COMPARATIVE ANALYSIS

Pharmacovigilance Systems in Five Asian Countries

Problem Statement

Despite an increase in access to medicines in low- and middle-income countries (LMICs), fully functional pharmacovigilance and regulatory systems are not yet in place. Strengthening regulatory and pharmacovigilance systems is a global imperative for preventing harm and improving outcomes in treatment and prevention programs. The Asia region both supplies and purchases medical products. A better understanding of the existing regulatory and pharmacovigilance systems in this region can help guide national governments and international donors towards effective and viable pharmacovigilance systems.

Background

The recent progress in increased access to medicines in low- and middle-income countries (LMICs) requires strengthening the regulatory and pharmacovigilance systems to protect the public from unsafe medical products. In many LMICs, pharmacovigilance systems are fragmented, weak, and unable to protect the public health, thereby compromising the significant improvement in health outcomes from greater access to medicines.

Recognizing the importance of assisting countries to protect the public from poor quality and unsafe medicines, the US Agency for International Development (USAID) and the US Food and Drug Administration (FDA) funded the Systems for Improved Access to Pharmaceuticals and Services (SIAPS) Program through an interagency agreement to assess pharmacovigilance systems in five Asian countries: Bangladesh, Cambodia, Nepal, the Philippines, and Thailand.

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 to Fight AIDS, Tuberculosis and Malaria [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. India was excluded from the South Asia region study as there were not adequate resources to cover a country of that size.

Study Objectives

There is little information about the pharmacovigilance systems in South Asia countries and even less from a comparative regional perspective. The objectives of this assessment were to—

- Benchmark the performance of national pharmacovigilance systems
- Identify replicable and successful experiences

- Map the contributions of donor agencies
- Recommend options for enhancing pharmacovigilance and post-market surveillance systems' capacity and performance

Methodology

SIAPS conducted a literature review of the regulatory and pharmacovigilance systems in the Asia region. SIAPS then undertook a comprehensive assessment of the pharmacovigilance systems in the five Asian countries selected—Bangladesh, Cambodia, Nepal, the Philippines, and Thailand. Local consultants analyzed the data collected across five areas of the pharmacovigilance system: Governance, Policy, Law, and Regulation; Systems, Structure and Stakeholder Coordination; Signal Generation and Data Management; Risk Assessment and Evaluation; and Risk Management and Communications.

Summary Results

Governance, Policy, Law, and Regulation. Of the five Asian countries assessed, Bangladesh, the Philippines, and 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. While all countries have drug legislation that includes provisions for medicine safety, their pharmacovigilance regulatory requirements vary greatly. Cambodia and the Philippines have legal provisions that require the pharmaceutical industry to report adverse events but only the Philippines conduct post-marketing surveillance of specified products based on stringent regulatory authority requirements. Generally, the countries do not explicitly require risk assessment, evaluation, and risk management practices in their national legislation.

Systems, Structures and Stakeholder Coordination. All countries under study have a national pharmacovigilance center. Thailand has a dedicated annual budget for pharmacovigilance activities. Cambodia and Thailand have national pharmacovigilance guidelines in place. Cambodia, Nepal, and Thailand have a medicines safety advisory committee that meets at least one time per year and has a documented decision-making process. Only Thailand's Advisory Committee has policies that address conflict of interest. Although all five countries incorporated product quality assurance regulations in their national regulatory authorities, only the Philippines has a formal quality management system and only Thailand has a WHO pre-qualified quality control laboratory. Cambodia, Nepal, the Philippines, and Thailand are official members of the WHO International Drug Monitoring Programme, and Bangladesh has initiated efforts to join.

Signal Generation and Data Management. All countries assessed have a standardized adverse events (AE) form. Thailand has forms for all health products and collect data on suspected adverse drug events, product quality issues, medication errors, and treatment failure. Thailand and the Philippines practice consumer reporting. The availability of AE reporting forms within service delivery points was limited. Only 41 percent of health facilities and 21 percent of pharmacies sampled across the five countries reported having AE forms at hand. SIAPS found significant underreporting in all countries with the exception of Thailand.

Risk Assessment and Evaluation. Risk assessment and evaluation was the weakest component of the pharmacovigilance system across all countries. Only the national regulatory authorities in Thailand reported 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 medicine 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 markets to be less than one percent, while Cambodia estimates the level of unregistered medicines at 30 percent. Bangladesh estimates high levels of unregistered medicines within the market as well. All five countries reported that medical products were both sampled and analyzed for quality in national laboratories in 2010. Encouragingly, Cambodia, the Philippines, and Thailand reported alerting health care workers and the public within three weeks of detecting a medicine safety concern. The Association of South East Asian Nations (ASEAN) post-marketing alert mechanism for sharing information appears to be an underused opportunity for collaboration to safeguard the supply chain in member countries.

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

Pharmacovigilance at the Service Delivery Level. SIAPS surveyed a total of 86 health facilities and 62 pharmacies across the five countries. Only one fourth of the private or community pharmacies surveyed were aware that there was a national pharmacovigilance center 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 forms available. In Nepal, Thailand, and the Philippines, one fourth of the facilities surveyed reported that they had received medicine safety bulletins from their national pharmacovigilance centers.

Pharmacovigilance in the Pharmaceutical Industry. The assessment included five clinical research organizations (CROs), seven medical device companies, and 38 pharmaceutical companies, including a multinational innovator, a multinational generic, and local innovator and generic manufacturers. Sixty-six percent of all pharmaceutical companies, 57 percent of medical device companies, and 80 percent of CROs have a pharmacovigilance or medicine safety unit. However, the performance of the

pharmaceutical industry's pharmacovigilance is below expectations in an already weak regulatory environment. More than one-third of pharmaceutical, biotechnology, and medical device companies do not submit adverse events reports on the national standardized forms in E2B compliant formats. Of the assessed companies, less than one-half (42 percent) of pharmaceutical companies and just more than half (57 percent) of medical device companies collected spontaneous adverse event reports, added the reports to the database and transmitted them to the national regulatory authorities. In 2011, causality was determined for only one-third of the reports. Risk assessment, evaluation, and risk management practices are not being implemented, presumably because there are no legislative requirements for doing so.

Pharmacovigilance at the Civil Society Level. Ten consumer groups, twenty-two professional organizations, and twenty-two 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 twenty percent of consumer groups reported that this knowledge exists among patients and consumers.

Capacity and Performance of Pharmacovigilance Systems in the Five Countries. The five countries were grouped according to the capacity and performance of pharmacovigilance systems. Bangladesh and Nepal have minimal organizational structures and capacity for pharmacovigilance—group 1. Cambodia has a policy and legal framework, basic organizational structures including guidelines, standard operating procedures, and a safety advisory committee—group 2. Group 3 includes the Philippines, a country that has the capacity to collect and evaluate safety data on the basis of legal and organizational structure. Thailand is in group 4 for countries that have performing pharmacovigilance systems to detect, evaluate, and prevent medicine safety issues.

Selected Recommendations and Options

At the national level—

1. **Strengthen regulatory policies and frameworks.**
   Countries should develop new pharmacovigilance systems to ensure that regulations are effective and in the public interest or revise and consolidate the system already in place. Alternatively, countries should review sections of existing legislation of medicines quality, safety, and post-marketing surveillance to ensure that legislation is congruent with other relevant local laws.

2. **Ensure regional and international regulations are harmonized.**
   Map differences and provide guidance on regulations that the country considers equivalent to regional or international standards. Develop guidance for industry to explicitly document its regional equivalencies. Governments can completely revise their pharmacovigilance legislation to make it convergent with that of stringent regulatory authorities and also consistent with the

regional harmonization guidelines within the specific Asia pacific region and other international guidance.

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

4. **Transform organizational structures to achieve integrated safety surveillance.**
   Governments should create a single pharmacovigilance center that can integrate adverse events reporting for all health products and consolidate post-marketing surveillance departments that bring together pharmacovigilance, product quality surveillance, routine inspections, and control of advertising and promotion into a single unit.

5. **Increase funding for pharmacovigilance.**
   Governments should consider reviewing resource allocations for regulatory activities and identify an evidence-based approach for allocating adequate resources for post-marketing surveillance activities. Alternatively, governments should explore new sources of funding including donor funding, user fees, and percentage of sales turnover.

6. **Strengthen spontaneous reporting.**
   Governments should adopt international reporting standards and explore opportunities to use new information technology for improving adverse events reporting. Governments should also look to consolidate or streamline reporting forms for all health products (drugs, biologics, vaccines, and medical devises) and for reporting on safety and quality issues.

7. **Confront falsified and substandard medicines.**
   Donors and partners should consolidate their support to expand WHO and regional harmonization initiatives and rapid alert systems as major instruments for responding to falsified and substandard products. Governments should be supported to improve their regulatory systems and enforcement capabilities for responding to fake products.

At the public health program level—

8. **Strengthen routine collection of information on the tolerability of medicines.**
   Governments 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 of treatment regimes.

9. **Develop sustainable risk assessment and evaluation activities.**
   Governments should explore opportunities for establishing sentinel sites for active surveillance by working closely with antiretroviral therapy,, TB, malaria, vaccines, and mass medicine administration programs.

10. Include pharmacovigilance in donation programs.

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

At the health facilities and service delivery level—

11. Inform health workers about the value of pharmacovigilance.

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

12. Streamline adverse events reporting.

The current adverse events reporting system is burdensome for the busy clinicians and the system does not motivate the reporter. Governments should consult with stakeholders in open forums to discuss the best approaches for improving adverse events reporting at the level of the health worker, facility, private pharmacy, consumer and pharmaceutical industry.

At the pharmaceutical industry level—

13. Strengthen industry commitment to pharmacovigilance.

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

14. Collaborate on Regulating Medical Devices and Developing a Vigilance System.

The medical device industry should collaborate with national regulatory authorities and regional harmonization initiatives to develop a medical device vigilance system.

At the civil society level—

15. Improve the visibility of pharmacovigilance as a public health priority.

Civil society's active involvement in pharmacovigilance systems depends not only on awareness of the legal mandate, structures, and systems in the the country but on how people understand the importance of drug safety for the public at large. Civil society should motivate their members' interest in pharmacovigilance as part of its role as watchdog for good governance in the pharmaceutical sector.

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