporting can be improved by designating regional PV centers, particularly in university hospitals where there is access to qualified physicians, pharmacists, and nurses. In South Korea, the adverse events reporting pattern was dramatically improved with the expansion of the regional PV centers (Kimura et al. 2011). Other options include raising public awareness of medicines safety and adverse events reporting among professional and consumers associations. This option can be beneficial in countries where the associations are already engaged in PV activities like the Thailand Adverse Drug Reaction's Community of Pharmacy Practice.
- Countries should consider adapting the Thailand Safety Monitoring Program or related programs to ensure the safety of new medicines introduced in their countries. Although the SMP has not been evaluated since it was established in 1991; anecdotal

reports indicate that the program has helped to improve adverse events reporting for new medicines and improved watchfulness for better understanding of the safety profile of the new medicine. Similar schemes by other regulatory authorities include the EMA black triangle, Japan Early Post-Marketing Phase Vigilance, and the China SFDA requirement for a five-year monitoring period for new medicines. These programs are specifically for new chemical entities or new routes and new indications for existing medicines. Re-examination or re-evaluation after such intensive monitoring provides opportunities to review the safety profile of the product again before allowing it to be used more widely.

Confronting Falsified and Substandard Products

Both passive and active methods are required for confronting the public health challenges of falsified and substandard medicines and health products. Passive method enables the reporting of products of suspected poor quality through the use of adverse events form by both health workers and consumers. The active approach to quality surveillance includes pre- and post-marketing activities that are conducted during production, procurement, distribution and storage of pharmaceutical products, before they reach the point of use. Pre-marketing activities include chemistry, manufacturing and control (CMC) management and GMP inspections of pharmaceutical manufacturers to identify potential quality problems during the production phase. At the procurement stage, the use of prequalified suppliers, including medicines prequalified under the WHO Prequalification of Medicines Programme, and mandatory product registration help to prevent substandard and falsified products from entering the supply system. Options for improving the monitoring of product quality include:

- National PV systems have traditionally focused on ADR reporting while product quality monitoring programs have been implemented in parallel, with limited coordination or integration of the two. This separation in the reporting and management of adverse events and product quality issues represents a missed opportunity, which limits the effectiveness and efficiency of a quality assurance system. PV systems are an optimal platform for the implementation and management of reporting of suspected product quality problems by health workers, patients and consumers as part of countries' overall quality assurance efforts. Many countries, including the United States, use their adverse events reporting system for the reporting of suspected product quality issues, including the use of the same form for both reports. Consolidating reporting within PV systems in this respect can be beneficial to developing countries, particularly to the extent that it makes the system more efficient and contributes to increase reporting. For the PV system, the integration of the two reporting mechanisms, including the use of a single standardized form, reduces the number of forms that need to be designed, implemented and managed and facilitates cross-referencing of report information related to the same product, but generated through the two different types of reports. For health workers, patients and consumers, a single form designated for their particular use and a single reporting procedure facilitates the process for them and reduces confusion, which might otherwise discourage them from reporting. It can also help with the leveraging of resources for both investigation and enforcement on the part of the regulatory authority. In the Philippines and Thailand which have product quality reporting forms for health workers and consumers to report directly to the PV program, the forms are integrated into, or are a subset of, the adverse events reporting form, as recommended here.

- Donors and SRAs should consolidate their support to expand the activities of the WHO rapid alert system as a vehicle for addressing the issues of falsified and substandard products. Cambodia and the Philippines are already participating in this program. A recent IOM report recommends that consistent use of the rapid alert form and eventually linking it to national PV systems would advance international discourse and give a more nuanced understanding of the extent and type of falsified, substandard, and unregistered medicines that circulate around the world (Institute of Medicine 2013).
- Donors and SRAs should provide support to NRAs of the studied countries to improve their regulatory systems and enforcement capabilities for addressing false products. The NRAs should also be supported to develop new legislations that can positively support efforts in this direction including the requirement for traceability for pharmaceutical products. The industry could be required to implement barcoding and other strategies to track and trace products. Barcoding can also facilitate product recalls and improve patient safety. A couple of LMICs regulatory authorities recently required barcoding of pharmaceutical products. Countries should empower consumers to be watchful vanguard for product quality. The assessment identified the key use of the reporting platform of PV to support product quality reporting. As more consumers become more familiar with these reporting tools, they should be empowered to be the watchdog for fake products.

PV Results in Public Health Programs

The assessment included interviews with representatives from 19 national HIV and AIDS, malaria, TB, and immunization programs across five countries.

Policy, Law, and Regulation

Among public health programs assessed, 16 of 19 (84%) reported having a policy document for PV or medicine safety and a policy document for product quality assurance.

Systems, Structure, and Stakeholder Coordination

Among public health programs analyzed, 37% were found to have a PV group or unit assigned responsibility for monitoring medicine safety within the program. And all but one of those reported that the PV unit had an official document with clear mandate, organizational structure, roles, responsibilities, and reporting lines. Two PHPs additionally reported having at least one dedicated staff member responsible for PV or medicine safety activities, for a total of 47%. Fifty three percent reported existence of a unit that provides query response service on ADRs and medicine safety information.

Funding for PV-related activities was found to be limited among PHPs within the five countries studied, with only 26% found to have dedicated funds available. Several PHPs reported having SOPs (53%) and guidelines (58%) in place that addressed elements of PV. In Cambodia and Thailand, where a national PV guideline exists, the assessment found that only 43% of PHPs reported having knowledge of their national PV guidelines. Two PHPs in Cambodia and one PHP in Nepal (16%) reported having a safety advisory committee or unit that is responsible for monitoring and discussing medicine safety related issues within the program that met at least once in 2011, has clear guidelines for decision making, and a guideline on conflict of interested related to decision making. Nearly all of the PHPs sampled were reported having basic communication technologies available to improve access to safety reporting and provide medicine information (84%) and a third have core medicine safety reference materials available and in use (63%). In all countries, healthcare providers such as physicians, pharmacists, and nurses within PHPs were trained on PV and medicine safety in 2011, for a total of 58%. Most (79%) were familiar with the national PV center as the coordinating body for PV within the countries studied and saw a role for their program in ensuring medicine safety within their program (table 25).

Signal Generation and Data Management

Less than half of the PHPs studied (42%) reported keeping a log or database of PV data collected and transmitting data to the national PV center. In some cases, PHPs were found to be conducting signal generation activities, yet failing to submit the ADR reports to the national PV center for analysis and regulatory decision making. Of the PHPs assessed, 58% had a national ADR form on hand within their program at the time of the assessment. Very

Table 25. Results of System, Structure, and Stakeholder Coordination in Public Health Programs

Indicator	Responses (%)
PV unit in place	7/19 (37%)
At least one staff member responsible for PV activities	9/19 (47%)
Unit that provides query response service on ADRs	10/19 (53%)
Funding available	5/18 (26%)
SOPs that address elements of PV	10/19 (53%)
Guidelines that address elements of PV	11/19 (58%)
Basic communication technologies available	16/19 (84%)
Medicine safety reference materials available	12/19 (63%)
Healthcare providers trained on PV activities	11/19 (58%)
Healthcare providers familiar with national PV center	15/19 (79%)

few (29%) collected information on product quality, medication errors (0%), or treatment failure (21%), in large part because of the lack of ADR national collection forms (table 26).

Risk Assessment and Evaluation

None of the PHPs studied were found to collect spontaneous ADR reports at expected levels—100 reports per million of the PHP's patient population—and also report those ADRs to the national PV center. The national immunization program in Bangladesh reported collecting 1,100 adverse events following immunization reports in 2011 against a patient population of 3.7 million children vaccinated, for example, though none of the reports were transmitted to the national PV unit. Two PHPs in Thailand documented adverse events within more than 1% of their patient population or more in 2011.

Risk assessment and evaluation activities in the PHPs studied were minimal. In 2011, three conducted product quality surveys, one conducted a medication error survey, and four conducted medicine utilization surveys. Half of the PHPs (8 of 16) reported active surveillance activities, though some activities were potentially targeted to disease instead of medicines safety surveillance.

Risk Management and Communication

Very few PHPs reported receiving at least one request per month for medicine safety information in 2011 (11%). In Thailand and Nepal, where the PV centers regularly publishes a medicine safety newsletter, only three of eight PHPs received the bulletin. Nearly all PHPs (89%) reported considering prequalification schemes such as the WHO prequalification or the Pharmaceutical Inspection Cooperative Scheme when making medicines procurement decisions, frequently linked to the procurement of products through donor mechanisms requiring such controls. Only about one-third of PHPs studied submit medicines for quality testing. In some countries, including Nepal, standard QC testing was not conducted prior to products' distribution in country when products were provided by reputable donors including the Global Fund because of an assumption that the quality of such products are already assured and medicine safety surveillance is therefore not necessary or beneficial to the program. Risk management plans are currently in place that is targeted at high-risk medicines in (53%) programs (table 27).

Table 26. Results of Signal Generation and Data Management in Public Health Programs

Indicator	Responses (%)
Database of PV data	8/19 (42%)
National ADR form	11/19 (58%)
Collect information on product quality	4/14 (29%)
Collect information on medication error	0/14 (0%)
Collect information on treatment failure	3/14 (21%)

Table 27. Results of Risk Management and Communication in Public Health Programs

Indicator	Responses (%)
Received at least one request per month for medicine safety information	2/19 (11%)
Reported consideration of prequalification schemes when making medicines procurement decisions	17/19 (89%)
Submit medicines for quality testing	1/3 (33%)
Risk management plans in place	10/19 (53%)

Limitations were found among PHPs related to managing medicine safety information. Only one PHP reported identifying medicine safety issues of local relevance from outside sources such as the WHO, EMA, FDA, or other relevant Asian sources in 2011. Better communication channels were found to be in place between PHPs and healthcare workers and the public. More than half of the PHPs studied (10 of 19 [53%]) reported less than three weeks between identification of a significant safety issue such as a serious adverse event and communication to healthcare workers and the public. Eleven conducted training related to medicine safety or PV in 2011. Medicine safety action other than ADR reporting was found to be limited within PHPs because of their role outside of national regulatory systems. However, almost half reported taking some action such as distributing medicine safety alerts received from the national PV center.

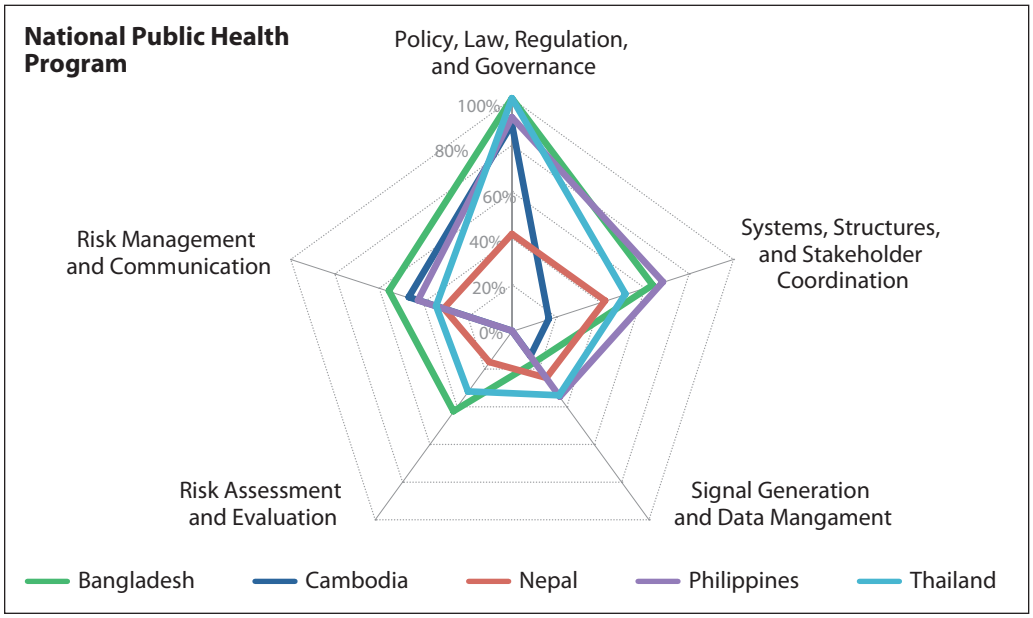
PV Capacity at the PHP Level

As evidenced by Figure 4, Nepal has the weakest PV system at the PHP level, while Bangladesh and the Philippines have the strongest. Almost all of the countries achieved 80-100% fulfillment in policy, law, and regulation.

Discussion

Policy documents that address the recognition of the need for the monitoring of the safety and quality of products are essential in the public health programs that deal with the entire population of a country. The results indicate that PHPs have challenges in establishing funding and structures for PV within their programs. These challenges limit the opportunities for using PV to inform treatment guidelines changes and for improving treatment outcomes. The PHP programs in most countries are equipped to collect clinical level data on patients. At the program level, the majority also routinely collects indicators for monitoring programs' performance. However, adverse events reporting are weak at the PHP.

Figure 4. National Public Health Program



Collecting data on real-life safety and effectiveness of medicines used on those programs and using the information will contribute to improving treatment outcomes. Doctor's notes on every patient on PHP whose treatment was switched most times indicate why the treatment was changed either the product was ineffective or patients could not tolerate the product. Both events are reportable adverse events. The reporting of medication errors is almost non-existent in the PHPs. Medication errors, for instance, the use of medicines when they are contraindicated, contributes to poor outcomes in HIV and AIDS programs. Substitution due to ARV toxicity can account for as much as 45.5% of treatment modification (Boulle et al. 2007). PV is particularly important for antiretroviral therapy programs because some patients will remain on antiretrovirals for their whole life, some of the long-term toxicity of the products has not been completely defined, and the effectiveness of treatment program can be compromised by problems related to toxicity. Monitoring long-term toxicity is therefore necessary and of value to the treatment programs (Bisson et al. 2003).

Public confidence on the efficacy of ARVs was part of the reasons why most patients agreed to seek care; safety concerns can negatively impact treatment continuation. Loss of confidence in the safety of ARVs could lead to poor adherence and the emergence of drug resistance, reduced demand for therapy, or inappropriate switching to more toxic or expensive medicines. All the countries studied are currently implementing public health programs (including vaccine programs, HIV and AIDS, TB, and malaria). Pharmacogenomics can be useful in understanding ARV-related hypersensitivity reactions that are human leukocyte antigen-associated. The work of the Thailand Pharmacogenomics Network and others can contribute in that direction. The cost for setting up and running safety studies can be prohibitive for developing countries, and many developing countries lack the systems to systematically review and translate the findings into practice. Conversely, routine surveillance can be less-prohibitive and the findings have more opportunities to be fed into quality improvement practices. LMICs could benefit more from leveraging existing surveillance systems for safety monitoring than relying only on ad hoc studies.

Options for Strengthening PV Systems at the PHP Level

Strengthening Routine Collection of information on the Tolerability of Medicines

Countries PHPs have several options they can adopt to improve adverse events data collection. They can encourage routine documentation of the reasons for treatment switches in the patient's case file, which can later be transcribed and processed as a report. Countries can also develop a system to transcribe patient records periodically and study the frequency of switches and tolerability of the medicines use. Data obtained should be shared with the PV center.

Improve PV Funding for within the Program

PHPS do not necessarily need to establish their own PV center, but they will benefit from identifying a staff responsible for PV who can collaborate with the national PV center. Having in place a medication safety or quality assurance staff member and providing specific funding for PV activities will improve patient safety within the program. Alternatively, PHPs also have the option to fund the national PV center with dedicated funds to study priority safety issues of interest to the program.

Develop Sustainable Risk Assessment and Evaluation Activities

In many of the countries studied, the PHPs have existing data collection systems for disease surveillance activities. Though typically fragmented, they have cohorts that can be used to study adverse events; therefore product safety surveillance can piggy-back on these systems. Countries should exploit these opportunities and develop an integrated safety surveillance system to support their public health programs. Countries should define their priorities in the areas of risk evaluation. The first step will be to have a formal process to determine research priorities on safety and quality of health products and identifying the need for post-authorization safety and effectiveness studies. Countries should explore opportunities for establishing sentinel sites for active surveillance, such as working with ART or TB programs to set up cohort event monitoring and then develop steps on how to use the information from safety studies to make decisions. Alternatively, PHPs can collaborate with their regulatory authorities, stringent regulatory authorities, and donors to form surveillance networks. There is a need for more collaboration and networking that can reuse existing infrastructure to conduct longitudinal studies. Such networks will enable countries to participate in cohort event monitoring collaborations. Observational cohorts based at health facilities are potentially valuable sources of information regarding medicine use, treatment effectiveness, adverse events, treatment discontinuations, program-based/systems-based treatment availability (or alternatively, stock-outs), and drug resistance (Miller, Nwokike, and Stergachis 2012) An example of a HIV cohort collaboration that includes safety surveillance is the US National Institutes of Health-sponsored International Epidemiologic Database to Evaluate HIV/AIDS cohort network. Also the Antiretroviral Pregnancy Exposure Registry, an ongoing surveillance on pregnancy outcomes for women receiving ARV medicines is another example of a collaboration of many stakeholders. The EMA developed the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance to strengthen post-authorization monitoring of medicinal products in Europe. These experiences can be reviewed to guide donor and SRAs in supporting the countries to set up similar cohort collaboration for the surveillance of safety of key products.

Include PV in Donation Programs

Donors and technical institutions that support providing medicines and health technologies should require their programs to conduct spontaneous reporting, active surveillance, and risk management, particularly for newer medicines, vaccines, and medical devices. Many countries receiving donated products for their public health programs from donors have limited capacity for post-marketing surveillance. The support from donors in making these medicines available has saved lives. Some of the donations from the global health initiatives such as PEPFAR and Global Fund have provided a life-line for the transforming the health system of those countries. After the initial focus on emergency provision of health interventions to those most in need, some of these global health initiatives are now focusing on the need for health systems strengthening. PEPFAR should do more to support PV systems in countries. This will become important as data for treatment guidelines revisions are increasingly needed and as patients remain longer on treatment, highlighting the need for data on long-term toxicity of the products. The launch of new medicines may provide opportunity and new challenges for PV as shown by the recent registration of bedaquiline by the USFDA with post-marketing surveillance conditions. The Global Fund has also recognized the need for supporting PV. A recent panel that reviewed the fiduciary controls and oversight mechanisms of the Global Fund recommended that the principal recipients be required to systematically invest more of grant budgets in PV programs that monitor the quality, usage, and efficacy of the drugs it buys, and that can track adverse events among patients and other post-marketing product defects.

PV Results at the Service Delivery Level

The assessment surveyed a total of 86 health facilities in the five countries. We defined health facilities as clinics and hospitals in both the public and private sector. A breakdown of the number and types of health facilities (public versus private) is presented in the table 28 below.

Table 28. Number of Health Facilities Surveyed

	Health facilities		
Country	**Public**	**Private**	**Total**
Bangladesh	14	9	23
Cambodia	6	5	11
Nepal	9	8	17
Philippines	15	8	23
Thailand	9	3	12
Total	53	33	86

In addition, 62 private or community pharmacies in the five countries were surveyed for the assessment. Community pharmacies in developing countries are often the first point of contact for patients seeking medicines. Thus, although physicians (and industry where mandated) have historically been the primary sources of adverse event reporting within countries, pharmacy workers also play an important role within PV systems, given their accessibility within communities and direct contact with consumers. Pharmacies also may serve a critical role within comprehensive PV systems as one of the primary sources of information for the general public regarding the use of medicines.

Policy, Law, and Regulation

An awareness of the policies, laws and regulations related to the monitoring and reporting of adverse events is important for private or community pharmacies to understand their role and responsibilities in the PV system. The assessment found that nearly half (47%) of the community pharmacies were aware of a national policy for monitoring and reporting adverse events; just over a third (37%) were also aware of the law and regulations related to the same.

Systems, Structure, Stakeholder Coordination

The assessment findings indicate that the majority of health facilities do not have internal systems and structures for PV that extend beyond those offered through the national system. Less than half of the public and private health facilities surveyed in the five countries have a PV center or unit, or designated staff for PV-related activities, within their facility (table 29). We defined a designated staff as someone who has PV-related functions in their job description irrespective of their primary roles. Such staff may be the medication safety

officer, quality assurance staff, pharmacists, nurse in charge of quality improvement, etc. Even fewer health facilities have a dedicated budget available for PV-related activities. Fifteen percent have a DTC at their facility. A quarter of the facilities reported having a copy of the national PV guidelines that have been updated within the last five years, all of which were in Thailand and the Philippines, while nearly a third reported having SOPs for PV-related activities, including ADR reporting. Twenty percent of all of the countries indicated that their healthcare workers had been trained on PV and medicine safety in the last year. For the provision of medicine information, 38% of the facilities have a medicine information or PV service that can address ADR and medicine safety-related questions and nearly half reportedly have core reference materials on medicine safety available at their facility. Over three-quarters have at least the minimum communication technologies to provide medicine information and access to medicine safety reporting. Although the majority of health facilities did not have strong systems and structures in place to manage medicine safety reporting and information provision in a centralized manner, a few of the respondents in the assessment noted that those matters were typically handled on the individual provider-level and in the patient-provider interaction.

A quarter of the private or community pharmacies surveyed are aware that a national PV center exists in their country (table 30). Nearly a third reported that they are aware of and have used a service to ask questions related to ADRs and medicine safety information. Our findings suggests that community pharmacies may also use services offered by sources other than just the national PV center, such as pharmaceutical companies. Eighty percent of pharmacies reported a role for pharmacies as PV stakeholders in ensuring medicine safety. Ten percent (n = 6), all of which were in Thailand and the Philippines, reported awareness of national guidelines for PV or PV policy equivalent.

Table 29. Results of Systems, Structure, and Stakeholder Coordination at Service Delivery Level

Indicator	Percentage
PV unit in place or designated staff for PV activities	~40%
Dedicated budget for PV-related activities	12%
DTC at facility	15%
National PV guidelines available and updated within last 5 years	25%
SOPs for PV related activities including ADRs	~33%
Healthcare providers trained on PV activities	20%
Medicine information or PV service that can address ADR-related questions	38%
Core reference materials on medicine safety at facility	~50%
Minimum communication technologies to provide medicine information and access to safety reporting	>75%

Table 30. Results of PV Related Activities Among Private Pharmacies Surveyed

Indicator	Percentage
Aware that national PV center exists in country	25%
Aware of and used a service to ask ADR related questions	~33%
Reported role for pharmacies as PV stakeholders in ensuring medicine safety	80%
Reported awareness of national guidelines for PV	10%

Signal Generation and Data Management

Although the ADR reporting form was the most commonly available PV-related form at the health facility level, less than half of the health facilities surveyed in the five countries had an ADR reporting form available at their health facility at the time of the assessment (table 31). Approximately a quarter of facilities had a form for reporting medication errors, less than a fifth had a product quality reporting form, and only 6% had a form for reporting treatment failures. The forms available included those provided by the national PV system and forms provided by individual public health programs and pharmaceutical companies. Adverse events may be more commonly reported in patients' files rather than recorded centrally or in the provided forms, which allows for individual assessment and action, but does not allow for trend analysis and risk assessment. A fifth of the health facilities surveyed had a consumer reporting form available for patients (table 31). Consumer reporting of suspected ADRs and other related medicine safety concerns seem to occur more often through personal communication between patients and medical staff, which puts the onus on healthcare providers to report the event and any other medicine-related problems through the formal forms and channels, where they exist.

Table 31. Results of Signal Generation and Data Management at Health Facilities Level

Indicator	Percentage
ADR reporting form available at health facility	41%
Form for reporting medication errors	~25%
Product quality reporting form	18%
Form for reporting treatment failures	6%
Consumer reporting form	20%

In addition to generating safety signals, health facilities can collect relevant medicine safety information not only from the ADR and other medicine-related reports submitted within their facility but also from other in-country sources, including medicine safety bulletins and alerts from regulatory authorities, PSURs, and additional published safety data generated from clinical trials, active surveillance activities, medicine utilization surveys, and product quality surveys. Medicine information centers within health facilities typically have the responsibility to collect and distribute such information. A quarter of the health facilities reported having an information system or database within their facility for collecting, collating, and managing PV data and other relevant medicine information from their facility, in-country sources, or international sources, such as WHO.

Given that pharmacies are a primary source of medicines and have direct contact with patients, they have an important role to play in generating signals for the PV system. The assessment found that 20% of private pharmacies have some kind of ADR reporting form available, 20% have a product quality reporting form, and 20% have a medication error reporting form (table 32). In many cases, the available data are from pharmaceutical companies or suppliers, rather than from the national PV center or MoH. To engage consumers in reporting suspected adverse events, product quality issues' and medication errors, reporting forms should be available at all service delivery points, including private pharmacies. Only 6% of the pharmacies surveyed had a consumer reporting form available at the time of the assessment. Substantial opportunity exists to improve the availability of these forms at the pharmacy level.

Table 32. Summary of Results among Private Pharmacies Surveyed

Indicator	Percentage
ADR reporting form	20%
Product quality reporting form	20%
Medication error reporting form	20%
Consumer reporting form	6%

Risk Assessment and Evaluation

Less than a third (26%) of the health facilities surveyed in the five countries for this assessment had received an adverse event form. However we could not determine how many of these reports were submitted to the national PV program (or a pharmaceutical company) in the last year. In Bangladesh and Nepal, none of the health facilities indicated that they had reported a suspected ADR to the national level, although in some cases they may have reported to a sub-national level, which would have then been responsible for reporting to the national level. Twenty-two of 84 facilities (25%) had submitted 100 spontaneous reports per million population served at their facility (or fraction thereof) in accordance with the WHO recommendation. Those that met the WHO target were from Thailand and the Philippines.

Assessing risk requires information not only on ADRs but also on product quality, medication errors, and medicine use. In 2011, the last full year preceding the assessment, product quality surveys had been conducted at one-fifth of the health facilities, medication error studies at one-quarter, and medicine utilization studies at one-fifth (table 33). The health facilities that carried out these surveys and studies were mainly in Thailand and the Philippines. The health facilities in Cambodia had not conducted any surveys or studies.

Approximately a quarter of the health facilities in the assessment in Thailand and the Philippines reported active surveillance activities that are currently on-going or have been carried out in the last five years.

All of the private pharmacies that reported collecting and submitting ADR reports were in Thailand, with the exception of one in Nepal. Two of the Thailand pharmacies have met the recommended threshold of spontaneous reports (i.e., more than 100 reports per million population served—6,952 reports in 2011). No private pharmacies in Bangladesh, Cambodia, or the Philippines reported collecting or submitting any ADR reports in the previous year (2011).

Table 33. Results of Risk Assessment and Evaluation at Service Delivery Level

Indicator	Percentage
Product quality surveys	20%
Medication error studies	25%
Medicine utilization studies	20%
Active surveillance activities (e.g., cohort studies)	~25%

Risk Management and Communication

The assessment found that over 33% of the health facilities use prequalification schemes in medicine procurement decision-making—in many cases because of the country's procurement policies, which mandate procurement of prequalified medicines when possible—to prevent the occurrence of adverse events related to poor quality products. Sixteen percent of the health facilities reported having sampled and analyzed > 95% of medicines for product quality in the previous year by sending samples to quality laboratories. Twenty percent have risk mitigation plans currently in place.

Twenty-four facilities (slightly above 25% to assessed facilities in study) in Nepal, Thailand, and the Philippines reported that they had received medicines safety bulletins from their national PV centers. Health facilities in all countries had received medicine bulletins of some kind, if not from the national PV center, then from the MoH, NGOs, or pharmaceutical companies. Whether the ADR signal generation came from the facility, the national PV center or another source, almost a third of the health facilities indicated that the average time from ADR signal generation to communication to HCWs and the public was less than three weeks. Just over 20% of the facilities had conducted at least one training or patient education program related to medicine safety in the last year. Fourteen percent had received and addressed at least one medicine safety information request per month in the previous year.

As indication of health facilities effectiveness in addressing medicine safety issues at the level of service delivery beyond basic reporting, approximately one-fourth of the total facilities reported that they had taken medicine safety action (other than reporting the ADR) in the last one year to inform clinical management, guideline revisions, regulatory decisions, or health worker and patient education. Eight facilities (9%) had identified medicine safety issues of local relevance from outside sources and acted on them locally in the last year (table 34).

Table 34. Results of Risk Management and Communication at Service Delivery Level

Indicator	Percentage
Use prequalification schemes in medicine procurement	>33%
Sampled and analyzed >95% of medicines for product quality	16%
Have risk mitigation plans in place for high risk ADR medicines	20%
Received medicines safety bulletins from national PV centers	~25%
Indicated average time from ADR signal generation to communication to HCWs < 3 weeks	~33%
Conducted training or patient education programs	~20%
Received and addressed at least one medicine safety information per month in previous year	14%
Reported taken medicine safety action (other than reporting ADR) to inform clinical management	~25%
Identified medicine safety issues of local relevance from outside sources	9%

Pharmacists' role in the community and direct interaction with patients makes pharmacies an important source of information for patients. It is therefore important that they receive all pertinent medicine safety information, from the national PV center or MoH as well as from industry, so that they can act and inform patients accordingly. Only three private pharmacies in the assessment (5%) reported that they had received and addressed at least

one medicine safety information request per month last year. Nearly a quarter (27%) received medicine safety bulletin (from the PV center or any other stakeholder, including industry) in the past year.

The same percentage of pharmacies was aware of strategies or plans (such as a medication guide) being implemented to mitigate and restrict the use of high-risk medicines due to safety concerns. Although the pharmacies' awareness of any public and community education activities on ADRs and medicine safety topics was 27%, nearly two-thirds (63%) who acknowledged to have received safety alerts, were aware of at least one medicine safety action other than ADR reporting, such as those taken by the regulatory authority or government institution as well as by pharmaceutical companies. The assessment findings indicate that private pharmacies' role in the national PV system has not been adequately realized in any of the five countries and that tremendous opportunity exists to engage them more fully and actively and maximize the benefits of their face-to-face interactions with patients, not only in terms of reporting but also in terms of disseminating information and educating the public.

Table 35. Results in Private Pharmacies Surveyed at Service Delivery Level

Indicator	Percentage
Received and addressed at least one medicine safety information request per month last year	5%
Received medicine safety bulletin in past year	~25%
Pharmacies aware of strategies or plans being implemented to mitigate and restrict use of high risk medicines	~25%
Pharmacies awareness of public and community education activities on ADRs	27%
Pharmacies aware of at least one medicine safety action other than ADR reporting to inform clinical management	63%

PV Capacity at the Health Facility Level

Figure 5 below illustrates not only the overall deficiencies in the functioning and capacity of health facilities within the PV systems assessed but also the substantial differences between countries. Although Thailand's health facilities have some shortcomings, they are currently functioning, and have the capacity to function at a notably higher level than the health facilities in the other countries. The health facilities in both Bangladesh and Nepal are contributing only minimally to the PV systems in their respective countries. It is notable that the strongest component of the PV system at the health facilities in all the countries was the systems, structure, and coordination component. This suggests that they have some of the means to improve the other components. Figure 6 depicts the PV system in private and community pharmacies in the five countries. Performance across all components of the PV system is weak however Philippines (awareness of existence of policy and regulations) and Thailand (risk assessment and evaluation) perform better than other countries.

Discussion

PV activities at the health services delivery points is very weak across all countries studied. From poor availability of adverse events reporting forms to lack of budget for PV-related activities, non-functional DTCs, no trainings, and lack of medicine safety information, it appears that PV is failing at the point where it is required the most—the interface between the health providers and patients. Clearly ensuring medicines safety to protect the patient

Figure 5. PV Capacity at the Health Facility Level

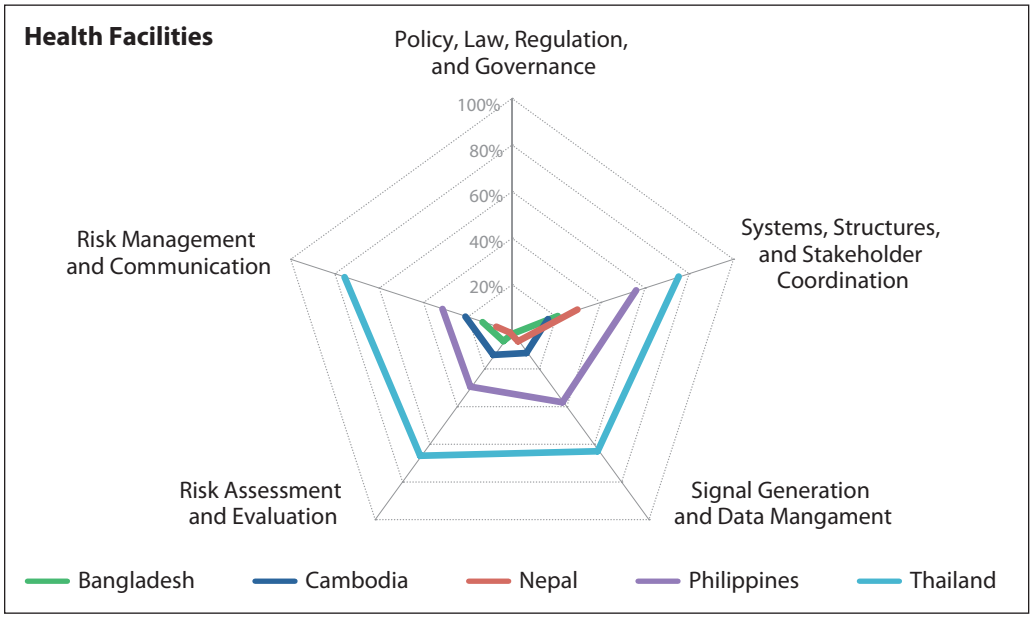
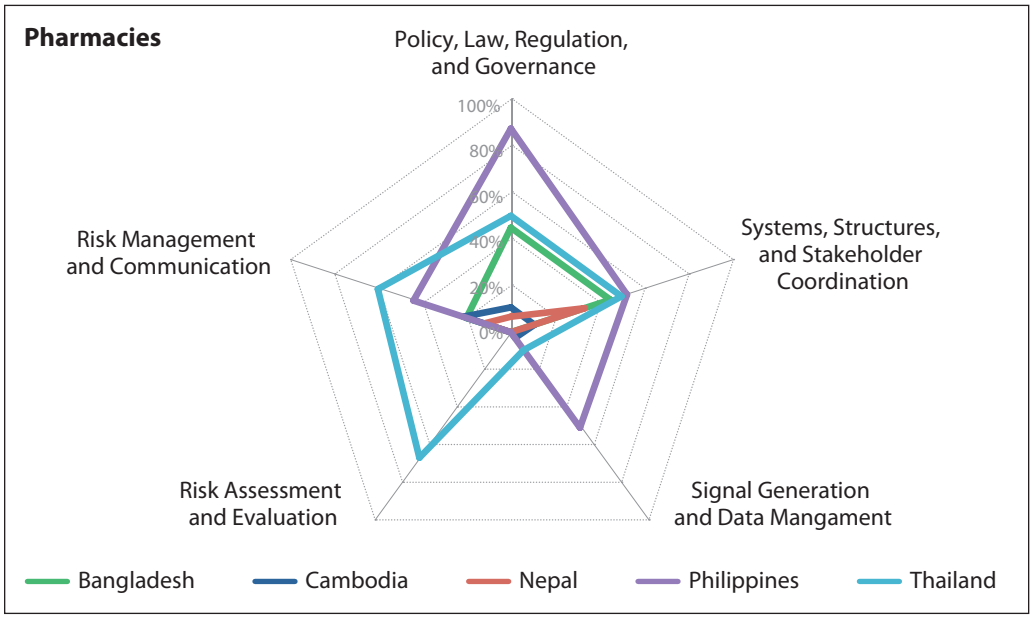


Figure 6. PV Capacity in Private and Community Pharmacies



and ensure optimal treatment outcomes is merely receiving adequate attention. The implications are that patients are exposed to preventable harm. Many high-risk medicines are in the national register of all the countries studied. For instance, biologics medicines (including abatacept, adalimumab, infliximab, rituximab, tocilizumab that are indicated for rheumatic diseases and trastuzumab and bevacizumab indicated for cancers) are in countries' national registers and used in some of the health facilities. Yet these facilities do not have guidelines for managing high-risk medicines and some do not have a medication safety or quality assurance staff. The use of medicines utilization reviews, risk management, and risk communication to the patient can help to make PV contributions to improvements in health outcomes more easily recognized. The successes achieved in establishing PV systems at the national levels should be followed through to the services delivery levels.

Options for Improving PV at the Service Delivery Level (Health Facilities and Community Pharmacies)

Inform Health Workers on the Value of PV

Healthcare providers are the bedrock for the identification of new concerns on the safety and effectiveness of medicines. Most of the important observations that led to the removal of harmful products from the market, including the case of thalidomide came from case reports from diligent physicians and other health workers. If health workers are trained to appreciate the contributions adverse events reporting can make to safeguard the patients, it may help to stimulate interest in PV.

Streamline Adverse Events Reporting

Unfortunately, the current spontaneous reporting system is laden with systematic and logistical challenges that need to be reformed to ensure health worker participation. The current reporting system is burdensome for the busy clinicians and the system does not motivate the reporter. A reporter who has taken the time to observe and send reports on an event is presumably interested in knowing about the outcome of the investigations and the next cause of action. Also in the medical records in most countries, the reasons for the switching or stopping of therapies are often noted. Health workers should be informed of the dual actions required when adverse events occur in clinical care; recognize and manage the event (clinical PV), and report the events (regulatory PV). Countries should consult with health workers in open forums to discuss on the best approaches for improving the roles of the staff, the health facilities, and their committees in PV.

Develop In-Service Training Curriculum on PV

Countries should consider options for developing in-service PV curriculum and incorporate it into health workers' regular trainings.

Transcribe Data from Patient Files

The study found that in many health facilities adverse events may be more commonly reported in patients' files as justification for treatment switches. Health facilities should collaborate with the national PV program to transcribe these events from the patient records and submit them to the PV center.

Strengthen DTCs

In most of the countries medicines utilization reviews are rarely conducted—a key role for the DTCs. Countries should consider options for strengthening the DTCs including making the committee's activities part of the performance indicators for doctors, pharmacists, and nurses.

PV Results in the Pharmaceutical Industry

The assessment included five clinical research organizations, seven medical device companies, and 38 pharmaceutical companies, including multinational innovator, multinational generic, and local innovator and generic manufacturers.

Policy, Law, and Regulation

Legal provisions and policy statements at the national level dictate the medicine safety regulations to which the pharmaceutical industry is required to adhere. Pharmaceutical industries are therefore encouraged to develop policies and procedures that define how they plan to ensure compliance to the national laws and policies. The assessment found that 29 of 38 pharmaceutical companies (76%), 5 of 7 medical device companies (71%), and 5 of 5 clinical research organizations (CROs) (100%) have updated internal policy statements on PV or medicine safety within the last five years. Fewer industry reported procedures to ensure compliance with national laws, as only 23 of 38 pharmaceutical company (61%), 4 of 7 medical device company (57%), and 1 of 5 CRO (20%) have SOPs to address PV and medicine safety in the quality system of the company, procedures that mention legal provisions for PV/medicines safety, and the submission of PSURs as required in country. Only Cambodia and the Philippines were found to have laws requiring market authorization holders to report serious ADRs to the NRA, and only Philippines and, to a limited extent, Thailand require post-market surveillance.

Whereas only Cambodia, Philippines, and Thailand (through the SMP program) has mandatory reporting requirements for the industry, the assessment found that 25 of 35 pharmaceutical companies (71%), 7 of 7 medical device companies (100%), and 3 of 5 CROs (60%) studied had mandatory reporting requirements for ADRs within the company. Another 28 of 35 pharmaceutical companies (80%), 3 of 7 medical device companies (43%), and 2 of 5 CROs (20%) reported mandatory requirements to conduct post-marketing surveillance. This discrepancy is likely due to global reporting requirements among multinational respondents who are required by SRAs to mandatorily report ADRs in countries where they market the product. All but two of the industry respondents reported procedures for addressing product quality assurance. Most have procedures for addressing PV or medicine safety information in advertising and promotional materials (32 of 38 pharmaceutical companies [84%] and 6 of 7 medical device companies [86%]).

Systems, Structure, and Stakeholder Coordination

Among industry representatives studied, 25 of 38 pharmaceutical companies (66%), 4 of 7 medical device companies (57%), and 4 of 5 CROs (80%) have a PV or medicine safety unit, either as a stand-alone unit or a subset, assigned responsibility for monitoring medicines safety. Of those, roughly half within pharmaceutical and medical device companies were found to be fully operational with a clear mandate, structure, delineation of roles and

Table 36. Results of Policy, Law and Regulation in the Pharmaceutical Industry

	Pharmaceutical companies, %	Medical device companies, %	Clinical research organizations, %
Updated internal policy statements on PV	76	71	100
PV procedures	61	57	20
Mandatory reporting requirements for ADRs	71	100	60
Mandatory requirements to conduct post-marking surveillance	80	43	20
Procedures for advertisements	84	86	n/a

responsibilities; have implemented PV-related activities in 2011; PV inspections conducted within the last five years and reports generated; and procedures for PV audits and inspections in the companies' quality systems. Industry representatives that reported having at least one staff member designated responsibilities for PV and medicines safety came from 30 of 38 pharmaceutical companies (79%) and 5 of 7 medical device companies (71%).

Nevertheless, funding for PV within industry sampled was found to be limited. Only 19 of 37 pharmaceutical companies (51%) and 3 of 7 medical device companies (43%) had dedicated funds available for PV-related activities in 2011. Less than half of the pharmaceutical and device companies reported having SOPs for PV and medicine safety both in place and followed (18 of 38 pharmaceutical companies [47%] and 3 of 7 medical device companies [43%]), though 4 of 5 (90%) of CROs reported have such SOPs in place. Quality control units were found to be present and functional in 24 of 37 pharmaceutical companies (65%) and 6 of 7 medical device companies (86%) studied.

Communication technologies for PV and provision of medicine information was found to be available and functional in nearly all industry respondents (36 of 38 pharmaceutical company [95%], 6 of 7 medical device company [86%], 5 of 5 CROs [100%]) and core reference materials for PV or safety were found to be available in most (28 of 38 pharmaceutical company [74%] and 6 of 7 medical device company [86%]). In 2011, staff members were trained on PV and medicine safety in 28 of 38 pharmaceutical company (74%), 6 of 7 medical device companies (86%), and 4 of 5 CROs (80%). When ask if they have system for preparing for PV inspections and if they have had an audit of the PV quality management system in the past 5 years, 63% of companies answered yes.

Table 37. Results of Systems, Structures, and Stakeholder Coordination in Pharmaceutical Industries

	Pharmaceutical companies, %	Medical device companies, %	Clinical research organizations, %
PV unit	66	57	80
At least 1 staff member designated responsibilities for PV	79	71	n/a
Dedicated funds available for PV	51	43	n/a
SOPs for PV in place	47	43	90
Quality control units	65	86	n/a
Have functional communication technologies for PV	95	86	100
Have core reference materials	74	86	n/a
Staff trained on PV	74	86	80

Signal Generation and Data Management

Among industry representatives studied, 16 of 38 pharmaceutical companies (42%), 4 of 7 medical device companies (57%), and 2 of 5 CROs (20%) reported being fully engaged in the generation of medicines safety signals. This includes a system for archiving and storage of medicine safety-related documents with transmitted data, a system that is ICH E2B compliant and tracks activities and workload; sufficient capacity for electronic submission of ADR reports to the NRA, and databases that use standard terminologies (i.e., MedDRA). The assessment found significant deficiency regarding use of the national ADR form. Although the national ADR form is readily available within each country, 15 of 38 pharmaceutical companies (39%), 3 of 7 medical device companies (43%), and 3 of 5 CROs (80%) did not have AE reporting forms available. Twenty-seven out of thirty-eight pharmaceutical companies [71%], 2 of 5 CROs [40%]), medical device error (1 of 7 medical device companies [14%]) has product quality reporting forms. For lack of efficacy (17 of 38 pharmaceutical companies [45%]) have reporting forms and none of the CROs have treatment failure forms (0 of 5 CROs).

Table 38. Availability of Forms in Pharmaceutical Industry

	Pharmaceutical companies, %	Medical device companies, %	Clinical research organizations, %
Product quality	71	14	40
Medical device error	n/a		n/a
Lack of efficacy	45	n/a	n/a
Treatment failure	n/a	n/a	0

Risk Assessment and Evaluation

Industry contributes to the risk assessment and evaluation of medical products by detecting safety signals for further evaluation and conducting studies such as Phase IV post-marketing surveillance studies, in the event that product safety profiles are incomplete or otherwise require further assessment and evaluation. Among the companies included in the assessment, it was found that less than half of pharmaceutical companies (16 of 38 pharmaceutical companies [42%]) and just more than half of medical device companies (4 of 7 medical device companies [57%]) and CROs (3 of 5 CROs [60%]) collected spontaneous ADR reports, put them in a database, and transmitted to the local NRA. In 2011, causality was determined for the majority of the records in the database in only a third (13 of 38) of pharmaceutical companies surveyed.

Pharmaceutical industry plays an important role in validating medicine safety signals of concern through post-marketing surveillance and product quality assurance activities. However, only a small percentage of industry conducted these types of activities in 2011. Two of 38 pharmaceutical companies (5%) and 2 of 7 medical device companies (29%) conducted product quality surveys; none and 3 of 7 medical device companies (4%) but none of the 38 pharmaceutical companies conducted surveys of medication/device errors , and, 6 of 38 pharmaceutical companies (16%) and none of the medical device companies conducted medicine/device utilization reviews. Within the last five years, active surveillance activities were reported to be conducted in 15 of 38 pharmaceutical companies (39%), 4 of 7 medical device companies (57%), and 1 of 5 CROs (20%) sampled (table 39).

Table 39. Results of Risk Assessment and Evaluation in Pharmaceutical Industry

	Pharmaceutical companies, %	Medical device companies, %	Clinical research organizations, %
Collect spontaneous ADR reports	42	57	60
Conduct product quality surveys	5	29	n/a
Conduct medication/device error surveys	0	43	n/a
Conduct medication/device utilization reviews	16	0	n/a
Conduct active surveillance activities	39	57	20

n/a denotes not applicable and that the indicator was not assessed

Risk Management and Communication

The assessment found that industry was an important source of medicine safety information among healthcare providers, pharmacists, and consumers. Medicine/device safety information requests were received and addressed at least once per month in 2011 in 12 of 38 pharmaceutical companies (32%), 2 of 7 medical device companies (29%), and 2 of 5 CROs (20%). A fifth of the pharmaceutical companies surveyed (8 of 38; 21%) reported the publication of medicine safety alerts in 2011.

Locally implemented risk mitigation plans that require EU or United States mitigation strategies to control distribution and use of high-risk medicines because of safety concerns was reported in 8 of 38 pharmaceutical companies (21%), and 3 of 5 CROs (60%); none of the 7 medical device companies issued reports. Medicine and medical device safety issues of local relevance were identified from outside sources and acted on locally in 2011 in 7 of 38 pharmaceutical companies (18%), 1 of 7 medical device companies (14%) and 2 of 5 CRO (2 %). Medicine safety information was reported to have been communicated promptly to healthcare workers and the public by nearly half of the pharmaceutical companies sampled (18 of 37; 49%), 2 of 7 medical device companies (29%) and 2 of 5 CROs (20%). Industry was aware of medicine safety action taken by the NRA (e.g., dear doctor letters) to inform clinical management, guideline revisions, regulatory decisions or health worker and patient education in 22 of 38 pharmaceutical companies (58%), 7 of 7 medical device companies (100%), and 2 of 5 CROs (20%).

Discussion

In the countries assessed, the pharmaceutical industry's engagement in medicine safety and product quality activities and involvement in their respective national PV systems are limited and do not fulfill the full potential of industry's role in ensuring the safety of pharmaceutical products and devices for patients. As the pictorial depictions of PV capacity in the pharmaceutical industry demonstrate (figures 7-9), industry performance across the five countries differ considerably, with Nepal showing the least capacity and Bangladesh, the Philippines, and Thailand showing comparably higher levels of capacity. Across all five countries and all three types of industry representatives—pharmaceutical companies, medical device companies and CROs—the lowest levels of capacity in the pharmaceutical industry are in the areas of risk assessment and evaluation and risk management and communication.

The pharmaceutical industry's limited involvement in PV activities is partly due to the inadequacies of national policies, laws, and regulations. Some laws and regulations do

Table 40. Industry PV Capacity and Activities

PV-related capacity and activities	Multinational innovator (n = 12)	Multinational generic (n = 12)	Local manufacturer (n = 14)	Total (N = 38) N, %	
PV unit or staff	8	11	10	29	76
PV SOP	9	10	7	26	68
> 5% of staff trained on PV in 2011	10	11	7	28	74
Adverse event reporting form	9	9	7	25	66
Product quality reporting form	9	9	10	28	74
Treatment failure reporting form	8	5	8	21	55
Collected ADR reports in 2011	9	9	7	25	66
Sent ADR reports to regulatory authority in 2011	6	5	4	15	39
Carried out post-marketing / active surveillance in 2011	3	7	5	15	39
Responded to PV information requests in 2011	3	5	3	11	29
Published and distributed medicine safety bulletins in 2011	1	4	3	8	21
Submitted and implemented risk management plans locally	3	3	1	7	18
Communicated AEs to HCW and public in < 3 weeks	9	6	5	20	53
Changed labels, package inserts, or box warnings in 2011	6	4	7	17	45

Figure 7. PV Capacity in Pharmaceutical Companies

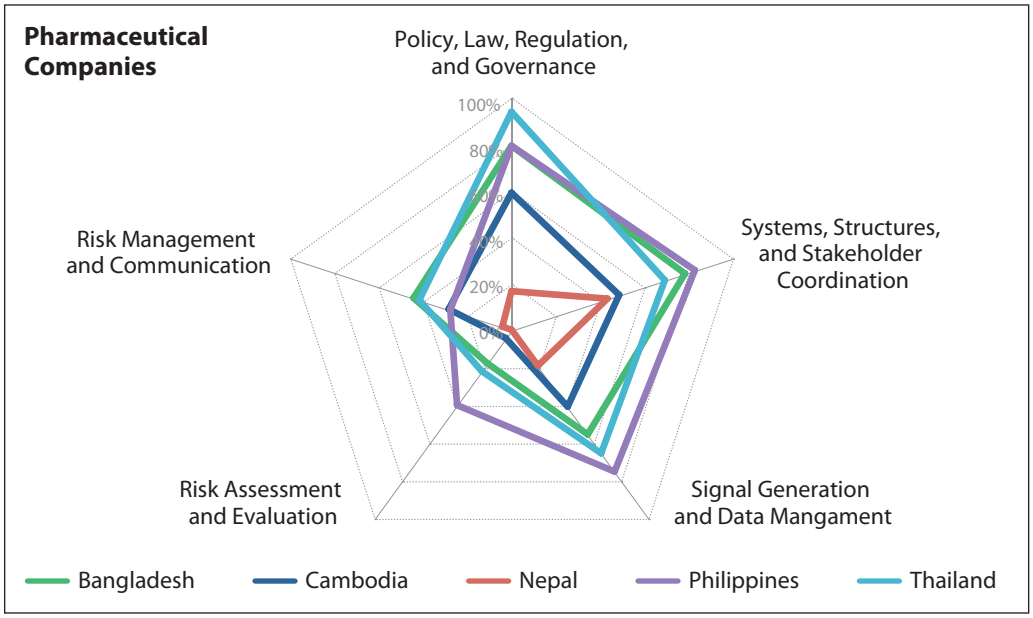


Figure 8. PV Capacity in Device Companies

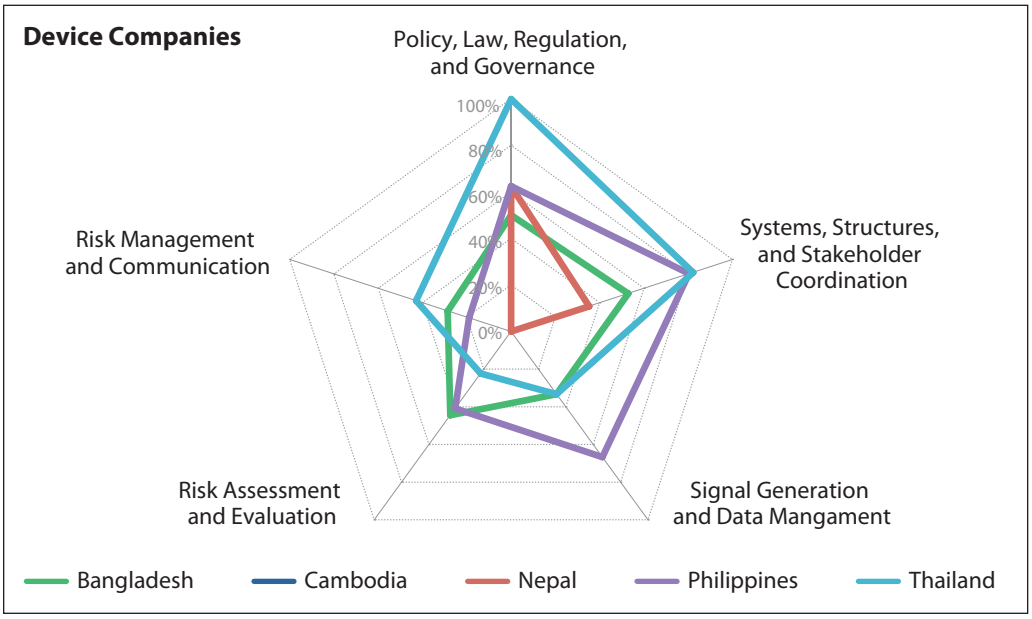
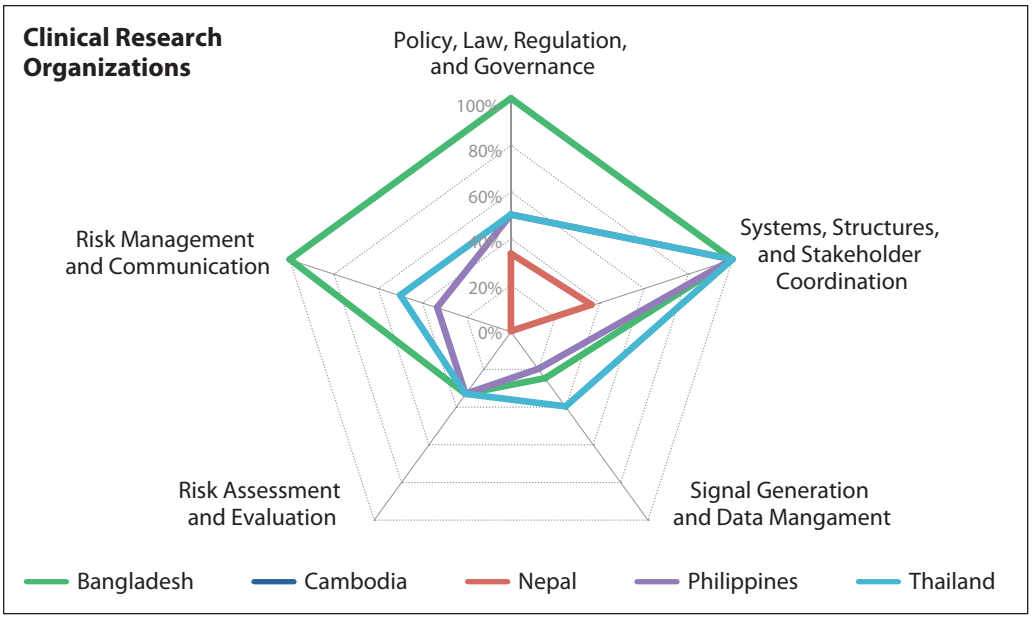


Figure 9. PV Capacity in Clinical Research Organizations



not require the industries to play a more active role through mandatory post-marketing surveillance, AE reporting, and product quality reporting and quality management, or the regulations are not effectively enforced. In the absence of legal provisions for safety and quality monitoring in some countries, industry is in a position to determine which PV-related activities serve their best interests, which tend to be more profit-driven and less public health-driven. To the extent that the pharmaceutical and medical device companies and CROs included in this study are implementing PV activities, the activities appear to be happening in parallel with the national PV system rather than as an integrated part of it. Opportunities exist across all study countries for governments to strengthen their regulation of industry and to improve and expand their PV activities to contribute to the public good

and give them a competitive advantage in the marketplace based on their compliance with international standards.

Options for Improving PV in Pharmaceutical Industries

Strengthen Industry Commitment to PV

The pharmaceutical industry is not doing enough to support PV activities in the countries studied. For instance, because there are limited provisions that require product sponsors to conduct the same or similar post-marketing surveillance activities for products as required by SRAs, the pharmaceutical industry operating in the countries do not conduct these activities. In the absence of adequate legislation and enforcement, due diligence and product stewardship should drive the industry to meet these requirements locally as they do in better regulated markets.

Implement Risk Management Plans

The industry should implement or offer to implement (where legal requirements do not exist) harmonized standards for risk management plans (RMPs) as they have with the EMA and other European competent authorities. The RMP should include safety specifications and PV plans in accordance with ICH E2E and a risk minimization plan. Industry should routinely scan worldwide safety literature and ensure that safety issues identified from outside sources for a product that is registered locally is promptly communicated to the NRA and consumers.

Improve Adverse Events Reporting

The pharmaceutical industry should strengthen their adverse events reporting system. They should have a staff responsible for PV, develop ADR report database that uses either the E2B or CIOMS I form, train all marketing staff members on the need to report, ensure ethical promotion, and conduct internal PV audits.

Implement PV Audits and Inspections

The industry should be proactive in addressing its responsibility for product stewardship and should collaborate with the NRAs to institute PV inspections.

Collaborate on Device Regulation and Vigilance

Among the countries studied, Cambodia, Philippines, and Thailand are members of the AHWP. Besides support for device classification and registration based on risk, industry should collaborate with the AHWP to support members and non-members within the region to develop strong device vigilance system as high-risk medical devices are increasing being used in these countries. From our study, device vigilance systems were not really functioning in the countries. For instance, when we asked if a form exists for spontaneous reporting of suspected device adverse events, we found that there are no forms in Cambodia, Nepal, and Thailand. Countries can start with adopting the Global Harmonization Task Force Medical Devices Post Market Surveillance: Global Guidance for Adverse Event Reporting for Medical Devices (GHTF 2006).

PV Results at the Civil Society Level

Civil society entities included in the assessment include consumer groups (n = 10), professional organizations such as medical, pharmacy, nursing, health professionals, and chemists (n = 22), and medical and pharmacy academia (n = 22).

Policy, Law, and Regulation

Among the consumer groups and medical professional associations assessed, few respondents reported awareness of the existence of a national policy for monitoring and reporting adverse events (20%) and 27% of professional associations or laws and regulations for monitoring and reporting adverse events (10% consumer groups) and 9% of professional associations [9%]).

Table 41. Results of Policy, Law, and Regulation at Civil Society Level

Indicator	Consumer groups	Professional associations
Aware of existence of national policy for monitoring ADRs	2/10 (20%)	6/22 (27%)
Aware of existence of laws and regulations for monitoring ADRs	1/10 (10%)	2/22 (9%)

Systems, Structure, and Stakeholder Coordination

The assessment found that about half of the professional associations studied reported having a member who is aware of the national PV center. Eighty percent of consumer groups reported that patients and consumers are unaware of the national PV center. Both consumer groups and professional associations reported low awareness of any service to ask questions related to ADRs and medicine safety—30% of consumer groups and 2 of 22 professional associations (9%). In Thailand and Cambodia, where national PV guidelines are in place, 4 of 5 (80%) professional associations reported awareness of the guideline, though no consumer groups reported awareness of the PV guideline. The assessment also found that consumer groups consistently reported a role in ensuring medicine safety in their country (80%) as did, albeit to a lesser extent, professional associations (55%). Out of 10 consumer groups and 22 professional associations studied, members from three (30%) and eight (36%) respectively serve on the national safety advisory committee in Bangladesh, Cambodia, and the Philippines. PV and medicine safety topics are taught in medical, pharmacy, nursing, and continuing education programs in 5 of 22 (23%) professional associations and 15 of 22 (68%) academic institutions studied. Healthcare professionals affiliated with 1 of 10 (10%) consumer groups and 10 of 22 (45%) professional associations received training in PV topics in 2011. Academic institutions studied reported awareness of a platform or a forum for coordination of PV activities across all stakeholders and viewed academia as an important stakeholder in ensuring medicine safety in their country (15 of 22 [68%]).

Table 42. Results of System, Structure, and Stakeholder Coordination at Civil Society Level

Indicator	Consumer groups	Professional associations
Member of the association is aware of national PV center	n/a	10/22 (45%)
Patients and consumers unaware of PV center	4/5 (80%)	n/a
Aware of any service to ask questions related to ADRs	3/10 (30%)	27
Aware of PV guideline	0	80
Reported role in ensuring medicine safety	8/10 (80%)	12/22 (55%)
Received training in PV	10	45

Signal Generation and Data Management

The assessment found that patient and consumer awareness of mechanisms to directly report medicine safety concerns to national PV centers was limited. In Thailand and the Philippines where a national consumer reporting form is available to consumers, only 2 of 7 (29%) consumer groups reported that patients and consumers are aware of a national consumer reporting form and encouraged to report directly to PV center.

Risk Assessment and Evaluation

The assessment found that some risk assessment and evaluation activities were undertaken by academic institutions in the countries studied, including product quality surveys (5 of 22 [23%]), medication errors studies (5 of 22 [23%]), and medicine utilization studies (4 of 22 [18%]) all in 2011, and active surveillance activities (8 of 22 [36%]) in the last five years.

Risk Management and Communication

The assessment found that the majority of professional associations were aware of medicine safety actions taken in country and thereby in a position to inform members. Although more than half of the professional associations reported receiving some sort of medicine safety bulletin in 2011 (12 of 22 [55%]), the same was reported by only a fifth of consumer groups. Respondents were found to be aware of strategies or plans, such as medication guides, to mitigate and restrict the use of high-risk medicines in 11 of the 22 professional associations studied and 2 of 10 of the consumer groups. Trainings in medicines safety topics were conducted in 2011 in a fifth of the consumer groups studied (2 of 10 consumer groups [20%]) and nearly a third of professional associations (14 of 22 PA [64%]). Respondents were aware of medicines safety action taken other than ADR reporting in 2011 in 3 of 10 consumer groups (30%) and 14 of 23 professional associations (61%).

PV Capacity in Civil Societies

In general, consumer groups make minimal contributions to the strength of the overall PV system, with notable exceptions in Bangladesh and the Philippines. Professional associations seem to have a greater influence, especially in Thailand.

Figure 10. PV Capacity in Consumer Groups

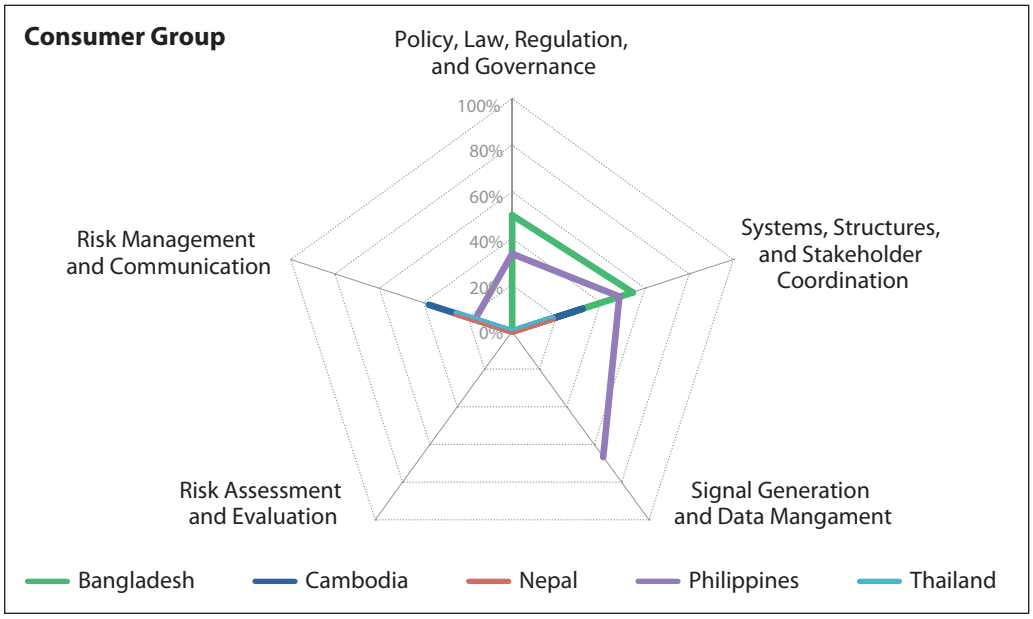
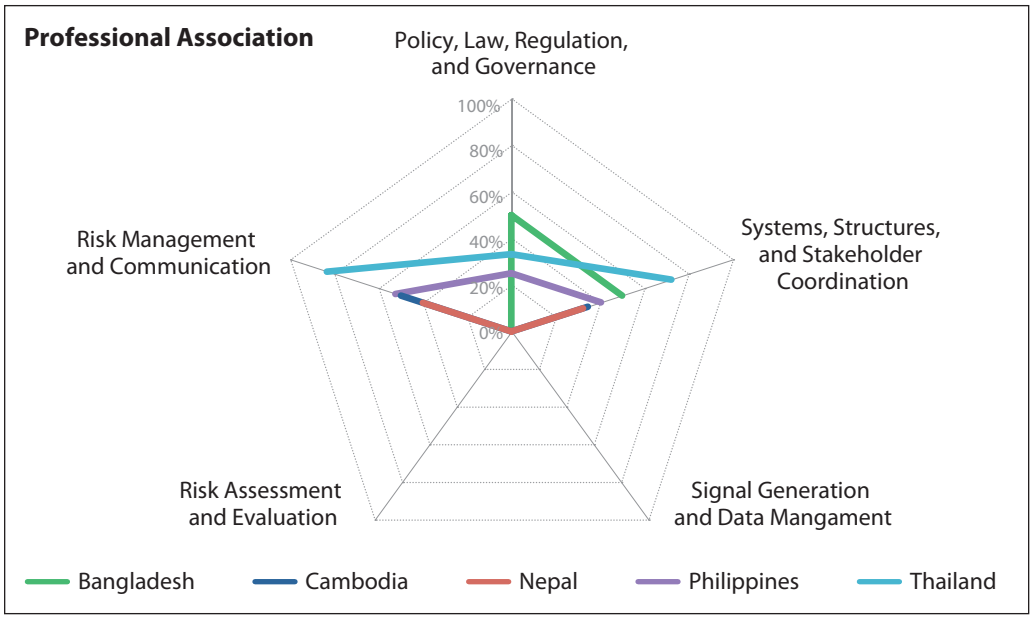


Figure 11. PV Capacity in Professional Associations



Discussion

Civil society has a significant role to play in PV systems both as a participant and beneficiary. The study results indicate that civil society is a relatively inactive group, and thus untapped resource, within the PV systems assessed. Awareness of PV services and activities, including the policies, laws and regulations that establish the legal mandate for them, is low, especially among consumer groups. Civil society partners' participation in their respective national PV systems and other PV-related activities is also very limited, even where PV systems provide an established mechanism for participation and the groups see a role for themselves in their country's PV system. Low consumer reporting rates in the two countries that have consumer reporting forms—the Philippines and Thailand—suggest that providing opportunities

and mechanisms alone does not ensure participation or even awareness and that more targeted efforts are needed to engage these partners. Professional associations and academic institutions, in particular, have a great deal to contribute to regional PV given the existing mechanisms for engaging medical and pharmacy professionals and researchers in PV efforts. For instance, academic institutions have research and training capacity, as well as specialized expertise, which are essential for effective PV. Governments and civil society groups themselves can be doing more to ensure that civil society is helping to improve and expand generating and disseminating information related to medicine safety.

Options for Improving PV in Civil Societies

Improve the Visibility of PV as a Public Health Priority

Civil society's active involvement in PV systems depends not only on awareness of the legal mandate, structures and systems for PV in the country but also on the society's understanding of its importance and how it affects them. The recommended starting point for engaging civil society is improving the visibility of medicine safety as a matter of public health importance and motivating members to get involved. The national PV center and the services it offers should also be made more visible to targeted groups and the general public, so that people know where to get and to provide information related to medicine safety and quality. Media campaigns and public service announcements that communicate key messages through multiple channels and platforms are good ways to help raise awareness.

Establish Accessible, User-Friendly Forms and Mechanisms for Civil Society Groups

Consumer reporting is an important source of information on suspected medicine safety and quality problems within a well-functioning PV system. In countries without consumer reporting forms, national PV centers are encouraged to develop a simple form designed specifically for that group. An effective consumer reporting form will capture only the essential information and will be clear and easy to fill out even for those individuals with low literacy and no background or training in a health-related field. Establishing easy mechanisms or platforms for consumer reporting, including the submission of forms, is also important for countries to improve the quality and frequency of reporting. Call centers or hotlines and websites, for instance, can help consumers submit information on medicine safety. In recognition that phone and internet services are limited among some populations in the region, more basic mechanisms can be established as well, including paper submissions direct to clinics and pharmacies, which can transmit the information to the PV center on the behalf of the patients and consumers.

Establish Collaborations with Academic Institutions for PV-Related Activities

Many academic institutions are already involved in PV-related activities, such as training for pharmacy and medical students and research on medicine use, safety, and quality. However, the results of their work are not always shared with or channeled through the national PV system and to the public. By establishing formal memorandums of understanding and setting up opportunities for effective coordination and communication, academic institutions and national PV programs can share resources and information, strategically divide responsibilities according to comparative advantage, and together make a greater impact.

Comparison of Performance and Capacity of PV in Selected Asia Countries

A comprehensive PV system is comprised of (1) governance, policy, law, and regulation, (2) system structure and stakeholder coordination; (3) signal generation and data management, (4) risk assessment and evaluation; and (5) risk management and communication. WHO defines the minimum requirements for a functional national PV system as having a national PV center, a spontaneous reporting system, a national database, a national PV advisory committee, and a communications strategy (WHO 2010c). To build on these minimum requirements and highlight the need for providing further details and indicators for monitoring all aspects of comprehensive PV systems and benchmarking these systems' performance, we developed the systems classification.

Methods

Using a set of indicators addressing all of the five PV components, SIAPS developed criteria for classification of countries into four groups. Tables 43a and 43b list the criteria for systems classification into these groups at the national level. Country-specific data for all indicators can be found in annex C. The groupings represent the level of achievement of countries in meeting the relevant indicators in a PV system.

The scoring of the classification scheme is as follows: core indicators are given 2 points each and the rest of the indicators are given 1 point each. The score of the indicators met is divided by the total score of all the indicators and multiplied by 100; if this value is >60% for each component, the country is said to meet the standard requirements for that component. The limitations in this scoring method are recognized. We do not have an explicit criteria or reference for the 60% cut off; establishing how well these PV components function is challenging, and even though responses were verified, the study data may still not be sufficient to determine the robustness and sustainability of countries PV system. However, this scoring facilitates easy recognition of where countries are working toward a functional PV system. Also achieving 60% in the PV components for resource-limited settings may be a reasonable expectation.

Similar to the approach used in an SPS report (Strengthening Pharmaceutical Systems (SPS) Program 2011), countries are classified into four groups based the capacity and performance of their PV systems—

- **Group 1:** Countries have no capacity or have minimal organizational structures and capacity for PV. Though there is relevant pharmaceutical legislation, there are no specific legal or structural frameworks for PV systems, and no coordinated passive or active surveillance in these countries. Any ongoing PV activities take place without national coordination. Bangladesh and Nepal belong to Group 1.

Table 43a. Classification Scheme for PV Capacity

PV component	Group 1	Group 2	Group 3	Group 4
Policy, law, and regulation	N	Y	Y	Y
System, structure, and stakeholder coordination	N	Y	Y	Y
Signal generation and data management	N	N	Y	Y
Risk assessment and evaluation	N	N	Y	Y
Risk management and communication	N	N	N	Y

Table 43b. Performance Card

	Bangladesh	Cambodia	Nepal	Philippines	Thailand
Policy, law, regulation, and governance	X	X	X	X	X
Systems, structures, and stakeholder coordination		X		X	X
Signal generation and data management				X	X
Risk assessment and evaluation					X
Risk management and communication		X		X	X
Group	Group 1	Group 2	Group 1	Group 3	Group 4

- **Group 2:** Countries have basic structure in place. The countries have policy and legal frameworks for PV. Additionally, most basic organizational structures, such as an institution with a clear mandate for PV, guidelines, and SOPs; a reporting form, and a safety advisory committee, are in place. Stakeholders' roles and responsibilities are recognized but not fully coordinated. The capacity to generate signals and evaluate the risks is limited in these countries. The spontaneous reporting system does not cover all sources of medicines-related problems. The PV system lacks active approaches to evaluate signals and implement effective risk management practices. Cambodia belongs to Group 2.
- **Group 3:** Countries have the capacity to collect and evaluate safety data on the basis of legal and organizational structure. The countries have organizational structure and policy framework to collect and collate safety data in a national database and evaluate the risks and benefits by both passive and active approaches. However, the capacity to manage the risks by taking appropriate preventative actions, develop a plan to actively monitor the risks, and communicate with stakeholders is lacking. The Philippines is classified as being in Group 3.
- **Group 4:** Countries have performing PV systems to detect, evaluate, and prevent medicine safety issues. The countries have the basic structures, both passive and active surveillance activities, and the capacity to evaluate the risks. Based on these, outcomes of PV activities inform regulatory actions and are communicated to stakeholders. It is unclear if the current situation will be sustained over time. Thailand is classified as being in Group 4.

Global and Regional Initiatives for Strengthening Pharmacovigilance Systems in Asia

A multitude of global, regional, and in-country institutions and programs are contributing to the strengthening of PV systems throughout Asia. Coordinating these efforts and establishing and strengthening links between them provides opportunities to maximize effectiveness and achieve greater impact through improved funding, technical support, capacity building, and information sharing.

Financing Institutions

The Global Fund has made strengthening PV a funding priority and encourages countries to include PV activities in its grant proposals and activities (Xuaref S, Daviaud J 2013). Prior to round 10, a total of six grants in the SEARO and WPRO regions had PV activities in progress. Under round 10, five grants in the two regions had PV activities planned: Indonesia (TB), Laos PDR (TB), Nepal (HIV and AIDS), Thailand (TB), and Vietnam (health system strengthening) (Lalvani 2012).

Bilateral donors, namely the European Commission and USAID, are also contributing targeted funding for PV in the region. Since 2010, the European Commission, in collaboration with WHO-UMC, has been supporting the Monitoring Medicines program, which focuses on improving consumer reporting, supporting countries to expand the scope of their PV activities, promoting improved use of existing global PV data, and developing focused surveillance methods in select countries (Uppsala Monitoring Centre). USAID funds two programs—Systems for Improved Access to Pharmaceuticals and Services (SIAPS) and Promoting Quality of Medicines (PQM)—that provide technical assistance to developing countries, including many in Asia, to strengthen their medicine safety and quality monitoring systems under PEPFAR and PMI.

Other financing institutions that are supporting targeted PV initiatives globally and in the region include the Bill & Melinda Gates Foundation, GAVI alliance, and UNITAID.

Technical Institutions and Programs

WHO provides global technical leadership in PV by providing norms, standards, and other forms of guidance that are developed across various departments and disease-specific programs (WHO). The WHO Advisory Committee on the Safety of Medicinal Products, made up of experts from the drug evaluation and drug policies and management advisory panels, provides advice on pharmaceutical safety issues for member states in all regions. In addition to disease-specific PV activities in HIV and AIDS, tuberculosis, malaria, and Chagas disease, WHO also focuses on vaccine safety (WHO).

UMC reviews and analyzes new ADR signals from the case report information submitted to the WHO ICSR global database (VigiBase) by national PV centers; strengthens information sharing through the publication of periodicals and newsletters; supplies national centers with tools, including computer software; and provides training and consultancy support (Uppsala Monitoring Centre).

Other international institutions providing general and disease-specific technical support and guidance in the area of PV in the Asia region include CIOMS, International Society of Pharmacovigilance, ICH, International Pharmaceutical Federation, Management Sciences for Health, Médecins Sans Frontières, and United States Pharmacopeia.

Vaccine safety is receiving specific attention from such organizations as Brighton Collaboration and the US FDA's Center for Biologics Evaluation and Research, which launched the Global Regulatory Utilization of Vaccine Safety Surveillance initiative in 2012 (Brighton Collaboration; USFDA). Organizations addressing PV in the context of new product development include the Drugs for Neglected Diseases Initiative, Medicines for Malaria Venture, and the Product Development Partnership Access Group ("Drugs for Neglected Diseases Initiative"; "Medicines for Malaria Venture"; "PDP Access Group").

Regional Institutions

The ASEAN pharmaceutical product working group has created the PMA system as part of the mutual recognition arrangement and overall harmonization effort in the region. The types of information shared in the alerts include product withdrawals, cancellations of registration and suspensions of sales, adulteration with pharmaceutical ingredients, quality issues, product label changes, and others.

The nonprofit organization Pan-Asian Clinical Research Association has established the PV Asia Network as a platform for PV professionals to network and exchange experiences, expertise, and information throughout the Asia-Pacific region. It supports the development and harmonization of PV in the region and incorporates professionals from sponsor companies, CROs, institutions, ethics committees, health authorities (as permitted by the regulations of such authorities), as well as related PV organizations (Pan-Asian Clinical Research Association). A complete mapping of international and regional institutions' efforts to strengthen PV globally as well as specifically in the Asia region is presented in annex D.

Conclusion

Great strides have been made in advancing access to medicines in low- and middle-income countries, thanks to the efforts of global health initiatives and also the increased commitment of national governments. At the heart of such efforts is ensuring the provision of safe, effective, and quality medicines. The permeation of products with unknown safety profiles or of spurious quality into global supply chains and the resulting adverse reactions from their use can diminish those significant improvements in access and compromise the success of public health programs that depend on such medicines.

National regulatory authorities (NRAs) are mandated to regulate the development, manufacturing, and marketing of medical products in their local markets. However, as the global supply chain grows in complexity, NRAs become increasingly responsible for protecting not only the local public but also consumers in markets beyond their own borders. Yet, as found from this study, most of the NRAs have limited capacity in PV. They lack the regulatory framework and governance structures mandated by legislation and regulations, including systems for accountability, transparency, and capacity for enforcement to ensure industry compliance to safety monitoring. Harmonization of regulatory requirements and international standards reduces duplication and regulatory burden. Countries PV legislations are not convergent, nor are they consistent with international standards, and discussions on the adoption of relevant international standards were very preliminary. PV systems and structures are weak and the ability to generate signals, evaluate them, and use the information for risk management and communication is limited.

There is a strong and urgent need to strengthen medicine safety systems both within and across national borders of countries in the Asia region. Developing and developed countries are both suppliers and recipients within an increasingly complex global medical product supply chain. Public health programs, global health initiatives, and indeed, entire health systems rely on safe, effective, and good quality medicines. However, fully functional PV and regulatory systems are not yet in place. A great challenge and opportunity exist to improve the systems and capacities required to assure patient safety and to improve health outcomes in Asia.

Annexes

A. Medication Mishaps And Related Regulatory Forms

B. Pharmacovigilance Profile

C. Country Profiles

D. Assessment Method

E. PV Topics in Curriculum

F. Thailand Health Product Adverse Event Report Form

G. Glossary

Annex A. Medication Mishaps and Related Regulatory Forms

Medication mishaps have helped in defining clearly the primary objective of pharmaceutical regulation which is to safeguard public health. Though legislation alone cannot resolve the challenges of ensuring safety of medicines, the examples below highlight the therapeutic mishaps that have catalyzed stricter and more effective medicines regulation. Those mishaps also contributed to the development of national regulatory authorities and the regulatory policy and framework that govern their activities.

Year or period	Event	Related regulatory reforms
1937–2011	About 700 deaths in more than 11 countries due to diethylene glycol poisoning; index case in US 1937, repeated occurrences in Nigeria 1990 and 2008, and high casualty in Panama where 365 died	In the United States led to the enactment of the Federal Food, Drug, and Cosmetic Act (1938) with the premarket notification requirement.
1956–1962	About 10,000 children from mothers who were exposed to thalidomide in Europe/Japan during pregnancy were born with severe malformations primarily phocomelia.	In reaction to this, WHO in 1961 developed the voluntary notification scheme and in 1961 the World Health Assembly requested the WHO
1999	At least 30 people died in Cambodia after taking counterfeit antimalarials	No information
2004	Up to 140,000 cases of serious heart disease attributed to rofecoxib (Vioxx)	Public criticism of US FDA drug approval and post-marketing surveillance system contributed to the enactment of the FDA Amendment Act of 2007 which provided FDA with enhanced statutory authority regarding post-market safety of drugs
2004–2008	Lack of disclosure of negative clinical trials data, suppression of results, and modification of pre-specified outcome measures in trials involving Paxil, Vioxx, and Zetia (ezetimibe)	Contributed to the enactment of Section 801 of the FDA Amendments Act
2005	More than 60,000 people in Niger were inoculated with a counterfeit meningitis vaccine resulting in about 2,500 deaths	*Le Monde* reported that the company that made the vaccine did not act against the counterfeiters as it feared that it might damage trade
2009	Mediator® is claimed to be responsible for around 3,100 hospitalizations and 1,300 deaths due to valvular insufficiency	The French agency for the safety of health products (AFSSAPS) was accused of "inexplicably tolerant of a drug with no real therapeutic value." The Mediator case led to the resignation of the head of AFSSAPS; dissolution of AFSSAPS and its replacement by the National Agency for the Safety of Medicines and Health Products (MSNA); and enactment of new legislation to strengthen drug safety in France.
2010	An international police operation led to the seizure of $20M in counterfeit and illegal medicines. The operation covered 8 countries in Southeast Asia: Cambodia, China, Indonesia, Laos, Myanmar, Singapore, Thailand, and Vietnam	Closure of 100 pharmacies and illegitimate drug outlets and more than 30 related arrests
2012	125 patients died from cardiac drug contaminated with an antimalarial	Pakistan addressed the jurisdictional confusion created by the passage of the amendment that decentralized public health. Federal government quickly established a central Drug Regulatory Authority
2012	Committee of the India parliament in its 59th report accuses the Central Drugs Standard Control Organization (CDSCO) of 'collusive nexus' between the industry, CDSCO, and medical experts.	The Ministry of Health and Family Welfare submitted Action Taken Report for addressing the identified weaknesses

Year or period	Event	Related regulatory reforms
2012 and 2013	More than 620 people were sickened and 44 died from methylprednisolone acetate injections manufactured by the New England Compounding Center (NECC), raising calls for more power for the FDA for the oversight of drug compounders.	Draft bill gives FDA authority over some pharmacies. Bill creates a new class of drug makers called "compounding manufacturers"
2013	Ranbaxy pleaded guilty to felony charges relating to the manufacture and distribution of adulterated drugs and agreed to pay a USD 150 million penalty and to settle civil claims under the US False Claims Act and related State laws for USD 350 million.	Case instituted against Ranbaxy in India

Annex B. Pharmacovigilance Profile

Governance

Country	Regulatory framework exists and assessed in last 5 years	Regulatory registers exist (medicines, personnel, premises)	Governance structures mandated by laws and regulations and in practice
Bangladesh	Yes	Yes	Yes
Cambodia	Exists but not assessed		Not fully in place
Nepal	Exists but not assessed		Not fully in place
Philippines	Yes		Yes
Thailand	Yes		Yes

Policy, Law, and Regulation

Country	Policy statements for PV or medicine safety (year published)	Legal provision for PV exists (year published)	Legal provision mandating MAHs to report serious ADRs exists (year published)	Legal provision mandating MAHs to conduct PMS* exists (year published)
Bangladesh	Yes (2005)	Yes (1940)	No	No
Cambodia	Yes (2010)	Yes (2007)	Yes (2011)	
Nepal	Yes (1995)	Yes (1978)	No	
Philippines	Yes (2011)	Yes (1987)	Yes (2011: PV policy)	Yes (1997)
Thailand	Yes (2011)	Yes (1967)	No	No

Note: PMS = Post-marketing surveillance

Country	Legal provision for product quality assurance (year published)	Legal provision for promotion and advertising (year published)
Bangladesh	Yes (1940)	Yes (1940)
Cambodia	Yes (2010)	Yes (2007)
Nepal	Yes (1978)	Yes (1978)
Philippines	Yes (1997)	Yes (2008)
Thailand	Yes (1967)	Yes (1967)

Systems, Structure, and Stakeholder Coordination

Country	PV center with a clear mandate, structure, roles and responsibilities exists	QC lab/unit with clear mandate, structure, functions exists
Bangladesh	PV center under NRA; No clear mandate	Yes
Cambodia	PV center under NRA	QC unit under MOH, not audited
Nepal	PV center under NRA; No clear mandate	
Philippines	PV center under NRA	Yes
Thailand		

Country	Medicine information service exists	Staff member for PV (≥1)	Dedicated budget for PV center	National PV guideline exists (year published)
Bangladesh	Yes, by PV center	Yes	No	No
Cambodia				Yes (2012)
Nepal				No
Philippines				
Thailand			Yes	Yes

Country	National PV SOPs for PV and QC	National safety advisory committee exists	National quality control advisory committee exists	Core communication technologies for PV
Bangladesh	No	No	No	No
Cambodia		Yes	Yes	Yes
Nepal	No (QC only)	No	No	
Philippines	Yes			
Thailand		Yes	Yes	

Country	Core PV reference material in PV unit/drug information center	Core PV topics in pre-service training curricula (> 70%)	Healthcare workers trained on PV
Bangladesh	Yes	Yes (3 of 3 academia)	Yes (HF, PHP)
Cambodia	No	Yes (1 of 2 academia)	Yes (NRA, PHP)
Nepal	Yes	Yes (7 of 7 academia)	Yes (PHP)
Philippines		Yes (7 of 7 academia)	Yes (HF, PHP)
Thailand		Yes (3 of 3 academia; 2 of 3 professional association)	

Country	Mechanism for coordinating PV activities across all stakeholders exists	WHO International Drug Monitoring Programme (year joined)	Quality management system for performing PV and QA activities
Bangladesh	No	Non-member (planned 2013)	No
Cambodia	Yes	Official (2012)	
Nepal		Official (2006)	
Philippines		Official (1995)	Yes
Thailand		Official (1984)	

Signal Generation and Data Management

Country	Coordination and collation of PV data from all sources in the country	Consumer reporting form for suspected ADRs	Spontaneous reporting form for suspected ADRs
Bangladesh	No	No	Yes
Cambodia	Yes	No	Yes
Nepal	Yes	No	Yes
Philippines	Yes	Yes	Yes
Thailand	Yes	Yes	Yes

Country	Product quality reporting form (or subset of ADR form)	Medication error reporting form (or subset of ADR form)	Treatment failure reporting form (or subset of ADR form)
Bangladesh	No	No	No
Cambodia	No	No	No
Nepal	No	No	No
Philippines	Yes	Yes	Yes
Thailand	Yes	Yes	Yes

Risk Assessment and Evaluation

Country	Spontaneous reporting > 100 per million population per year (no. of reports in 2011)	ICSRs with Causality Assessed > 50% (% assessed)	Survey on quality of pharmaceutical products in the last 1 year
Bangladesh	No (0)	No (n/a)	NRA, academia, PHP
Cambodia	No (83)	Yes (100%)	NRA
Nepal	No (35)	No (0%)	—
Philippines	No (3,351)	No (35%)	Academia, health facilities
Thailand	Yes (57,573)	Yes (78%)	NRA, academia, PHP

Country	Medication error studies in the last year	Medicine utilization studies in the last year	Active surveillance activities in the last 5 years
Bangladesh	Academia, PHP	PHP, industry, health facilities	Academia, industry, PHP, health facilities
Cambodia	—	NRA	—
Nepal	—	Health facilities	Academia, PHP
Philippines	Academia, health facilities	Academia, health facilities	Academia, health facilities
Thailand	Academia	Academia	NRA, PHP, academia, health facilities, industry

Risk Management and Communication

Country	Medicine safety information requests received and addressed in 2011 (≥ 1 per month)	Medicine safety newsletters or bulletins planned and published in 2011 (≥ 70%)	Prequalification schemes used in medicine procurement decisions (i.e. WHO-GMP, PIC/S)
Bangladesh	No	No	Yes
Cambodia			
Nepal		Yes (3 issues/year)	Yes (immunization)
Philippines	Yes	No	Yes
Thailand		Yes (1 issue/month)	

Country	Unregistered medicines in pharmaceutical market < 3%	Medicines sampled that were analyzed for product quality (% failure)	Risk mitigation plans for high-risk medicines in place	No. of medicine safety issues identified and acted on from external sources
Bangladesh	No (–)	69% (0.04% failed)	No	0
Cambodia	No (est. 30%)	100% (4.6% failed)	Yes	
Nepal	Yes	83% (27% failed)	No	
Philippines		97.4% (no data)	Yes	
Thailand	Yes (< 1%)	100% (10% failed)		2

Risk Management and Communication (continued)

Country	Time from ADR signal generation to communication to HCWs and Public <3 weeks	Public education activities on ADRs or medicines safety	Medicine safety regulatory actions taken other than ADR reporting in last 1 year (see key below)
Bangladesh	No	No	e, f
Cambodia	Yes		b, h
Nepal	No	Yes, limited	b, c, d, e
Philippines	Yes	Yes	a, d, f, h
Thailand			a, b, d, g, h

a) Label or package insert changes/boxed warning
b) Treatment guidelines, medicine formulary, or essential medicine list changes
c) MoH memo or circular referencing safety data
d) Product recalls
e) Withdrawal of product license
f) Suspension of marketing authorization
g) Risk management activities recommended because of new safety data
h) Dear Dr. letters or safety alerts

Annex C. Country Profiles

Bangladesh

Pharmaceutical Profile

Pharmaceutical Market	
Population (2011)*	150.5 million
Gross domestic product per capita (USD, 2011)*	744
Market size: pharmaceuticals (USD, 2011)†	1.5 billion
Market size: medical devices (USD, 2011)†	174 million
Number of medicines registered (2012)‡	32,245
Total pharmaceutical expenditure per capita (USD, 2006)§	5.7
Total expenditure on healthcare (TEH) per capita (USD, 2009)‖	19
Total pharmaceutical expenditure as a percentage of TEH per capita	31%
Health workforce per 10,000 population (2011)#	0.20
Public expenditure on pharmaceuticals (2006)§	94.7
Financing mechanisms for pharmaceuticals§	Public (11%), Private/Other (89%)

Medicines Policy	
Existence of a national medicines policy	National Drug Policy, 2005. MOHFW, Government of the People's Republic of Bangladesh†
Legal provision for medicines legislation	The Drugs Act of 1940† Also see the Drug Rules of 1945, the Bengal Drug Rules of 1946, the Drug (control) Ordinance of 1982, and the Drug Policy of 2005†
Patent provisions (main)**	The Constitution of Bangladesh, 2004 Trademarks Act, 2009 (Act No. XIX of 2009) (2009) The Patents and Designs Act (Act No. II of 1911) (2003) Copyright Act 2000 No. 28 of 2000 (as amended up to 2005) (2000) World Trade Organization (WTO) - Agreement on Trade-Related Aspects of Intellectual Property Rights (TRIPS Agreement) (1994) (January 1, 1995)

Pharmaceutical Production Status	
Pharmaceutical manufacturing plants†	(allopathic pharmaceutical manufacturing companies)

* World Bank Database, accessed date 30/08/2012
† Business Monitor International Bangladesh Pharmaceuticals and Healthcare Report 2013
‡ Bangladesh Directorate General of Drug Administration
§ WHO World Medicines Situation 2011 Annex
‖ WHO National Health Account Database, 2009
WHO World Health Statistics 2012
** WIPRO

Pharmacovigilance Profile

Policy, laws, and regulations	The Drug Act of 1940 National Drug Policy of 2005
Name of regulatory authority/website	Directorate General of Drug Administration www.dgda.gov.bd
Mandate of regulatory authority	Registration, licensing and import control, inspection, QC, PV, control of promotion, control of clinical trials
How products get into the market	Registration by the DGDA, database of registered products available: www.dgda.gov.bd
Joined the WHO program	Not yet a member of the WHO Programme for International Drug Monitoring
Significant events	2008 reports of poor-quality generic miltefosine for visceral leishmaniasis that contained no active pharmaceutical ingredient
E2B compliance	Not applicable
Medical terminology used	Not applicable
Type of reports in PV database	None
Total number of ICSRs in the database	None
Quantitative methods used in signal generation	Not applicable
Newsletter or bulletin published	Not regularly published

Cambodia

Pharmaceutical Profile

Pharmaceutical Market	
Population (2011)*	14.3 million
GDP per capita (USD)*	$900, 2011
Market size: pharmaceuticals (USD, 2011)†	178 million
Market size: medical devices (USD, 2011)†	27 million
Number of medicines registered (2011)‡	10,000 (est.)
Total expenditure on healthcare per capita (USD, 2010) §	$29
Total pharmaceutical (TPE) expenditure per capita (USD, 2006)‖	$9.3, 2006
Public expenditure on pharmaceuticals per capita (USD, 2006)‖	$1.3, 2006
TPE as % total expenditure on healthcare per capita (2006)‖	21%, 2006
Health workforce per 10,000 population#	10.8
Financing mechanisms for pharmaceuticals#	Public (14%), Private/Other (86%)

Medicines Policy	
Policy, laws, and regulations	National Medicine Policy (1996) National Medicine Policy (2010)† Law on the Management of Pharmaceuticals (1996)†† Law on the Management of Pharmaceuticals (amended 2007) Pharmaceutical Sector Strategic Plan 2005-2010
Patent provisions (main)**	The Constitution of the Kingdom of Cambodia (1999) Law on the Management of Pharmaceuticals (1996, 2007) Law on Patents, Utility Models and Industrial Designs (2003) Law on Copyright and Related Rights (2003) Law concerning Marks, Trade Names and Acts of Unfair Competition of the Kingdom of Cambodia (2002) WTO TRIPS Agreement (1994)

Pharmaceutical Production†	
Total no. of pharmaceutical manufacturing plants	8
No. of pharmaceutical manufacturing plants:	
pharmaceutical active ingredients	0
finished pharmaceutical dosage forms	8
packaging finished pharmaceutical dosage forms	8
No. of research-based pharmaceutical industries	0
No. of generic pharmaceutical (including branded generics) manufacturers	8
No. of nationally owned pharmaceutical industries (public and private)	8

* World Bank Database , accessed date 30/08/2012
† Business Monitor International Cambodia Pharmaceuticals and Healthcare Report 2012
‡ Cambodia MOH, DDF
§ Global Health Expenditure Database
‖ World Medicines Situation
WHO World Health Statistics 2012
** World Intellectual Property Organization
†† National Assembly of Cambodia

Pharmacovigilance Profile

Policy, laws, and regulations	National medicines policy (1996 and 2010) National pharmaceutical law Pharmaceutical Strategic Plan 2008-2015 ADR Monitoring and related Matters guidelines (2012)
Name of regulatory authority/website	DDF: www.ddfcambodia.com
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	Registration by DDF, list of registered products available (10,171)
Joined the WHO program	Official member, 2012
Significant events	Chloramphenicol injection and capsule withdrawn from National Essential Drug List
E2B compliance	Through VigiFlow (E2B-compliant, web- based portal)
Medical terminology used	WHO-ART
Type of reports in PV database	Spontaneous reports
Total # of ICSRs in the database	> 137 total, 83 in 2011
Quantitative methods used in signal generation	The Bayesian Confidence Propagation Neural Network (BCPNN)
Newsletter or bulletin published	Yes, but not regularly published as planned (funding constraint)

Nepal

Pharmaceutical Profile

Pharmaceutical Market	
Population (2011)*	30.5 million
Gross domestic product per capita (USD, 2011)*	$619 per capita
Gross domestic product (USD, 2011)*	$18.9 billion
Market size: pharmaceuticals (USD, 2009)†	$187.64 million
Market size: medical devices (USD, 2009)	Included in above
Number of medicines registered‡	10,316 per WHO
Total expenditure on healthcare per capita (USD, 2010)§	$29, USD
Total pharmaceutical expenditure per capita (USD, 2006)§	$4.7
TPE as % total expenditure on healthcare per capita§	16%
Public expenditure on pharmaceuticals per capita (USD, 2011)‡	$0.9
Health workforce per 10,000 population (2010)‖	16.1
Financing mechanisms for pharmaceuticals‡	Public (19%), Private (81%)

Medicines Policy	
Policy, laws, and regulations	Drug Act 2035 (1978)# National Drug Policy, 1995# National Medicines Policy (draft)** Drug Investigation and Inspection Rules, 2040 (1983) Drug Registration Regulation, 2038 (1981) Drug Standards Regulation, 2043 (1981) Regulation on Constitution of Drug Consultative Council and Drug Advisory Committee, 2037 (1970)
Patent provisionsf	The Interim Constitution of Nepal 2063 (2007); The Patent, Design and Trade Mark Act, 2022 (1965); Copyright Act, 2059 (2002); Copyright Rules (2004); WTO TRIPS Agreement (1994)

Pharmaceutical Production††	
Total no. of pharmaceutical manufacturing plants	45
No. of pharmaceutical manufacturing plants:	
pharmaceutical active ingredients	None
finished pharmaceutical dosage forms	45
packaging finished pharmaceutical dosage forms	1
No. of research-based pharmaceutical industries	None
No. of generic pharmaceutical (including branded generics) manufacturers	None
No. of nationally owned pharmaceutical industries (public and private)	45

* World Bank Database, accessed date 30/08/2012
† Nepal National Health Account (2006 – 2009)
‡ WHO Nepal Pharmaceutical Country Profile
§ WHO National Health Accounts Database
‖ WHO World Medicines Situation
WHO Nepal Pharmaceutical Country Profile
** World Intellectual Property Organization: Nepal
†† Nepal Department of Drug Administration

Pharmacovigilance Profile

Policy, laws, and regulations	Drug Act 2035 (1978) National Drug Policy, 1995 National Medicines Policy (draft)
Name of regulatory authority / website	Ministry of Health and Population, Department of Drug Administration (DDA) www.dda.gov.np
Mandate of regulatory authority	Manufacturing, export/import, sales, distribution, storage
How products get into the market	Registration by DDA for import, production, sales, distribution
Joined the WHO program	Official member (2006)
Significant events	Not applicable
E2B compliance	Through VigiFlow (E2B-compliant, web-based portal)
Medical terminology used	WHO-ART
Type of reports in PV database	Spontaneous reports from 6 regional PV centers; AEFI reports
Total number of ICSRs in the database	411 through 2012 (35 in 2011)
Quantitative methods used in signal generation	WHO Drug Database quarterly scan using BCPNN
Newsletter or bulletin published	Drug Bulletin of Nepal, Three newsletters per year

The Philippines

Pharmaceutical Profile

Pharmaceutical Market	
Population (million, 2011)*	94.9 million
Gross domestic product per capita (USD, 2011)*	2,370
Market size: pharmaceuticals (USD, 2011)†	2.91 billion
Market size: medical devices (USD, 2011)†	297 million
Number of medicines registered (2012)‡	32,069
Total expenditure on healthcare per capita (USD, 2009)§	77
Total pharmaceutical expenditure per capita (USD, 2006)‖	21.3
Public expenditure on pharmaceuticals per capita (USD, 2006)‖	2.1
TPE as percentage of total expenditure on healthcare per capita	28%
Health workforce per 10,000 population (2011)#	10.2 physicians; 53.1 nursing and midwifery personnel; 5.4 licensed pharmacists; 11.0 pharmaceutical personnel
Financing for pharmaceuticals	Public (10%), Public/Other (90%)

Medicines Policy	
Policy, laws, and regulations	Foods, Drugs and Devices, and Cosmetics Act, 1987[5] The Generics Act, 1988[6] Universally Accessible Cheaper and Quality Medicines Act, 2008[7]
Patent provisions**	Constitution of the Republic of the Philippines, 1987 Intellectual Property Code of the Philippines, 1997[8] Universally Accessible Cheaper and Quality Medicines Act, 2008[7] WTO TRIPS Agreement (1994)

Pharmaceutical Production Status†† (2012)	
Pharmaceutical manufacturing plants	301
No. of pharmaceutical manufacturing plants	301
No. of pharmaceutical manufacturing plants:	
producing pharmaceutical active ingredients (2011)	0
producing finished pharmaceutical dosage forms	93
packaging finished pharmaceutical dosage forms	22
No. of research-based pharmaceutical industries	24
No. of generic pharmaceutical (including branded generics) manufacturers	70
No. of nationally owned pharmaceutical industries (public and private)‡‡	4

* World Bank Database, accessed date 30/08/2012
† Business Monitor International Philippines Pharmaceuticals and Healthcare Report 2013
‡ Directorate General of Drug Administration
§ WHO National Health Account Database, 2010
‖ WHO World Medicines Situation 2011 Annex
WHO World Health Statistics 2012
** WIPRO
†† FDA database as of June 2012
‡‡ Includes only data from government-owned – Philippines Institute of Traditional and Alternative Health Care (PITAHC)
5 Executive Order No. 175
6 Republic Act No. 6675
7 Republic Act No. 9502
8 Republic Act No. 8293

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 and advertising, control of clinical trials
How products get into the market	Registration by FDA Philippines, list of registered drugs: www.fda.gov.ph/registered-drugs
Joined the WHO program	Official (1995)
Significant events	Not applicable
E2B compliance	Through VigiFlow (E2B-compliant, web- based portal)
Medical terminology used	WHO-ART
Type of reports in PV database	Spontaneous reports, AEFI reports, reports from industry
Total number of ICSRs in the database	13,390 (2006 – 2011), 3,351 (2011)
Quantitative methods used in signal generation	BCPNN
Newsletter or bulletin published	No, medicine safety alerts published on website

Thailand

Pharmaceutical Profile

Pharmaceutical Market	
Population (2011)*	69.5 million
Gross domestic product (USD, 2011)*	4,972 per capita
Market size: pharmaceuticals (USD, 2011)†	4 billion
Market size: medical devices (USD, 2011)†	1.11 billion
Number of medicines registered (item, 2011)‡	24,087 human medicines; 2410 medical devices; 60 narcotics; 28 controlled substances
Total expenditure on healthcare per capita (USD, 2010)*	179
Total pharmaceutical expenditure per capita (USD, 2011)†	70
TPE as % of total healthcare expenditure per capita (2010)	39.1%
Public expenditure on pharmaceuticals per capita (USD, 2011)†	42.5
Health workforce per 10,000 population (2011)§	Physicians: 3.0; Nurses/midwives: 15.2; Pharmaceutical personnel: 1.2; Dentistry personnel: 0.7; Environmental and public health workers: 0.4
Financing mechanisms for pharmaceuticals	Public (88%), Private/Other (12%)*

Medicines Policy	
Legal Provision for Medicines Legislation‡	Drug Act 1967 Psychotropic Substances Act 1975 Narcotics Act 1979
Existence of National Medicines Policy‖	National Drug Policy A.D.2011 and National Drug System Development Strategy A.D.2012-2016
Patent provisions#	The Permanent Constitution of the Kingdom of Thailand (2007) Thai Patent Act B.E. 2522 (1979), as amended by Patent Act (No. 2) B.E. 2535 (1992) and the Patent Act (No. 3) B.E. 2542 (1999) WHO TRIPS Agreement (1994)

Pharmaceutical Production Status‡ (2011)	
Total no. of pharmaceutical manufacturing plants	724 (163 modern medicine, 561 traditional medicine)
No. of pharmaceutical manufacturing plants:	
producing pharmaceutical active ingredients	6
producing finished pharmaceutical dosage forms	721
packaging finished pharmaceutical dosage forms	25
No. of research-based pharmaceutical industries	15
No. of generic pharmaceutical (including branded generics) manufacturers	724
No. of nationally owned pharmaceutical industries (public and private)	724

* World Bank Database, accessed date 30/08/2012
† Business Monitor International Thailand Pharmaceuticals and Healthcare Report 2013
‡ Thai FDA, 2011
§ WHO World Health Statistics 2012, Accessed 30/08/2012
‖ WIPO, Accessed 27/08/2012
WHO World Health Statistics 2012, Accessed 30/08/2012

Pharmacovigilance Profile

Policy, laws, and regulations	Drug Act (1967) National Drug Policy (2011) Strategy on National Drug System Development 2012-2016
Name of regulatory authority/website	Thai Food and Drug Administration www.fda.moph.go.th
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	Registration by Thai FDA, List of registered drugs vaccines: drug.fda.moph.go.th/ zone_service/ser020.asp
Joined the WHO program	Official (1984)
Significant events	Hepatic injury associated with Cassia siamea (leaf) and increasing the frequency of pure read cell anemia associated with erythropoietin (detected from Thai FDA database)
E2B compliance	INTDIS format
Medical terminology used	WHO-ART for ADR terminology ATC code for medicine ICD-10 for indication
Type of reports in PV database	Spontaneous reports, AEFI reports, active surveillance reports, product quality reports, PSURs, reports from PHPs
Total number of ICSRs in the database	57573 in 2011
Quantitative methods used in signal generation	Reporting Odd Ratio (ROR), implemented since 2006
Newsletter or bulletin published	Medicinal and Health Product Bulletin (quarterly) and HPVC Newsletter (occasionally for safety and information alerts)

Annex D. Assessment Method

Literature Search

In each of the countries assessed, a literature search was conducted to identify articles published in peer-reviewed journals with methods, outcomes, or both relevant to PV and medicine safety. The following search terms were used:

"OR" OR "adverse effect" OR "side effect monitoring" OR "drug safety" OR "drug toxicity" OR "adverse events following immunization" OR "AEFI" OR "pharmacovigilance" OR "pharmacoepidemiology" OR "medicine safety" OR "active surveillance study" OR "adverse reaction study" OR "post marketing surveillance" OR "product surveillance") AND "[country]."

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. Additional information was obtained from:

- National medicines policy
- National medicines legislation
- Regulatory systems, governance, and policy
- National lists of registered products and the list of licensed pharmaceutical premises
- Organization charts
- Annual center report and activity reports
- Relevant committee meeting minutes
- Reports on pharmaceutical market size and industry medicine safety activities
- Reports of recent safety events and recent reviews

Site Selection

Several sites were chosen based on various criteria (see "Study Methods" section within report for more detailed information). The table below summarizes some of the sites that were chosen in each of the individual countries.

Selected Sites Visited Across Studied Countries

	Bangladesh	Cambodia	Nepal	Philippines	Thailand	Total
National	6	9	8	9	10	42
Public Health Programs	4	3	4	5	7	23
Health Facilities	23	11	17	23	12	86
Pharmacies	10	14	15	32	3	74
Consumer Groups	1	2	3	3	1	10
Pharmaceutical Industries	9	3	4	9	12	37
Academia	3	2	7	7	3	22

Indicator-Based Pharmacovigilance Assessment Tool (IPAT)

An analysis of each countries' PV system was determined using the indicator-based pharmacovigilance assessment tool (IPAT) developed by the USAID-funded Strengthening Pharmaceutical Systems (SPS) program. More specific information about the indicators included in IPAT can be found here: http://pdf.usaid.gov/pdf_docs/PNADS167.pdf

Annex E. PV Topics in Curriculum

Modules	Sessions	Contents
Fundamental Topics		
1. Regulatory PV	Overview of national medicine policy and regulatory system	▪ National medicines policy ▪ Legislations and regulations related to medicines and health products ▪ PV as described in the medicine policy in the legislations
	History and overview of PV	▪ History of medicine regulation ▪ History of PV ▪ Evaluating safety throughout the life cycle of a medicine
	Overview of national guidelines for medicine safety surveillance	▪ National PV guidelines ▪ Roles and responsibilities of stakeholders in PV ▪ ADR notification system ▪ List of tools used in medicine safety
2. Risk identification	Definitions and classification of adverse events	▪ Definitions in PV ▪ Classifications and types of ADR, medication error, and poor product quality ▪ Adverse events predisposing factors
	Adverse event reporting	▪ Spontaneous reporting ▪ Keys areas of the adverse event notification form ▪ Strengths and limitations of spontaneous reporting ▪ Sources of spontaneous reports
	Causality assessment and signal generation	▪ Causation and hypothesis generation ▪ Causality assessment ▪ Signals, their sources and characteristics ▪ Strengths /weaknesses of methods used to identify safety signals
3. Risk evaluation	Active surveillance	▪ Active surveillance method ▪ Active sentinel surveillance system ▪ Drug event monitoring ▪ Registries ▪ Record linkage studies ▪ Descriptive studies (drug utilization studies)
	Comparative observational studies	▪ Cohort studies ▪ Case-control studies ▪ Targeted clinical investigations
4. Patient safety, risk management, and communication	Medication error and patient safety	▪ Types and causes of medication errors ▪ Sentinel event reporting ▪ Strategies for reducing medication error
	Medicine information and risk communication	▪ Sources of information on medicines ▪ Hierarchy of evidence ▪ Use of information technology in risk communication ▪ Systems and strategies for providing information on medicines
	Risk management strategies	▪ Principles of risk management ▪ Scope and objectives of risk management ▪ Risk management strategies

Modules	Sessions	Contents
Electives: PV in Public Health Programs		
5 (a). HIV and AIDS	ARVs and opportunistic infection medicines	▪ Medicines used in the national guidelines for the management of opportunistic infections and HIV and AIDS ▪ Burden of ARV-related morbidity and mortality ▪ Measures to reduce ARV-related morbidity ▪ Improving adverse event reporting in antiretroviral therapy program
5 (b). TB	Anti-TB medicines	▪ Medicines used in the national guidelines for the management of TB ▪ Burden of anti-TB medicines adverse events ▪ Measures to reduce adverse events related to anti-TB medicines ▪ Improving adverse event reporting in the national TB program
5 (c). Malaria	Antimalaria medicines	▪ Medicines used in the national guidelines for the management of malaria ▪ Burden of antimalaria medicines adverse events ▪ Measures to reduce adverse events related to malaria medicines ▪ Improving adverse event reporting in the national malaria program
5 (d). PV in pediatrics, vaccine/ immunization	Vaccines and mother and child health products	▪ Vaccines used in the national immunization guidelines ▪ Burden and challenges of monitoring adverse events in pediatrics, vaccines, and family planning health products ▪ Adverse events following immunization and measures to reduce vaccine-related adverse events ▪ Improving adverse event reporting in the national malaria program

Annex F. Thailand Health Product Adverse Event Report Form

HPVC No. .....

Reference no. of reporter/source of report .....

Health Product Adverse Event Report Form

(all information will be held confidentially by the government)

❑ Initial
❑ Follow up No. .....
Ref no. .....

Source of Report ❑ Spontaneous Reporting ❑ Intensive Monitoring ❑ Clinical Trial

Patient Information

Patient ID ❑ HN..... ❑ AN.....	Patient type ❑ IPD ❑ OPD	Race ❑ Thai ❑ Other specify	Age	History of allergies ❑ No ❑ Yes (please specify) .....
Patient Initials (first, last)	Gender ❑ Male ❑ Female		Weight	Underlying disease / other relevant conditions (specify ICD code, if known).....

Health Product Information

Type of Health Product ❑drug/narcotics, and psychotropic substance ❑ new drug (SMP) ❑ food ❑ cosmetic ❑ medical device ❑ hazardous substance

Product Name (Generic name/Trade name, dosage form, let no and exp. date for biological product, and part use for herbal product)	S , O I *	Dose and Administration (strength, quantity, unit, frequency, route)	Starting date (d/m/y)	Discontinuing date (d/m/y)	Disease/reason for use (specify ICD code, if known)	Source of product (1 or 2)

*S = Suspected product , O = Other/concomitant product , I = Product interaction

Source of product: 1 = hospital , 2 = other source (please specify)

Adverse Event Information

Adverse Events (describe event and/or technical term)	Labeled or non-labeled ADR	Positive laboratory findings and physical evidence
Date of onset (d/m/y).....		

Seriousness
- ❑ non-serious
- ❑ Serious (choose only one)
  - ❍ Death (d /m /y).....
  - ❍ Life-threatening
  - ❍ Hospitalization-initial or prolonged
    - △ in-patient hospitalisation
    - △ prolongation of hospitalization
  - ❍ Persistent or significant disability/incapacity
  - ❍ Causes a congenital anomaly/birth defect
  - ❍ Medical significant

(please specify) .....

- ❑ Dechallenge
  - ❍ Definite improvement
  - ❍ No improvement
  - ❍ Unknown
- ❑ Continued use
  - ❍ Same dose
  - ❍ Reduced dose
  - ❍ Changed administration
- ❑ Rechallenge
  - ❍ Recurrence
  - ❍ No Recurrence
  - ❍ Unknown
- ❑ No rechallenge performed

Outcome (after the adverse event)
- ❑ Recovered without sequelae
- ❑ Recovered with sequelae
- ❑ Recovering
- ❑ Not yet recovered
- ❑ Died -
  - ❍ due to adverse reaction
  - ❍ drug may be contributory
  - ❍ unrelated to drug (please specify) .....
- ❑ Loss of follow up

Source of Event/Reporter Information

Person making diagnosis .....

Occupation ❑ Physician ❑ Pharmacist ❑ Nurse ❑ other (please specify) .....

Evaluator/reporter.....

Occupation ❑ Physician ❑ Pharmacist ❑ Nurse ❑ other (please specify) .....

Date of report (d/m/y).....

Source of event.....

Province .....Tel.....

Source of reporter.....

Province .....Tel.....

Cause of Event

❑ **Product reaction (ADR/vaccine reaction)** - Causality assessment categories
- ❍ Certain
- ❍ Probable
- ❍ Possible
- ❍ Unlikely
- ❍ Unclassified (please specify reason) .....

- ❑ **Medication error**
- ❑ **Programmatic error** (vaccine)
- ❑ **Coincident** (vaccine)
- ❑ **Product defect**
- ❑ **Accident**
- ❑ **Suicide**
- ❑ **Misuse/in appropriate use**
- ❑ **Other** (please specify reason) .....

Annex G. Glossary

Active surveillance: The collection of case safety information as a continuous, preorganized process. It includes a wide range of active approaches to detect and evaluate risks, such as cohort event monitoring, registries, sentinel sites, epidemiological studies (case control study, cohort study, cross sectional study), and phase 4 clinical trials.

Adverse event: Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. It may be due to poor product quality, medication error, or known or unknown pharmacological properties.

Adverse drug reaction: A response to a drug which is noxious and unintended and which occurs at doses normally used in humans for the prophylaxis, diagnosis, or therapy of disease, or for the modification of physiological function.

Bayesian Confidence Propagation Neural Network: Automated data mining program used by the Uppsala Monitoring Centre. This produces information component values for drug-event combinations. These can be plotted as graphs over time to examine any trend. A positive signal will have information component values that become more significant over time as more cases are included.

Benefit/risk analysis: Comparing the therapeutic benefits from having a medical intervention to the risk of causing adverse effects

Case control study: Study that identifies a group of persons who experienced the unintended drug effect of interest (cases) and a suitable comparison group of people without the unintended effect (control). The relationship of a drug to the drug event is examined by comparing the cases and control with regards to how frequently the drug is present.

Causality assessment: The evaluation of the likelihood that a medicine was the causative agent of an observed adverse event. Causality assessment is usually made according to established algorithms.

Clinical trial: A systematic study on pharmaceutical products in human subjects (including patients and other volunteers) to discover or verify the effects of or identify any adverse reaction to investigational products, or to study the absorption, distribution, metabolism, and excretion of the products with the objective of ascertaining their efficacy and safety.

Cohort event monitoring: A surveillance method that requests prescribers to report all observed events, regardless of whether or not they are suspected ADRs, for identified patients receiving a specific drug; also called prescription event monitoring.

Counterfeit medicines: Products that are deliberately and fraudulently mislabeled with respect to identity and/or source.

Drug use study/Medicine utilization review: A program to review medicine prescribing, dispensing, or patient use of medicines.

Effectiveness/Real-life effectiveness: The outcome or result of applying a particular drug, medical treatment, or service in a particular group of patients or the performance of a product under real-life conditions.

Efficacy: The scientifically demonstrated ability of a therapeutic agent or procedure to consistently affect a specific predictable desirable health intervention within a given population under defined conditions.

Falsified medicines/Fake medicines: A medicine that falsely represents a product's proper active ingredient, source, or both

High-risk medicines: Those medicines that have a heightened risk of causing significant or catastrophic harm when used in error.

Individual case safety report: A report that contains information describing a suspected ADR related to the administration of one or more medicinal products to an individual patient.

Market authorization: An official document issued by the competent drug regulatory authority for the purpose of marketing or free distribution of a product after a satisfactory evaluation for safety, efficacy and quality.

Medication errors: Any preventable event that may cause or lead to inappropriate medication use or patient harm while medication is in the control of the healthcare professional, patient, or consumer.

Medical Dictionary for Regulatory Activities: A medical terminology used to classify adverse event information associated with the use of biopharmaceuticals and other medical products (e.g., medical devices and vaccines). Coding these data to a standard set of MedDRA terms allows health authorities and the biopharmaceutical industry to more readily exchange and analyze data related to the safe use of medical products.

Pharmacoepidemiology: Study of the use and effects of drugs in large populations.

Pharmacovigilance (PV)/medicine safety: The science and activities relating to the detection, assessment, understanding, and prevention of adverse effects or any other possible drug-related problems. The aims of PV are early detection of hitherto unknown adverse reactions and interactions, detect increases in frequency of known adverse reactions, identify risk factors and possible mechanisms underlying adverse reactions, and estimate quantitative aspects of benefit/risk analysis, and disseminate information needed to improve drug prescribing and regulation. The scope of PV includes adverse reactions, medication use errors, product quality complaints, and lack of efficacy.

Pharmacovigilance system: PV systems that include all entities and resources that protect the public from medicines-related harm, whether in personal healthcare or public health services. The system addresses the need for both active and passive approaches to identify and assess medicines-related problems, effective mechanisms to communicate medicine safety information to healthcare professionals and the public, collaboration among a wide range of partners and organizations, and incorporation of PV activities at all levels of the health system.

Post-marketing surveillance: The systematic process of monitoring the use of medical products after a product has been approved. PV is part of post-market surveillance.

Product quality survey: A study that has sampled and tested the quality of medicines according to a standard procedure of quality surveillance.

Product life-cycle: Period from pre-market animal and human safety testing to widespread clinical use beyond original indications

Quality: The suitability of either a drug substance or drug product for its intended use. This term includes such attributes as the identity, strength, and purity (from ICH *Q6A Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances*)

Quality assurance: An organized arrangement (processes and systems) of all elements that influence the quality of the product. It involves inspection of compliance with Good Manufacturing Practices, assessment of documentation on product quality submitted by the manufacturer, sampling and testing of medicines from the market or different entry points, and systematic evaluation of reported quality problems through the PV system.

Registries: A list of patients presenting with the same characteristic(s). This characteristic can be pregnancy (pregnancy registry), a disease (disease registry), or a specific exposure (drug registry).

Risk management/risk management plans: A set of activities designed to identify, characterize, prevent, or minimize risks related to the medicine; to assess the effectiveness of those interventions; and to communicate those risks to patients and healthcare providers.

Safe: Free from unacceptable risk

Sentinel sites: The selected sites that can provide complete and accurate information on reported adverse events, such as data from specific patient subgroups.

Serious adverse events: Any untoward medical occurrence that at any dose results in death; is life-threatening; requires inpatient hospitalization or prolongation of existing hospitalization; results in persistent or significant disability/incapacity; or is a congenital anomaly/birth defect.

Signal: Reported information on a possible causal relationship between an adverse event and a drug, the relationship being unknown or incompletely documented previously that may be a new adverse effect or a change in the character or frequency of an ADR that is already known.

Spontaneous reporting: Unsolicited communication by healthcare professionals or consumers that describes one or more suspected adverse events in a patient who was given one or more medicinal products and that does not derive from a study or any organized data collection scheme.

Stringent regulatory authorities: Members, observers, or associates of the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use.

Substandard medicines: Products whose composition and ingredients do not meet the correct scientific specifications and that are consequently ineffective and often dangerous to the patient.

Treatment failure: Unexpected failure of a drug to produce the intended effect as determined by previous scientific investigation.

VigiBase: WHO's International Adverse Drug Reaction Database.

VigiFlow: A sophisticated case report management system created by the Uppsala Monitoring Centre for the submission of spontaneous ADR reports.

WHO-ART: WHO terminology for coding clinical information in relation to drug therapy.

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APPENDIX 2: PAPER 2 – Actions of the National Regulatory Authorities in 10 Low- and Middle-Income Countries Following Stringent Regulatory Authority Safety Alerts on Rosiglitazone

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Actions of the National Regulatory Authorities in 10 Low- and Middle-Income Countries Following Stringent Regulatory Authority Safety Alerts on Rosiglitazone

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Abstract

On September 23, 2010, the US Food and Drug Administration and the European Medicines Agency issued safety alerts for medicines containing rosiglitazone. The authors monitored the actions of national regulatory authorities (NRAs) from 10 low- and middle-income countries to identify the time lag between the issuance of safety alerts by these two stringent regulatory authorities and any actions by these select NRAs. Two NRAs outside Africa took regulatory actions related to safety of rosiglitazone within 2 weeks of stringent regulatory authority safety alerts. For the 7 of the 8 African NRAs where the authors could confirm the date of regulatory action, the median time lag before some regulatory action was 43 days, although there was considerable variability in time to regulatory action. Low- and middle-income countries should create or strengthen systems for timely consideration and management of emerging safety issues for products that they have registered.

Keywords

pharmacovigilance, rosiglitazone, drug safety, FDA, Africa, Asia

Introduction

On September 23, 2010, the US Food and Drug Administration (FDA) issued a safety alert indicating that the agency would require that the manufacturer develop a restricted access program for rosiglitazone under a risk evaluation and mitigation strategy.[1] On the same day, the European Medicines Agency (EMA) implemented an immediate suspension of the marketing authorization for rosiglitazone-containing antidiabetic medicines, resulting in the drug no longer being available in the European Union.[2] The FDA and the EMA took these steps on the basis of their review of data on the elevated risk of cardiovascular events associated with rosiglitazone, including acute myocardial infarction and stroke. Both the FDA and the EMA are considered to be stringent regulatory authorities (SRAs). SRAs are defined by participation in the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use or its observers, such as Health Canada, or it associates, such as Australia, through legally binding mutual recognition agreement.[3]

Globally, national regulatory authorities (NRAs) must consider data on emerging safety risks against benefits in determining what medicines should be available in their countries and under what circumstances. Pharmacovigilance informs such benefit-risk decisions during the postapproval phase. However analyses of drug safety systems in low- and middle-income countries (LMICs) have reported considerable variation and gaps in the infrastructure, resources, and practices among national pharmacovigilance programs.[4,5] Notably, surveys reported variability in the types of regulatory actions taken as a result of information collected by the pharmacovigilance system in respondent countries. Many LMICs lack some

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Table 1. Regulatory actions with rosiglitazone by selected low- and middle-income countries.

	Regulatory Actions[a]				
Country	Suspension	Enforcement	Communication Method	Date of Action	Lag Time,[b] d
Ghana	Yes		Safety alert	Nov 29, 2010	67
Kenya	Yes		Safety alert (e-shot)	Oct 13, 2010	20
Namibia	Yes		Safety alert	Nov 10, 2010	48
Nigeria		Yes	Safety alert + press release	Oct 9, 2010	16
Tanzania	Yes		Not available	Nov 5, 2010	43
Uganda	Yes		Not available	Not available	N/A
Senegal	Yes		Safety alert	Oct 12, 2010	19
South Africa	Yes		Safety alert	Jul 5, 2011	285
India	Yes		Safety alert	Oct 7, 2010	14
Indonesia	Yes		Safety alert	Sep 24, 2010	1

[a]Suspension of market authorization and enforcement of risk management practices.
[b]Refers to time elapsed between stringent regulator authority alert and action by national regulatory authority, in days.

or all of the World Health Organization's (WHO's) basic elements of a pharmacovigilance system.[6] These countries often lack the capacity to conduct periodic benefit-risk analyses throughout the life cycle of products in their market. As such, when medicine safety evidence is critically reviewed and disseminated by SRAs, it has the potential for global impact. Safety information is often exchanged between regulatory authorities and the WHO, facilitated by the WHO Collaborating Centre for International Drug Monitoring, Uppsala, Sweden. For example, the WHO publishes a periodic pharmaceutical newsletter in collaboration with the monitoring program to disseminate information on safety and efficacy of pharmaceutical products. The WHO Pharmaceuticals Newsletter reported, in the fifth edition of 2010, on the new FDA restrictions on rosiglitazone and the suspension of marketing authorization in Europe. It also reported on the 2010 suspension of marketing authorization of rosiglitazone in New Zealand and new restrictions in Canada.[7,8]

One of the core indicators of the Indicator-Based Pharmacovigilance Assessment Tool for assessing pharmacovigilance systems in developing countries is the average time lag between the identification of a safety signal of a serious adverse drug reaction or other significant medicine safety issue and communication of this information to health care professionals and the public.[9] Advocates for improved access to medicines in LMICs use the metric "drug lag" in indicating how long it took before an essential medicine licensed by SRAs is introduced by developing countries. At the other extreme of drug lag is "safety lag"—that is, how long it takes developing countries to react to a regulatory action taken by SRAs on a product that is also marketed in their countries. Herein, we analyzed the time lag between the safety announcements on rosiglitazone by SRAs as represented by the FDA and EMA and actions taken by NRAs from selected LMICs, using rosiglitazone as the case study.

Materials and Methods

We studied 10 NRAs: 8 within Africa—Ghana, Kenya, Namibia, Nigeria, Tanzania, Senegal, South Africa, and Uganda; 2 from outside Africa—India and Indonesia. These countries were selected on the basis of their having rosiglitazone registered in their countries and the likelihood that data might be available regarding NRA regulatory actions. We reviewed updates on global regulatory activities using Thomson Reuters IDRAC and Cortellis regulatory intelligence weekly alert,[10,11] WHO Drug Information, WHO Pharmaceuticals Newsletter, WHO Model Lists of Essential Medicines,[12] and the Consolidated List of Products Whose Consumption and/or Sale Have Been Banned, Withdrawn, Severely Restricted or not Approved by Governments,[13] We also searched the websites of the 10 NRAs, including their list of registered medicines, where available, and we followed up with key informants' interviews as needed to validate responses and collect additional information, as appropriate. We calculated the median time lag in days from the date of the first announcement by the SRAs (September 23, 2010, as the index date) to the date of regulatory action by the NRAs. We considered actions as any communication related to safety of rosiglitazone, not limited to safety alerts, product recalls, and withdrawals.

Results

The two NRAs outside of Africa took regulatory actions related to safety of rosiglitazone within 2 weeks of SRA action. Indonesia took regulatory action a day after the SRA's announcement and India, 14 days after. For the 7

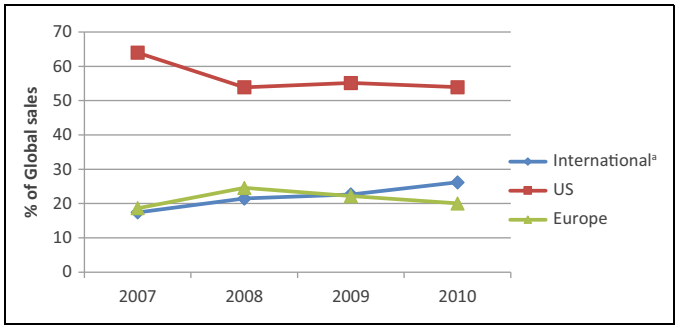

Figure 1. Regional contributions to global sales of Avandia as a percentage of global sales, 2007-2010.[22] "International" refers to non-US, non-European sales.

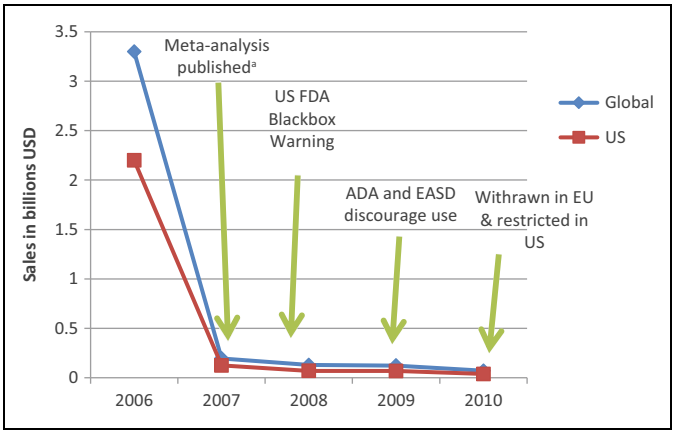

Figure 2. Sales dynamics of rosiglitazone-containing products, 2006-2010.[17] ADA, American Diabetes Association; EASD, European Association for the Study of Diabetes.

of the 8 African NRAs where we could confirm date of regulatory action, the median time lag before regulatory action in the African countries was 43 days. Although the average number of days to regulatory action is recommended as a drug safety indicator, the median better reflects the time lag across the countries studied in this instance. South Africa was an outlier with 285 days elapsed before performing any documented regulatory action.

All the countries studied, except for Nigeria in the first instance, took regulatory actions to suspend the market authorization consistent with the decision of the EMA. Nigeria's Agency for Food and Drug Administration and Control—in its letter on the enforcement of risk management commitment to GlaxoSmithKline, the market authorization holder—requested that the company obtain comprehensive information on patients exposed to rosiglitazone-containing products, ensure that the products are restricted to specialist hospitals and used on a named-patient basis, and submit a report of patients' evaluation by physicians 6 months from the date of notification. The agency indicated that it would make a final pronouncement on continued marketing or otherwise of rosiglitazone-containing products by April 2011. Eventually, the agency announced that GlaxoSmithKline withdrew all rosiglitazone-containing products in Nigeria.[14] Neither the EMA nor any of the 10 NRAs reacted to the FDA's November 25, 2013, removal of some prescribing and dispensing restrictions on rosiglitazone-containing products.

We also reviewed the sales data of rosiglitazone-containing products. Figure 1 shows the percentage of sales in the US, the EU, and the rest of the world from 2007 to 2010. While the percentages of sales of Avandia were in decline in the US and the EU from 2009 to 2010, there was modest increasing trend in the rest of the world. Others noted reductions in utilization of rosiglitazone-containing products after the initial EMA press release and FDA warning on cardiovascular risk in May 2007.[15,16] Figure 2 shows the global and US sales of rosiglitazone-containing products in accordance with key safety milestones. The drop in sales is pronounced following publication of the meta-analysis.[17]

Discussion

The regulatory history of rosiglitazone serves as a case study for the need to continuously evaluate benefit-risk throughout a medical product's life cycle. The decisions by the FDA and the EMA to restrict or suspend the use of rosiglitazone were guided by available evidence as of 2010. Numerous studies underscored the adverse effects and unfavorable benefit-risk balance of rosiglitazone. In a meta-analysis conducted by Nissen and Wolski,[17] patients who were followed for at least 24 weeks from 42 different trials were analyzed. The authors found a significantly increased risk of myocardial infarction among patients treated by rosiglitazone, as compared to other medications (odds ratio [OR], 1.43; 95% CI, 1.03-1.98). The same authors updated their meta-analysis in 2010 and reported that rosiglitazone significantly increased the risk of myocardial infarction (OR, 1.28; 95% CI, 1.02-1.63), although the relation with cardiovascular mortality was not significant (OR, 1.03; 95% CI, 0.78-1.36).[18] An observational study based on Medicare claims data in the elderly reported that compared to pioglitazone, rosiglitazone increased the risk of stroke (hazard ratio [HR], 1.27; 95% CI, 1.12-1.45), heart failure (HR, 1.25; 95% CI, 1.16-1.34), and all-cause mortality (HR, 1.14; 95% CI, 1.05-1.24).[19] In the RECORD study, whose primary outcome was cardiovascular hospitalization, Home et al[20] confirmed the increased risk of heart failure among patients treated by rosiglitazone; the HR was 2.10 (1.35-3.27). On November 25, 2013, the FDA announced the removal of the prescribing and dispensing restrictions on rosiglitazone-containing drugs that was instituted in 2010. This more recent FDA action was based

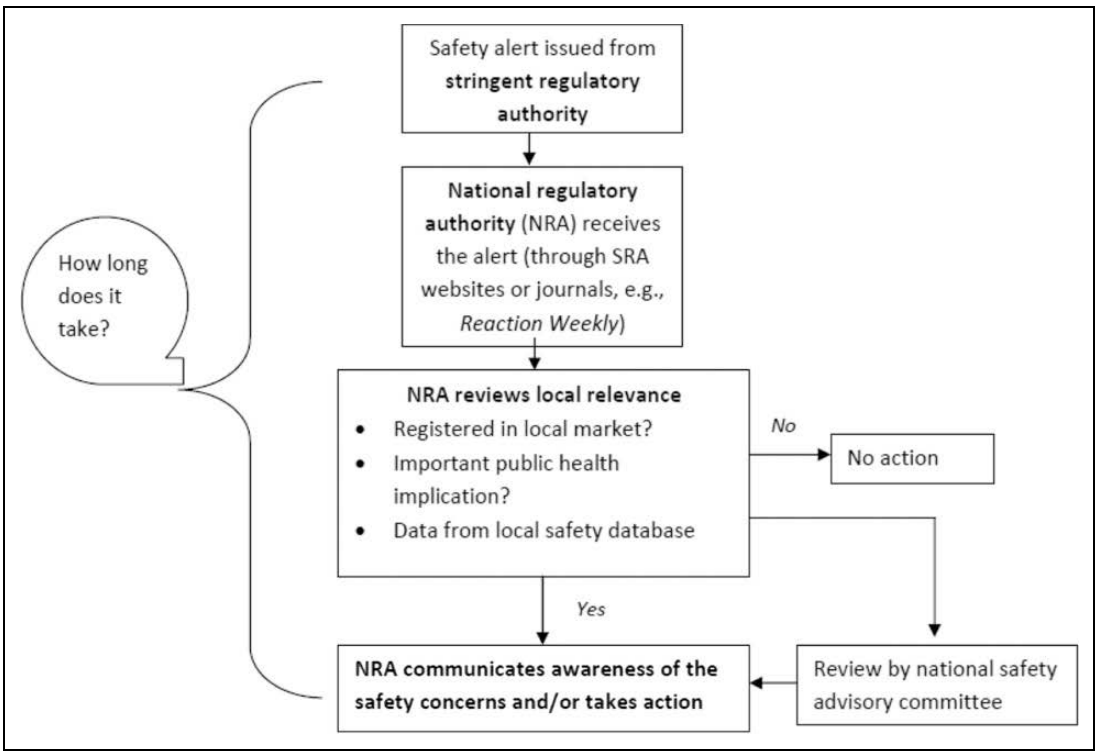

Figure 3. Proposed process for national regulatory authorities to react to emerging safety issues.

on reevaluation of the RECORD trial conducted by the Duke Clinical Research Institute.[21]

Determination of the benefit-risk balance of medicines should be an ongoing activity throughout a medical product's life cycle. As new information becomes available, regulatory decisions can be issued, qualified, or even reversed. These decisions should be based on thorough analysis of available safety information. With regard to measuring safety time lag, the delays in the observed NRA actions may be explained by the lack of a systematic approach for utilizing safety alerts from external sources, a situation that was revealed by the recent evaluation of African pharmacovigilance systems in sub-Saharan Africa.[4] Better global collaboration among NRAs is needed along with improved information exchange practices.

In this study, we considered regulatory actions as any communication related to safety of rosiglitazone. A system for scanning emerging safety issues could have triggered timely communication to health care professionals in LMICs. Figure 3 proposes a process for NRAs to react to emerging safety issues. It is also conceivable that the inconsistency in the actions taken between the US (restriction of use) and the EMA (full suspension) may have created some ambivalence among regulators from LMICs.

Our study is limited by the relatively small number of countries assessed. Although this limits generalizability, we believe that our findings remain informative and illustrate the presence and utility measurement of a safety lag between SRAs and LMICs with weaker drug regulatory systems. We were unable to verify the reasons for delayed regulatory actions across the countries studied, particularly in South Africa: a country with more resources relative to the others and where more timely regulatory action would have been expected. Although all the NRAs in our study eventually suspended the market authorization, this case highlights the importance of building strong pharmacovigilance systems, as the benefit-risk considerations may vary across countries according to disease epidemiology and products available in the local market.

Conclusion

LMICs should create systems for timely identification and management of emerging safety issues, especially for products that they have registered and their populations are using. One of the challenges in the practice of pharmacovigilance is to globally reduce safety lag inequity. The harmonization of standards, the use of common terminologies, and the sharing of information can help reduce safety lag and continued exposure

to potentially harmful products. A systematic approach for risk management based on external safety alerts and the use of tools may improve the timely use of safety data for local decision making in LMICs. Pharmacovigilance performance metrics such as the Indicator-Based Pharmacovigilance Assessment Tool should be used by countries to monitor their safety systems.[9]

Author Note

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Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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APPENDIX 3: PAPER 3 – Registration timelines on antiretroviral medicines in Ghana and Kenya

Research Letters

AIDS 2020, **34**:1093–1099

Registration timelines of antiretroviral medicines in Ghana and Kenya

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This study examines registration timelines of antiretroviral medicines (ARVs) in Ghana and Kenya, to assess whether prior reviews by the US Food and Drug Administration Tentative Approval or WHO prequalification (WHO/PQP) affect in-country approval timelines. Data were collected from online and national databases. Median in-country review period in Ghana was 9 months compared with 25 months in Kenya. ARVs with Tentative Approval and WHO/PQP status did not benefit from shorter in-country review periods.

In 2001, the WHO established its prequalification program (WHO/PQP) to facilitate access to medicines that meet unified standards of quality, safety and efficacy for HIV/AIDS, malaria and tuberculosis especially in resource-constrained countries [1]. In support of PEPFAR (The President's Emergency Plan for AIDS Relief) programs, the United States Food and Drugs Administration (USFDA) in 2004, also developed a regulatory pathway that uses Tentative Approval and expedited review processes to enable timely access to ARVs [2–5]. The extent to which these stringent regulatory authority (SRA) initiatives have impacted marketing authorization timelines in PEPFAR recipient countries, is not known.

This study aimed to:

(1) Assess the time between USFDA Tentative Approval of ARVs and WHO/PQP, and the time when these products received approval from National Medicines Regulatory Authorities (NMRAs) in Ghana and Kenya
(2) Assess the review period (time between application for marketing authorization and approval) within each NMRA
(3) Compare the review period of ARVs with USFDA Tentative Approval or WHO/PQP status with ARVs without prior Tentative Approval or WHO/PQP status

Ghana and Kenya were selected based on potential availability of data and the interest of their NMRAs to participate in the study. Two other African countries did not respond to the study invitation. The list of registered ARVs, and the dates of application and approval of marketing authorization were obtained from the databases of the NMRAs. Each ARV was defined by its International Nonproprietary Name, brand name, strength, formulation, and manufacturer. For Ghana, data were collected on ARVs registered between January 2002 and September 2018. For Kenya, data were available for ARVs registered between January 2002 and December 2014. USFDA Tentative Approval and WHO/PQP approval dates of these ARVs were collected from online databases [2,6]. ARVs that were not approved by NMRAs at the time of data collection were excluded. Data collection occurred in 2017 to 2018.

Data were analyzed using SAS version 9.4 [7]. Outcome measures were:

(1) Time (in months) between USFDA Tentative Approval and NMRA approval
(2) Time between WHO/PQP approval and NMRA approval
(3) In-country review period: time between application for marketing authorization and approval
(4) Difference between median in-country review periods (using the Wilcoxon rank sum test) for:
    (a) ARVs with and ARVs without Tentative Approval status
    (b) ARVs with and ARVs without WHO/PQP approval status

Timelines were described using the median, minimum, and maximum values.

Data for all 194 ARVs registered in Ghana were analyzed. Out of 185 ARVs registered in Kenya, marketing authorization application and approval dates were available for 28 and 140, respectively.

Overall, the time between USFDA Tentative Approval and NMRA approval ranges from 1 to 98 months with a median of 21 months (Table 1). The median timeline was shorter in Kenya compared with Ghana (13 vs. 21 months). Overall, the time between WHO prequalification and NMRA approval ranges from 1.6 to 127 months with a median of 19 months (19 months in Ghana compared with 22 in Kenya).

The median in-country review period was shorter in Ghana than in Kenya (9 vs. 25 months). However, review periods vary widely in each country – 1–86 months in Ghana and 2–74 months in Kenya.

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Table 1. Time (months) between United States Food and Drugs Administration Tentative Approval or WHO prequalification and the National Medicines Regulatory Authorities approval.

	Mean	Median	Minimum	Maximum
USFDA Tentative Approval to NMRA approval				
Ghana ($N=68$)	30.7	21.2	2.6	98.3
Kenya ($N=25$)	16.1	13.3	0.8	53.2
Overall ($N=93$)	33.1	21.0	0.8	98.3
PQP approval to NMRA approval				
Ghana ($N=31$)	32.0	19.3	1.9	127.4
Kenya ($N=29$)	27.4	22.4	1.6	81.4
Overall ($N=60$)	29.8	19.3	1.6	127.4

NMRA, National Medicines Regulatory Authorities; USFDA, United States Food and Drugs Administration.

In Ghana, there was no significant difference in the median review period of WHO prequalified and non-WHO prequalified ARVs ($P=0.9902$) (Table 2). However, ARVs with Tentative Approval status had a statistically significant longer review periods compared with ARVs without Tentative Approval status (16.4 vs. 7.7 months, $P=0.018$).

In Kenya, WHO/PQP or Tentative Approval status did not significantly affect the median in-country review periods for ARVs (Table 2). This finding in Kenya should be interpreted with caution because of the small sample sizes of ARVs with Tentative Approval and WHO/PQP status (four and three, respectively).

This study has generated useful evidence on in-country marketing authorization timelines and how countries have not leveraged the full benefits of USFDA Tentative Approval and WHO/PQP programs.

The median time between Tentative Approval or WHO prequalification and NMRA approval in the two study countries were 21 and 19 months, respectively. It has been reported that companies delay in submitting marketing authorization applications to NMRAs [8,9]. This may be one reason for these long time gaps.

The median review period for ARVs registered in Ghana and in Kenya were 9 and 25 months, respectively. This finding is consistent with findings from a study involving 26 African countries where review periods ranged from 3 months to 5 years [10]. Long review periods represent a barrier to timely access to ARVs.

This study also showed that ARVs already approved by SRAs such as USFDA Tentative Approval and WHO/PQP were not given expedited review in-country. Paradoxically in Ghana, ARVs with Tentative Approval status have a significantly longer in-country review period compared with ARVs with no Tentative Approval status. It has been documented elsewhere that many NMRAs do not rely on SRAs, in performing their regulatory functions [10]. This lack of harmonization in regulatory activities can lead to duplication of functions, increased cost and delayed access to medicines [11,12].

Initiatives are underway to enable the WHO and NMRAs in LMICs use USFDA's reviews to expedite registration processes and promote timely access to medicines [13,14]. In 2019, the Food and Drugs Authority of Ghana adopted a policy to expedite the evaluation of products that have been approved by SRAs [15].

This study has a few limitations. The study was not designed to be representative of the entire African region. However, as the first study of its kind, it contributes to existing knowledge and generates relevant hypothesis for future regionally representative studies. The missing data for Kenya may have introduced bias. Additionally, registration of a product does not imply it is available for use in-country.

Conclusion

Antiretroviral medicines with USFDA Tentative Approval and WHO/PQP status did not benefit from shorter review periods in Ghana and Kenya. More needs to be done to harmonize regulatory practices to ensure timely access to medicines.

Table 2. Comparing median in-country review periods for antiretrovirals with stringent regulatory approval status and antiretrovirals without stringent regulatory approval status.

	Median in-country review period (months)			
	Ghana		Kenya	
ARVs without USFDA Tentative Approval status	7.7 ($N=54$)	$P=0.018$	26.3 ($N=20$)	$P=0.4014$
ARVs with USFDA Tentative Approval status	16.4 ($N=26$)		15.6 ($N=4$)	
ARVs without WHO/PQP status	13 ($N=32$)	$P=0.8802$	25.7 ($N=21$)	$P=0.5746$
ARVs with WHO/PQP status	16 ($N=31$)		15.3 ($N=3$)	

ARVs, antiretrovirals; PQP, prequalification; USFDA, United States Food and Drugs Administration.

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Conflicts of interest

There are no conflicts of interest.

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Who are the persons living with HIV who might refuse to participate in HIV cure-related clinical trials with treatment interruption?

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Achieving a HIV cure has become a research priority. As any improvement of knowledge, which could help scientists design new HIV cure-related clinical trials (HCRCT) depends on the risks potential participants are willing to accept, it is important to understand who will agree or refuse to participate and in which proportions. By providing insights into factors associated with reluctance toward HCRCT participation, our results may help clinicians in patient recruitment.

Achieving a HIV cure has become a research priority, implying the need for HIV cure-related clinical trials (HCRCT) with analytical antiretroviral treatment interruption (ATI) [1–13]. In the current context of modern, well tolerated, combined antiretroviral therapy (cART), clinical and biological HCRCT-related issues cannot be disconnected from associated ethical questions or from the consequences on the daily lives of persons living with HIV (PLWH) who will participate in HCRCT [14–26]. As any improvement in knowledge regarding future HCRCT depends on the risks that potential participants