

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

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About SPS

The Strengthening Pharmaceutical Systems (SPS) Program strives to build capacity within developing countries to effectively manage all aspects of pharmaceutical systems and services. SPS focuses on improving governance in the pharmaceutical sector, strengthening pharmaceutical management systems and financing mechanisms, containing antimicrobial resistance, and enhancing access to and appropriate use of medicines.

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Key Words

Pharmacovigilance, medicine safety, post-marketing surveillance; adverse drug reaction; Ukraine

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ACRONYMS

AIDS	acquired immune deficiency syndrome
ADE	adverse drug event
ADR	adverse drug reaction
ART	antiretroviral therapy
ARV	antiretroviral
CAPA	corrective and preventative action [procedure]
CRO	clinical research organization
DTC	Drug and Therapeutics Committee
EMA	European Medicines Agency
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
EU	European Union
FDA	US Food and Drug Administration
FDU	Fund of Development of Ukraine
GHTF	Global Harmonization Task Force
GMP	Good Manufacturing Practices
GVP	Good Pharmacovigilance
HCW	health care worker
HIV	human immunodeficiency virus
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
IPAT	Indicator-Based Pharmacovigilance Assessment Tool [SPS]
LDM	local device manufacturer
LE	lack of efficacy
LM	local pharmaceutical manufacturer
MAH	marketing authorization holder
MDC	multinational device company
MDR-TB	multidrug-resistant tuberculosis
MedRA	Medical Dictionary for Regulatory Activities
MGC	multinational generic pharmaceutical companies
MIBP	medicinal immunobiological preparations
MIC	multinational innovator pharmaceutical companies
MoH	Ministry of Health
NGO	nongovernmental organization
NRA	national regulatory authority
PHP	public health program
PIC/S	Pharmaceutical Inspection Convention and Pharmaceutical Inspection Co-operation Scheme
PSUR	Periodic Safety Update Reports
PV	pharmacovigilance
PVAE	post-vaccination adverse events
REMS	risk evaluation and mitigation strategy
QMS	quality management system
QPPV	qualified person for pharmacovigilance
RMP	risk management plan
SAUMP	State Administration of Ukraine for Medicinal Products
SEC	State Expert Center of the Ministry of Health, Ukraine

SOP	standard operating procedure
SPS	Strengthening Pharmaceutical Systems Program
SRA	stringent regulatory authority
SUSAR	suspected unexpected serious adverse reactions
TB	tuberculosis
USD	US dollars
UNAIDS	Joint United Nations Programme on HIV/AIDS
USAID	US Agency for International Development
WHO	World Health Organization

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EXECUTIVE SUMMARY

The pharmacovigilance system safeguards the public through efficient and timely identification, collection, assessment, and communication of medicine-related problems. Recent increases in the availability and use of relatively new essential medicines such as antiretroviral medicines (ARVs) for HIV/AIDS and medicines newly indicated for multidrug-resistant tuberculosis (MDR-TB) have escalated the need to monitor and promote their safety and effectiveness. Because adverse drug reactions (ADRs) are among the most important factors resulting in interruption of antiretroviral therapy (ART) and anti-TB treatment, monitoring and managing adverse reactions to ARVs is important. As public health programs (PHPs) expand access to ARVs and reserve medicines for drug-resistant TB, the need to systematically conduct pharmacovigilance activities within these programs to better identify potential safety problems and their risk factors for specific populations of patients and to inform treatment guidelines revisions is increasingly recognized. A comprehensive pharmacovigilance system comprises more than adverse events data collection and should include both active and passive surveillance methods, effective mechanisms to communicate medicine safety information to health care professionals and the public, and incorporation of pharmacovigilance activities into the various levels of the health system and public health programs.

The Strengthening Pharmaceutical Systems (SPS) Program, in collaboration with the State Expert Center (SEC) of the Ukraine Ministry of Health (MoH), assessed Ukraine's pharmacovigilance system to benchmark capacity and performance at each level of the health care system and used the results to develop recommendations for improving the safety of medicinal products and medical devices in Ukraine. The assessment was conducted using SPS's Indicator-based Pharmaceutical Assessment Tool (IPAT). Data was collected from document reviews and interviews with pharmacovigilance experts and key informants across more than 55 health institutions and organizations in Ukraine.

Selected Assessment Results

Policy, Law, and Regulation

Ukraine is clearly moving in the right direction in its mission to harmonize its regulations with the European Union (EU) pharmacovigilance regulations. Regulations equivalent to EU ones are in place for critical aspects of pharmacovigilance. The MoH and the SEC are focusing on implementing recently passed legislation, developing a national pharmacovigilance guideline, and including a section in Ukraine's Law "On Medicines" that addresses pharmacovigilance and requires mandatory or voluntary reporting of adverse events. However, with regards to medical devices, there are currently no regulations that provide the legal basis for the post-marketing safety monitoring.

Systems, Structures, and Stakeholder Coordination

National units specifically mandated to address medicine safety, vaccine and other medicinal immunobiological preparations (MIBP) safety, and post-marketing quality surveillance, exist and have designated staff whose responsibilities are specified in their job descriptions. The units all have clear mandates, structures, and roles and responsibilities. The SEC's mandate

on pharmacovigilance is focused on ADRs/lack of efficacy of medicinal products and adverse events that result from the use of medicines in clinical practice. The State Administration of Ukraine for Medicinal Products (SAUMP) is responsible for the quality control of medicines and the registration of medical devices. The absence of device safety surveillance, dedicated budgets for pharmacovigilance activities, the lack of standard operating procedures (SOPs), postgraduate training courses in pharmacovigilance, trained human resources for pharmacovigilance (e.g. clinical pharmacists), and resources such as reference books and bulletins are issues that need to be addressed to strengthen medicine and device safety in Ukraine.

Signal Generation and Data Management

The assessment showed that Form #137/o “ADR/lack of efficacy (LE) form for medicinal products allowed for medical use” is widely available at all types of health facilities and at all levels of the health care system. There are no dedicated forms for reporting medication errors to the SEC as this is not required under existing Ukrainian legislation and for reporting product quality defects to the SAUMP. The SEC maintains a database for medicines and MIBP safety reports that is the basis for generating signals and for regulatory decision making on medicinal product safety. The SAUMP has a central database for all quality-related data for medicinal products, medical devices, and equipment. A comprehensive database to collect information on suspected adverse events from all sources in the country has not been established and a database for collecting device safety reports does not exist because of the lack of a legislative basis for post-marketing device surveillance.

Risk Assessment and Evaluation

Ukraine has made very good progress in improving ADR reporting for medicinal products since 2005; in 2011 alone, reporting increased by 21 percent. In 2011, the SEC entered 8,918 ADR reports into the national database, which is equivalent to 195 reports per million inhabitants for that year. However over 50 percent of health institutions did not submit any ADR reports and about 21 percent of the reports submitted in 2011 were not entered into the database because of inconsistent or incomplete reporting, duplicate reporting, or lack of feedback from the reporter. The assessment identified very limited active surveillance activities in Ukraine.

Risk Management and Communication

Risk management and communication is a component of pharmacovigilance with high impact in preventing harm from medicinal products. In Ukraine as in Europe, risk management practices are evolving. Although some risk management elements are in place in Ukraine, the assessment findings indicate that opportunities for preventing harm from the use of medicines and vaccines are not being fully exploited. Safety communications and publications do not seem to get to all the health facilities. Findings indicate that engagement of SEC regional affiliates in communication activities varies; communicating safety to health care workers and the community was not reported as a routine activity in the health facilities visited.

Pharmacovigilance in Public Health Programs

The immunization program has structures for safety surveillance in place and linkages with the SEC are well established. The assessment identified that there are opportunities for the HIV and TB programs to engage more actively in pharmacovigilance without duplicating the efforts of other government institutions. The current legislation does not clearly identify mechanisms for interaction and coordination on pharmacovigilance between the national HIV and TB programs, and the agencies responsible for pharmacovigilance. Although Form #137/o is widely available at HIV and TB facilities, reporting rates for the TB program are somewhat low and few epidemiological or active surveillance studies were performed in the last year by all three public health programs (PHPs). Although hotlines exist, medicine information services to respond to pharmacovigilance-related queries are not yet well developed. Assessment findings also indicate that risk management and communication activities are currently minimal in the TB and HIV programs with few public education activities related to medicine safety. The development of pharmacovigilance trainings for ART prescribers is encouraging and replicating similar efforts for TB program staff is important.

Pharmacovigilance and Medical Device Safety in the Pharmaceutical Industry

Overall, the findings related to pharmacovigilance policies and systems, structures, and coordination were encouraging although there are some differences between local manufacturers and the multinational companies. However, when compared to most multinational companies interviewed, local manufacturers did not have certain pharmacovigilance policies as part of their corporate policies; this was not a requirement under Ukrainian legislation at the time of the interviews (December 2011). For local manufacturers, the lack of pharmacovigilance-related information resources, systems for scanning the global literature, and formal mandatory training programs for staff are common gaps in structures and procedures. Findings indicate the greatest weaknesses lie in risk assessment and evaluation and also in risk management and communication. ADR reporting to the companies is low and none of the companies interviewed had conducted any active surveillance activities in the last five years. Similarly, risk management plans and risk mitigation activities are absent in most multinational generic and local manufacturers interviewed and communication activities are minimal across all types of companies sampled.

Interviews with two medical device companies found that the multinational device company has some policies, procedures, systems, and structures in place for device vigilance but these are mostly related to monitoring product quality at the local level. The local device company's policy and procedures only pertain to monitoring quality and primarily concern device manufacture and registration, rather than post-marketing safety surveillance. The findings for risk assessment and evaluation, and for risk management and communication indicate the absence of any such activities by the two companies interviewed.

Selected Recommendations

Full details of the assessment recommendations are provided in the report. Below are selected recommendations for immediate attention.

- The MoH should update the Law “on Medicines” by incorporating articles on pharmacovigilance. Also the MoH in coordination with SAUMP should develop and implement Ukrainian Laws and Orders related to post-marketing surveillance of medical devices.
- The SEC should strengthen the implementation of the pharmacovigilance provisions recently introduced into Ukrainian legislation including those that are relevant to the industry.
- The MoH and the SEC are advised to consider setting up a risk evaluation unit in the Post-Marketing Surveillance Board.
- The MoH and the SEC should develop comprehensive national pharmacovigilance guidelines and require health facilities and PHPs to improve adverse events reporting.
- The Government of Ukraine is advised to consider providing a dedicated budget for pharmacovigilance to develop and conduct training courses for health care staff.
- The pharmaceutical industry should immediately develop or further enhance their policies, systems, and structures to facilitate full compliance to local regulations on pharmacovigilance.
- The SAUMP should develop tools to improve the reporting of product quality problems from health workers and consumers.
- The MoH and the SEC should develop a system for the reporting, collection, and evaluation of information on medication errors from health workers and consumers.
- The SEC should develop risk management practices to ensure safe medicines use and prevent occurrences of preventable adverse reactions. The SAUMP and the SEC should explore opportunities to improving information sharing among themselves and the public on the safety and quality of health products in Ukraine.
- Industry should conduct risk management activities and collaborate with the SEC to improve safety communication to health workers and consumers.

INTRODUCTION

Definition and Scope of Pharmacovigilance

The World Health Organization (WHO) defines pharmacovigilance as "the science and activities relating to the detection, assessment, understanding, and prevention of adverse effects or any other possible drug-related problems."¹ There is an incomplete understanding of the safety of new medicines at the point of registration. Data on the safety of new medicines are mainly derived from pre-authorization clinical trials in controlled settings. However, clinical trials are limited by restricted exposure, narrow perspective, and short duration, making it imperative to monitor for safety and effectiveness even after approval, especially when the product is used in large populations.²

Post-marketing surveillance is crucial to quantify previously recognized adverse drug reactions (ADRs), identify unrecognized adverse drug events (ADEs), and to evaluate the effectiveness of medicines in real-world situations as well as to decrease mortality and morbidity associated with adverse events.³ Now, the scope of pharmacovigilance has now broadened to include additional critical issues such as medication errors, product quality, and treatment failure in addition to the traditional focus on ADRs. Although ADEs are common, many of them are preventable. The growing problem of poor quality or counterfeit medicines is another reason why pharmacovigilance requires active attention.

The aims of pharmacovigilance are to⁴—

- Improve patient care and safety in relation to the use of medicines and all medical and paramedical interventions.
- Improve public health and safety in relation to the use of medicine.
- Detect problems related to the use of medicines and communicate the findings in a timely manner.
- Contribute to the assessment of benefit, harm, effectiveness, and risk of medicines, leading to the prevention of harm and maximization of benefit.
- Encourage safe, rational, and more effective (including cost-effective) medicines use.
- Promote understanding, education, and clinical training in pharmacovigilance and its effective communication to the public.

¹ WHO. 2004. *WHO Policy Perspectives on Medicines (Pharmacovigilance: Ensuring the Safe Use of Medicines)*. Available at http://whqlibdoc.who.int/hq/2004/WHO_EDM_2004.8.pdf

² Nwokike, J. 2009. *Technical Assistance for the Establishment of a Pharmacovigilance and Medicine Safety System in Rwanda*. Submitted to the U.S. Agency for International Development by the SPS Program. Arlington, VA: Management Sciences for Health.

³ Eguale, T., et al. 2008. Detection of adverse drug events and other treatment outcomes using an electronic prescribing system. *Drug Safety* 31(11): 1005–16.

⁴ WHO. 2006. *The Safety of Medicines in Public Health Programmes*. Geneva: WHO.

Implementing a comprehensive pharmacovigilance system requires efforts beyond data collection on adverse events and should include mechanisms for risk identification, risk evaluation, and risk minimization and communication. Spontaneous ADR reporting and other forms of data collection for early warning on medicine safety are part of the risk identification process. Active surveillance is a key tool in risk evaluation. Risk minimization and communication are the preventive part of pharmacovigilance and include strategies for mitigating known risks, communication of drug safety information, and promotion of rational medicines use. However, pharmacovigilance activities in many countries are fragmented and often do not address all components of a comprehensive pharmacovigilance and medicine safety system.

What Happens in the Absence of Functional Pharmacovigilance Systems

When a pharmacovigilance system does not exist, ADEs still occur but the size and magnitude of the problem is completely unknown. Besides the impact of ADEs on morbidity and mortality and the attendant costs to health systems, ADEs also have other associated costs in terms of the loss of confidence in the health system, economic loss to the pharmaceutical industry, nonadherence to treatment, and development of drug resistance.⁵

Some possible consequences of no pharmacovigilance system include the occurrence of preventable ADRs and the escalating costs of health care delivery. It is estimated that over 70 percent of ADRs that resulted in hospitalization could possibly or definitely be avoided.⁶ Patients who experienced ADEs were hospitalized an average of 8 to 12 days longer than patients who did not suffer from ADEs, and their additional hospitalization cost 16,000 US dollars (USD) to USD 24,000.⁷ Medicines can also be used inappropriately; WHO estimates that worldwide more than 50 percent of all medicines are prescribed, dispensed, or sold inappropriately, while 50 percent of patients fail to take their medicines correctly.⁸ Other consequences include increases in therapeutic switches, use of more expensive regimens, drug resistance, higher patient drop-out, and nonadherence. Unsafe and poor quality products in the supply chain may result in harm to patients or even death.

Need for Pharmacovigilance for Public Health Programs

Recent increases in the availability and use of relatively new essential medicines such as antiretroviral medicines (ARVs) for HIV/AIDS and reserve medicines for multidrug-resistant tuberculosis (MDR-TB) have escalated the need to monitor and promote their safety and effectiveness. While the use of new therapies and the large population covered has the potential for benefitting the population, there is also a risk of harm. WHO recommends that

⁵ Strengthening Pharmaceutical Systems (SPS) Program. 2011. *Safety of Medicines in Sub-Saharan Africa: Assessment of Pharmacovigilance Systems and their Performance*. Submitted to the US Agency for International Development by the SPS Program. Arlington, VA: Management Sciences for Health.

⁶ Pirmohamed, M., S. James, S. Meakin, et al. 2004. Adverse Drug Reactions as Cause of Admission to Hospital: Prospective Analysis of 18,820 Patients. *British Medical Journal* July 3; 329(7456): 15–19.

⁷ Agency for Healthcare Research and Quality. Reducing and Preventing Adverse Drug Events To Decrease Hospital Costs. Available from <http://www.ahrq.gov/qual/aderia/aderia.htm#ast>

⁸ WHO Policy Perspectives on Medicines—Promoting Rational Use of Medicines: Core Components. Available from <http://apps.who.int/medicinedocs/pdf/h3011e/h3011e.pdf>

pharmacovigilance should be an integral part of every public health program (PHP) that uses medicines to optimize the use of scarce health resources and prevent potential tragedies.⁹

Despite their lifesaving effects, ARVs are associated with safety issues ranging from mild and transient side effects to short- and long-term serious ADRs. Medicine safety can vary considerably due to the presence of comorbid conditions such as TB, malnutrition, reliance on traditional or alternative therapies, and likelihood of medicine interactions. Because ADRs are among the most important factors resulting in interruption of antiretroviral therapy (ART)^{10,11} and anti-TB treatment,^{12,13} monitoring and managing adverse reactions to ARVs is important. As PHPs expand access to ARVs and reserve medicines for drug-resistant TB, the need to systematically conduct pharmacovigilance activities within these programs to better identify potential safety problems and their risk factors for specific populations of patients and to inform treatment guidelines revisions is increasingly recognized.

Countries should incorporate pharmacovigilance, including both active and passive surveillance, into ART and TB programs and link these activities to the national system. Active surveillance involves methodically searching for exposures and health outcomes, often at sentinel site facilities, to identify potential safety problems and their risk factors for specific patient populations. Because these methods involve obtaining a denominator of persons exposed to medications of interest, calculation of rates of ADEs is possible. Better understanding of toxicities associated with use of ARV and anti-TB medicines can help PHPs provide more accurate information and expectations to patients regarding long-term toxicities and to improve advice given to patients by clinicians about timing of initial therapy, choice of regimen, and drug substitutions or discontinuations.¹⁴

What Is a Pharmacovigilance System?

A medicine safety 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 efficient mobilization of various stakeholders and resources at all levels and in all sectors.¹⁵ A country's pharmacovigilance system should incorporate activities and resources at the facility, state, national, and international levels, and foster collaboration among a wide range of partners and organizations that contribute to ensuring medicine safety. Figure 1 presents the framework for a comprehensive pharmacovigilance system that identifies the structures,

⁹ WHO Policy Perspectives on Medicines—Promoting Rational Use of Medicines: Core Components. Available from <http://apps.who.int/medicinedocs/pdf/h3011e/h3011e.pdf>.

¹⁰ d'Arminio Monforte A., A. C. Lepri, G. Rezza, et al. 2000. Insights into the reasons for discontinuation of the first highly active antiretroviral therapy (HAART) regimen in a cohort of antiretroviral naive patients. I.CO.N.A. Study Group. Italian Cohort of Antiretroviral-Naïve Patients. *AIDS* 14(5): 499–507.

¹¹ Zhou et al. 2007. Experience with the use of a first-line regimen of stavudine, lamivudine and nevirapine in patients in the TREAT Asia HIV Observational Database. *HIV Medicine* 8: 8–16.

¹² Nathanson E. et al Adverse events in the treatment of multidrug-resistant tuberculosis: results from the DOTS-Plus initiative. *International Journal of Tuberculosis and Lung Diseases* 8(11):1382–1384

¹³ Xia Y. et al Design of the Anti-tuberculosis Drugs induced Adverse Reactions in China National Tuberculosis Prevention and Control Scheme Study (ADACS). *BMC Public Health* 2010, 10:267
<http://www.biomedcentral.com/1471-2458/10/267>

¹⁴ Bissona, G., R. Gross, V. Miller, et al. 2003. Monitoring of Long-Term Toxicities of HIV Treatments: An International Perspective. *AIDS* 17: 2407–17.

¹⁵ Strengthening Pharmaceutical Systems (SPS) Program. 2009. *Indicator-Based Pharmacovigilance Assessment Tool: Manual for Conducting Assessments in Developing Countries*. Submitted to the U.S. Agency for International Development by the SPS Program. Arlington, VA: Management Sciences for Health.

people, and functions that are needed for making national and local decisions that prevent medicine-related problems and reduce associated morbidity and mortality. This approach highlights the need for building capacity to carry out both passive and active methods and how these approaches complement each other in ensuring a robust system for addressing medicine safety issues.

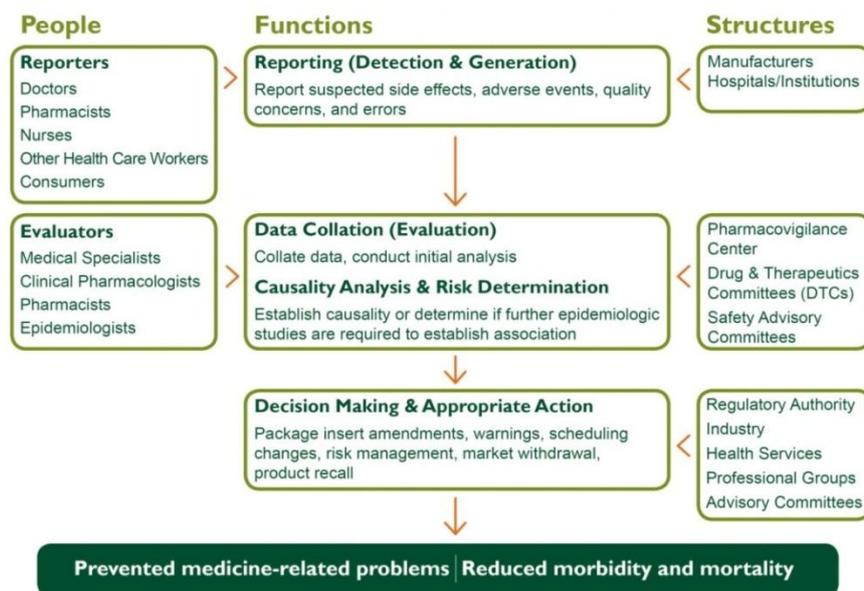


Figure 1. The Pharmacovigilance Framework¹⁶

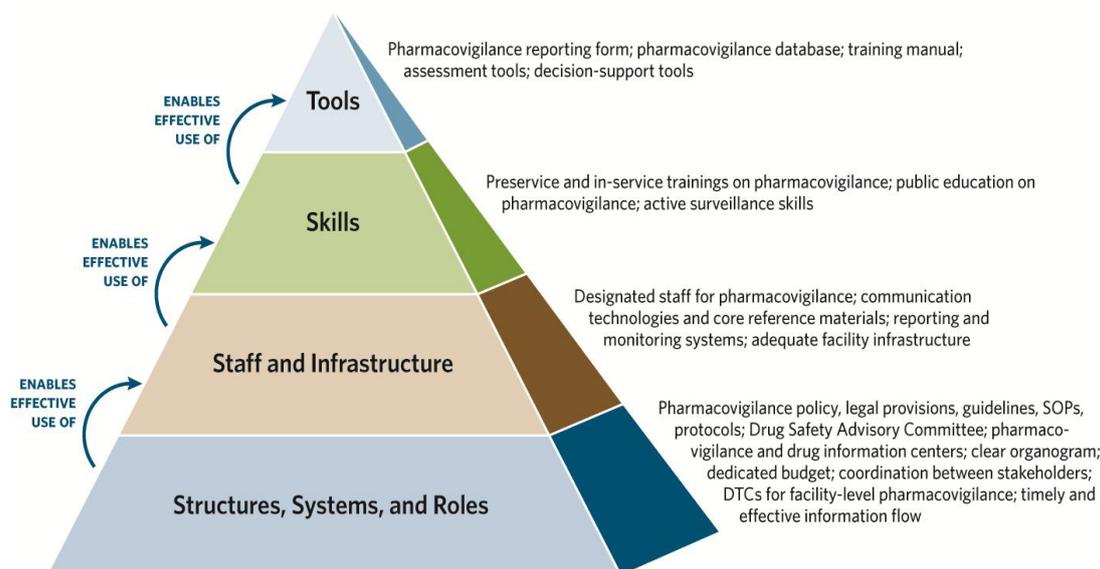


Figure 2. Capacity-Building Model for Pharmacovigilance

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

¹⁶ 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.

Developing, implementing, and sustaining a comprehensive medicine safety system requires in-country capacity building to address gaps related to health structure, systems, and roles; staff and infrastructure; skills; and tools. Figure 2 depicts for each tier key capacity-building needs for achieving a fully functional and sustainable pharmacovigilance system. Structural and systems capacity-building requires developing a functional and sustainable regulatory and organizational structure and guidelines for medicine safety monitoring. Roles and responsibilities of the various stakeholders which include expert advisory committees, government institutions, PHPs, hospital and health providers, pharmaceutical industry, and consumers need to be clearly defined. Providing adequate staffing and infrastructure, ensuring new staff skills and competencies, and institutionalizing appropriate tools to support improved data collection, analysis, and reporting build upon these foundational capacities.

Global Standards for Pharmacovigilance

The International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) develops guidelines to help harmonize regulatory requirements to ensure that safe, effective, and high quality medicines are developed and registered in the most resource-efficient manner. In particular, the ICH guidelines E2A to E2F cover guidelines for the design, planning, reporting, and evaluation of pre- and post-authorization safety data and the conduct of pharmacovigilance systems.¹⁷ The topics include clinical safety data management for expedited reporting, individual case safety reports, periodic safety update reports (PSURs), post-approval safety data management, pharmacovigilance planning for industry, and development safety update reports from clinical trials.

These guidelines are adopted by stringent regulatory authorities (SRAs) such as the European Medicines Agency (EMA) and US Food and Drug Administration (FDA). Standardization and harmonization of guidelines are beneficial as they prevent duplication of effort, enhance information sharing, minimize risk to public health, and reduce the time and resources for medicines development. Countries like Ukraine can benefit from the ICH guidelines by modeling their pharmacovigilance regulations and guidelines to the ICH or, at the minimum, ensuring that their guidelines are equivalent to ICH ones. Ensuring equivalence as a step towards harmonization will assist countries to ensure that their regulatory practices meet the most stringent requirement and also reduce regulatory burden for regulatory systems and the pharmaceutical industry, particularly those used to complying with requirements in other ICH countries such as in the European Union (EU).

EMA Medicine Safety System

EU Regulation Number 1235/201034 and Directive 2010/84/EU35, adopted by the European Parliament and European Council in 2010, govern pharmacovigilance systems in regulatory authorities in EU member states and pharmaceutical companies. Volume 9A of the Rules Governing Medicinal Products in the EU provides pharmacovigilance guidelines for marketing authorization holder (MAHs), regulatory authorities, electronic exchange of

¹⁷ The International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use. Efficacy Guidelines. Available at <http://www.ich.org/products/guidelines/efficacy/article/efficacy-guidelines.html>

pharmacovigilance in the EU, and pharmacovigilance communication.¹⁸ The EU regulatory pharmacovigilance system includes the member states' competent authorities, the European Commission as the competent authority for medicinal products authorized centrally in the EU, and the EMA which coordinates pharmacovigilance systems in the EU. At the time of the assessment, the EMA's Pharmacovigilance Working Party made recommendations on the safety of medicines and the investigation of ADRs associated with medicines on the EU market to the Committee for Medicinal Products for Human Use.¹⁹ This committee was responsible for conducting both pre- and post-authorization assessments of medicines in the EU.

The EMA's Pharmacovigilance and Risk Management Sector manages Eudravigilance, a central database that contains case reports received from over 40 regulatory agencies in member states and pharmaceutical companies. In accordance with the ICH E2B guideline, Volume 9A requires that all adverse events in the database be coded in Medical Dictionary for Regulatory Activities (MedDRA) terminology. Volume 9A requires additional reporting requirements for adverse reactions during breastfeeding, use of medicinal products in children, medication errors, overdose, abuse and misuse, and lack of efficacy. The MAHs are required to electronically submit ADR reports and PSURs via national regulatory authorities (NRAs) to EMA. Under new regulations, MAHs will be able to submit the reports directly to EMA's electronic database. The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) established by the EMA in 2006 to strengthen post-authorization monitoring of medicinal products in Europe,²⁰ comprises EU research institutions, databases, and registries covering rare diseases, therapeutic fields, and adverse events of interest. In addition to facilitating multicenter, independent post-authorization studies that focus on risk-benefit, ENCePP launched the E-Register in 2010, which provides a publicly accessible resource for the registration of pharmacoepidemiological and pharmacovigilance studies.

The member states, the EMA, and the European Commission exchange information regarding new safety concerns, particularly those resulting in major changes to the marketing authorization status, revocation, or withdrawal of a product through EU rapid alert and incident management systems. A rapid alert is circulated within one day for concerns requiring urgent action to protect public health (e.g., when a member state suspends the marketing and use of medicinal products). The rapid alert system is also used to send notifications concerning medicine quality defects or counterfeits.²¹ The EMA has a risk management system complying with the ICH-E2E guideline requiring MAHs to submit an EU risk management plan (RMP) for all newly authorized medicines that contains safety specification, a pharmacovigilance plan, an evaluation of the need for risk minimization

¹⁸ The European Commission. 2008. Volume 9A of the Rules Governing Medicinal Products in the European Union: Guidelines on Pharmacovigilance for Medicinal Products for Human Use. Available at http://ec.europa.eu/health/files/eudralex/vol-9/pdf/vol9a_09-2008_en.pdf

¹⁹ EMA. 2005. Mandate, Objective and Rules of Procedure for the CHMP Pharmacovigilance Working Party. Available at http://www.ema.europa.eu/docs/en_GB/document_library/Other/2010/02/WC500073703.pdf

²⁰ The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) website. Available at <http://www.encepp.eu/events/index.html>

²¹ EMA. 2011. Compilation of Community Procedures on Inspections and Exchange of Information. Available at http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2009/10/WC50004706.pdf

activities, and, if there is a need for additional risk minimization activities, a risk minimization plan.^{22,23}

The new EU pharmacovigilance legislation effective on July 2, 2012, is of particular interest. It is hoped that the new legislations and guidelines will strengthen the EU pharmacovigilance system to become more robust and transparent to better safeguard patients and public health. The key changes in the legislation include establishing a pharmacovigilance risk assessment committee; clarifying the roles and responsibilities of everyone involved in the monitoring the safety and efficacy of medicines in Europe, and strengthening coordination to lead to more robust and rapid EU decision making. Other significant changes include involving patients and health care professionals in the regulatory process, such as direct consumer reporting of suspected ADEs, and improving collection of key information on medicines through risk-proportionate, mandatory post-authorization safety and efficacy studies. Other significant changes are improving transparency and communication, including publishing agendas and minutes of the pharmacovigilance risk assessment committee, and the possibility of holding public hearings.²⁴ To help improve transparency, the EMA launched a website for the online publication of suspected side effect reports.²⁵

Indicator-Based Pharmacovigilance Assessment

In 2009, the US Agency for International Development (USAID)-funded Strengthening Pharmaceutical Systems (SPS) Program developed the Indicator-based Pharmacovigilance Assessment Tool (IPAT) for assessing where a country stood in achieving a functional pharmacovigilance system.²⁶ IPAT is a comprehensive performance metric for monitoring and evaluating pharmacovigilance systems in developing countries. The tool supports evidence-based options analysis and development of relevant and feasible recommendations reflecting each country's local realities, existing regulatory capacity and priorities; identified system gaps and resource availability. Additionally, the tool's standardized and indicator-based approach allows longitudinal measurement of progress after recommended interventions are implemented. IPAT has 43 indicators—26 core and 17 supplementary—that address five pharmacovigilance and medicine safety system components.

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

²² Regulation (EU) No 1235/2010 of the European Parliament and of the Council of 15 December 2010.

Available at <http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2010:348:0001:0016:EN:PDF>

²³ The European Commission. 2008. Volume 9A of the Rules Governing Medicinal Products in the European Union: Guidelines on Pharmacovigilance for Medicinal Products for Human Use. Available at http://ec.europa.eu/health/files/eudralex/vol-9/pdf/vol9a_09-2008_en.pdf

²⁴ European Medicines Agency. New pharmacovigilance legislation comes into operation http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2012/07/news_detail_001553.jsp&mid=WC0b01ac058004d5c1

²⁵ European database of suspected adverse drug reaction reports. <http://www.adrreports.eu/EN/index.html>

²⁶ Strengthening Pharmaceutical Systems (SPS) Program. 2009. *Indicator-Based Pharmacovigilance Assessment Tool: Manual for Conducting Assessments in Developing Countries*. Submitted to the U.S. Agency for International Development by the SPS Program. Arlington, VA: Management Sciences for Health.

The tool is modular so different segments of the health system, for example, PHP managers, can use the indicators relevant to them to monitor various medicine safety issues. The IPAT indicators are set out in annex A.

BACKGROUND

Assessment Objectives

The SPS Program has received funding from the USAID Ukraine to assist the Ministry of Health (MoH) of Ukraine and other local partners to address pharmaceutical management issues related to the management of anti-TB and ART-related medicines. Objectives of technical assistance include supporting the development of appropriate pharmaceutical management policies to help assure the quality and safety of TB and HIV/AIDS medicines. In 2011, the SPS Program worked with the State Expert Center (SEC) of the Ukraine MoH to adapt the IPAT and, in 2012, to conduct a comprehensive assessment of the country's pharmacovigilance and medicines safety system.

This assessment complements previous efforts and provides additional value in benchmarking Ukraine's pharmacovigilance system capacity and performance at each level of the health care system. The assessment objectives were to—

- Provide a comprehensive description and analysis of Ukraine's pharmacovigilance system and document the current level of performance
- Identify potential strategies for strengthening pharmacovigilance system capacity and performance

Methodology

The SEC reviewed the IPAT indicators and questions prior to the assessment. SPS made suggested changes and adapted the questions for interviewing pharmaceutical companies and medical device manufacturers on their pharmacovigilance systems and procedures. Staff from the WHO Country Office in Ukraine also reviewed the IPAT indicators and provided input.

The assessment primarily involved document reviews (annex B) and structured interviews with key informants. SPS worked with the SEC to identify key informants to interview, institutions to visit, and pharmaceutical companies and medical device manufacturers to include—

- Structured interviews were conducted with national- and regional-level key informants and respondents from health facilities using the assessment questions to respond to the indicators in IPAT (annex A). Also interviewed were representatives from universities with pharmacy and medical schools and local nongovernmental organizations (NGOs) working in health.
- Structured interviews were performed with pharmaceutical companies and medical device manufacturers using adapted IPAT questions.
- A literature search was conducted to identify published pharmacovigilance and medicine safety studies that had been conducted in Ukraine. Also SPS searched the clinical trials database²⁷ supported by the US National Institutes of Health to identify

²⁷ <http://www.clinicaltrials.gov/>

active Phase III and IV trials that had an outcome measure designated as a safety issue.

- Additional feedback was collected from respondents to address locally relevant issues or questions and to inform the development of recommendations.

A term “pharmacovigilance system” is used in this report to denote a system for the monitoring of safety of products including ADRs, medication errors, product quality, and therapeutic ineffectiveness.

Selection of Study Sites

The assessment of the pharmacovigilance system in Ukraine using the IPAT required selection of key informants at the national level, including from the SEC and the State Administration of Ukraine for Medicinal Products (SAUMP), PHPs, pharmaceutical companies, university departments, and local NGOs involved in medicines safety. Convenience sampling was used to ensure coverage and representation of each stakeholder in Ukraine’s pharmacovigilance system. At the regional level, six oblasts were selected and interviews were held with SEC regional affiliates and SAUMP territorial subdivisions. Representative samples were also selected from health facilities at various levels of the health care system. At the health facility, data was usually collected from the person responsible for pharmacovigilance or his or her representative. Although the assessment used the preceding outline as a guide in identifying key informants and sites, ultimate selection was informed by logistical challenges and availability of key respondents.

The respondents from the following sites were not available for an interview—

- Clinical and Preclinical Studies Board, SEC
- Division of State Registration of Medical Devices, SAUMP
- SAUMP territorial subdivision, Kyivska oblast
- SAUMP territorial subdivision, city of Kyiv

Table 1 lists the data collection sites visited from March to May 2012, the pharmaceutical companies visited in December 2011, and medical device manufacturers interviewed in April 2012.

Table 1. List of Sites Assessed

Data Collection Sites	Number of Respondents
MoH, SEC, SAUMP, and National Level	
SEC	2
SAUMP	2
Universities	2
NGOs working in health	3
Pharmaceutical companies	11
Medical device manufacturers	2
PHPs	
State Service on HIV and Other Socially Dangerous Diseases	2

Data Collection Sites	Number of Respondents
The All Ukrainian Center for Tuberculosis Control, MoH of Ukraine	1
MoH Public Health Board, Department for Prevention of Communicable Diseases	1
Ukrainian AIDS Center	1
Regional Level	
SEC Regional Affiliates	6
SAUMP territorial subdivisions	4
Health Facilities (32)	
Number of Sites	
Oblast-level hospitals	7
<i>Adults</i>	5
<i>Children</i>	2
City- and rayon-level hospitals	7
<i>Adults</i>	5
<i>Children</i>	2
Polyclinics	6
<i>Adults</i>	3
<i>Children</i>	3
Oblast-level TB dispensaries	6
Oblast-level AIDS centers	6
Health Facilities by region (32)	
City of Kyiv	6
Kyivska oblast	7
Kharkivska oblast	6
Khmelnitska oblast	4
Rivnenska oblast	4
Zhytomyrska oblast	5

Limitations

The assessment did not collect data from a representative number of health facilities, particularly lower-level ones. Hence, the situational analysis of the medicine safety system in treatment facilities may not be generalizable or comparable across regions. Other limitations that may affect the assessment's findings include non-verification of responses to assessment questions, conflicting feedback from respondents, reliance on the data collector's judgment, and imprecision in transforming responses to quantitative forms.

PHARMACOVIGILANCE IN UKRAINE—ASSESSMENT FINDINGS, ANALYSIS, RESULTS, AND RECOMMENDATIONS

Introduction

Ukraine with its population of 45.8 million (January 1, 2011)²⁸ has a gross domestic product of 3,061 USD per capita (2011). Expenditures on health totaled 445 USD per capita in 2009,²⁹ approximately 7 percent of the gross domestic product. The country has an estimated pharmaceutical market size of USD 3.353 billion (2011) with retail sales comprising 86 percent and hospital sales 13.9 percent of the total.³⁰ 13,272 medicines are registered in Ukraine³¹ and generic medicines comprise 80 percent of the total.³² The large number of medicinal products in circulation in Ukraine presents a considerable challenge for post-marketing surveillance and requires robust systems and structures for pharmacovigilance to be in place, active methods of data collection, and well developed risk management activities to protect the population from harm.

Ukraine has the most severe HIV epidemic in Eastern Europe and Central Asia and the second highest burden of TB in the European region after Russia. The Joint United Nations Programme on HIV/AIDS (UNAIDS) estimates that 350,000 people aged 15 or over were living with HIV in Ukraine in 2009, with an adult prevalence rate of 1.1 percent.³³ The estimated incidence of TB in 2010 was 101 per 100,000 population and MDR-TB made up about 16 percent of all newly detected cases.³⁴ Improving coverage of ART for persons who need it is a priority for the Ukraine MoH and its partners. At the end of 2010, 22,697 people were receiving ART, an estimated 13 percent of those who need it.³⁵ Under the current National AIDS Program Operational Plan (2011–2013), the aim is to provide 40,000 patients with ART by 2013.³⁶ Efforts are also underway to scale-up diagnosis and treatment of patient with MDR-TB. Increased access to ARVs and medicines to treat MDR-TB will require commensurate efforts to monitor and assess the risks and benefits of these products, especially in patients with comorbid conditions.

Policy, Law, and Regulation

Existence of a policy that contains essential statements on pharmacovigilance indicates that a country has given high-level attention and commitment to improving medicine safety and quality and provides a broad direction for implementation. Similarly, existence of relevant laws and regulations provides clear directions to ensure compliance by relevant parties and stakeholders and gives a legal basis for monitoring and action. WHO recommends that key

²⁸ State Statistics Service of Ukraine: population as of January 1, 2011. <http://www.ukrstat.gov.ua/>

²⁹ WHO National Health Observatory data base (2009)

³⁰ http://medpharmconnect.com/Ukrainian_market/Ukrainian_Pharmaceutical_Market.htm

³¹ Ministry of Health of Ukraine State Expert Center website 06.13.2012 <http://www.pharma-center.kiev.ua/view/index>

³² Data of the Department of Regulatory Policy MoH 12.03.2012

³³ UNAIDS. 2010. *Report on the Global AIDS Epidemic 2010*. Geneva: UNAIDS.

³⁴ WHO. 2011. *WHO Report 2011 Global Tuberculosis Control*. Geneva: WHO.

³⁵ WHO. 2011. *Global HIV/AIDS response: epidemic update and health sector progress towards universal access: progress report 2011*. Geneva: WHO.

³⁶ UNAIDS 2009. *Comprehensive External Evaluation of the National AIDS Response in Ukraine*. Kyiv: UNAIDS.

elements of pharmacovigilance should be included in national medicines policies and legislation/regulations are developed for medicine monitoring.³⁷

The regulations of SRAs such as the EMA and the FDA require MAHs to report drug or device-related adverse events that occur in all countries where their products are marketed. In the EU, regulations (EC) No. 726/2004 (particularly chapter 3) and Directive 2001/83/EC (Title IX) as amended by Directives 2004/24/EC, 2004/27/EC, and 2010/84/EU, and Regulation (EU) No. 1235/2010 describe the obligations of Competent Authorities and MAHs to set up pharmacovigilance systems to collect, analyze, and evaluate information on suspected adverse events and requirements for expedited and periodic reporting by MAHs. The EMA and FDA have stringent requirements for the regulated industry to monitor safety of registered products. Both agencies also require MAHs to conduct post-marketing safety studies and implement risk minimization activities for high-risk medicines and products with unresolved safety concerns.^{38, 39} The EMA requires MAHs to have a qualified person for pharmacovigilance (QPPV). The guidelines on reporting adverse events related to medical devices in the EU is set out by MEDDEV 2.12/1 rev.7⁴⁰ (medical device vigilance system) and by MEDDEV 2.12/2 rev.2⁴¹ (post market clinical follow-up studies) which promote a standard approach consistent with the SG2 guidelines for device vigilance of the Global Harmonization Task Force (GHTF).

The assessment findings with regard to the policy, laws, and regulations in Ukraine are summarized in table 2. Orders issued by the MoH to regulate pharmacovigilance activities contain essential statements that emphasize the government's commitment to improving medicine and vaccine safety. Responses from key informants indicate that a policy document that will contain relevant statements on pharmacovigilance is under development. Ukraine is in the process of adapting its legislation to EU legal standards in compliance with the Law of Ukraine of March 3, 2004 No. 1629-IV "On National Program for National Legislation Adaptation to EU Standards." The new EU pharmacovigilance legislation came into effect in July 2012. The associated guidelines including the Good Pharmacovigilance (GVP) Guidelines are under development and pending EU approval. Ukraine is in the process of translating those modules that have EU approval with the intent to adapt and implement them locally.

In Ukraine, the pharmaceutical legislation is comprised of the Law of Ukraine "On Medicines" of April 4, 1996, No. 124/96-VR (as amended), Decrees issued by the Cabinet of Ministers, and Orders and Recommendations issued by the MoH.⁴² Medicinal products as defined in the Law "On Medicines" are single or multiple ingredient products of natural, synthetic, or biotechnological origin used for the prevention of pregnancy, for prophylaxis,

³⁷ WHO. 2004. Pharmacovigilance: Ensuring the Safe Use of Medicines. WHO Policy Perspective on Medicines (9). Available at <http://apps.who.int/medicinedocs/pdf/s6164e/s6164e.pdf>

³⁸ European Union. Legislation Volume 9: Guidelines for pharmacovigilance for medicinal products for human and veterinary use. Available at http://ec.europa.eu/health/files/eudralex/vol-9/pdf/vol9_10-2004_en.pdf

³⁹ FDA. Draft guidance for industry: postmarketing safety reporting for human drug and biological products including vaccine. 2001. Available at <http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Vaccines/ucm074850.htm#INTRODUCTION>

⁴⁰ Available at http://ec.europa.eu/health/medical-devices/files/meddev/2_12_1_ol_en.pdf

⁴¹ Available at http://ec.europa.eu/health/medical-devices/files/meddev/2_12_2_ol_en.pdf

⁴² Joint Evaluation Mission WHO/EURO, Delegation of EU Commission in Ukraine and USAID Regional Mission for Ukraine, Belarus and Moldova. July 2008. *Procurement and Supply Management of HIV/AIDS and Tuberculosis Medicines and Related Commodities in Ukraine.*

Table 2. Policy, Law, and Regulation

	Medicinal products	Medicinal immunobiological preparations (MIBP)	Medical devices
Pharmacovigilance (PV) policy	Planned	Planned	
PV law or regulation	✓	✓	
Legal provision for MAHs to report adverse events	✓	✓	
Legal provision for MAHs to conduct post-marketing safety activities	✓	✓	
Essential component of PV policy and regulation	Need for monitoring for adverse events	✓	✓
	Establishment of PV center	✓	✓
	Scope of PV ^a		
	Both passive and active approaches	✓	✓
	Roles and responsibilities of stakeholders	✓	✓
	Information sharing	✓	✓

^a Adverse events (ADRs, post-vaccination adverse events [PVAEs], device safety adverse events) product quality, medication or use errors and for medicinal products, treatment failure

diagnosis, and treatment of human diseases, or intended to change physiological state and functions. The law addresses the development (preclinical studies, clinical trials including rights of patients, and state registration), manufacture, state quality control (authorities, competence of state executive authorities and protection under the law), importation, exportation, and sale of medicinal products. The wording is general and more detailed provisions are included in Decrees of the Cabinet of Ministers and MoH Orders which are developed in alignment with EU provisions.⁴³ Ukraine’s Law “On Medicines” does not address pharmacovigilance and has no section that specifically requires mandatory or voluntary reporting of adverse events. An amendment to the Law and a draft article on pharmacovigilance were prepared and submitted to the MoH in 2008 and again in 2009. In 2012, following the MoH of Ukraine Collegium resolution of July 17, 2012, the MoH is expected to submit the draft article for approval. Articles 13 to 16 of the Law “On Medicines” grants authority for the quality control of medicinal products to the SAUMP and vests it with relevant powers which are set out in the Decree of the President of Ukraine (2011) No. 440 “On Approval of Regulations on State Service of Ukraine on Medicines and Health Products.”

MoH Order of 12.27.2006 No. 898 “About Approval of Procedure for Surveillance over Adverse Reactions to Medicinal Products Permitted for Medical Use” (as amended by MoH Orders No. 778 of September 14, 2010, No 568 of September 6, 2011, and No. 1005 of December 29, 2011) provides the regulatory basis for the post-marketing safety monitoring of medicinal products in Ukraine. It was drafted in accordance with the European Commission’s

⁴³ Joint Evaluation Mission WHO/EURO, Delegation of EU Commission in Ukraine and USAID Regional Mission for Ukraine, Belarus and Moldova. 2008. *Procurement and Supply Management of HIV/AIDS and Tuberculosis Medicines and Related Commodities in Ukraine.*

Directive 2001/83/EC and Council Regulation (EC) 726/2004. Order No. 898 entrusts the SEC of the MoH with conducting surveillance over adverse reactions to medicinal products, lists definitions and criteria to establish frequency of ADRs, and sets out detailed provisions on ADR and lack of efficacy reporting obligations (forms, time limits) and PSUR submission (contents, and frequency), and requirements for safety studies.

The 2011 amendment to Order No. 898 significantly expands pharmacovigilance capabilities in Ukraine. The amendment—

- Enhances the role of the MoH as the central healthcare executive authority for the implementation of the provisions of Order No 898 and pharmacovigilance activities at health facilities;
- Regulates the interactions of all state structures dealing with safety surveillance of medicinal product;
- Expand post-marketing surveillance for medicinal product safety to biological products, including vaccines and blood products;
- Update the adverse event/lack of efficacy reporting form and extends ADR reporting to all medical personnel, including doctors, nurses, doctor's assistants, obstetricians, pharmacists and pharmacy assistants, and also to consumers or their representatives;
- Strengthens requirements for pharmacovigilance in health care facilities, and improved statistical reporting of adverse events at health facilities by oblast health administration bodies;
- Mandates MAHs and pharmaceutical manufacturers to have a pharmacovigilance system for collecting, evaluating, and submitting information on adverse reactions and other relevant data,(includes QPPV, standard operating procedures [SOPs] and database), and a risk management system (including plans if needed). Improving ADR form design and completion and the performance of post-marketing surveys on medicine safety and efficacy are other requirements;
- Provides a mandate for auditing MAH pharmacovigilance systems;
- States pharmacovigilance transparency and reporting requirements.

MoH Orders No. 531,⁴⁴ No. 654,⁴⁵ and No. 736⁴⁶ address medicine safety and efficacy monitoring in inpatient health care facilities (interactions between the SEC and MoH subdivision and health facilities and with accreditation commissions; inclusion of chief therapy specialists as staff or contracted members of the SEC; cooperation with SAUMP territorial divisions; information technologies for safety and efficacy monitoring; and, clinical

⁴⁴ Order of the Ministry of Health of Ukraine of 07.24.2009 No. 531 “On approving the order of medicines safety and efficacy monitoring and inpatient health care facilities”

⁴⁵ Order of the Ministry of Health of Ukraine of 09.01.2009 No. 654 “On approval of plan of measures for improving postregistration surveillance over safety and efficacy of medicinal products in hospitals”

⁴⁶ Order of the Ministry of Health of Ukraine of 08.31.2010 No. 736 “On measures for implementation of monitoring of safety and efficacy of medicinal products in hospitals”

pharmacist or designated person responsibilities for monitoring, analysis, and submission of data to the SEC). Other MoH Orders address the contribution of formulary committees to post-marketing monitoring,⁴⁷ coordination and information sharing between the SEC and the SAUMP to strengthen quantity control effectiveness on medicinal products in circulation,⁴⁸ procedures for prohibition,⁴⁹ re-registration of medicinal products^{50, 51} including requirements for additional studies,⁵² and reporting of suspected unexpected serious adverse reactions during clinical trials.⁵³

For vaccines, antitoxins, and TB allergen, MoH Order of 08.16.2011 No 595 “On the Procedure of Prophylactic Immunization in Ukraine and Control of Immunobiological Medicines Quality and Circulation” provides additional provisions for monitoring product safety and actions and details responsibilities of physicians, health facility heads, and agencies including MoH and SEC’s Department of Immunobiological Medicines and Immunoprophylaxis. Order No 595 includes the prophylactic immunization schedule and medical contraindications, requires that individuals and caregivers are warned about possible reactions, and provides detailed instructions on post-immunization adverse event surveillance and responses in cases of post-vaccination adverse events (PVAE) or lack of efficacy, group reactions, hospitalization, or death (forms, reporting, time limits, investigations including setting up of dynamic response groups, time limits for conducting investigations and reporting findings).

Findings from interviews and review of the MoH and SEC websites reveal that Ukraine is implementing EU regulatory requirements for pharmacovigilance such as consumer reporting, and online reporting of adverse events/lack of efficacy by medical workers, MAHs, and patients or their representatives. Responses from key informants indicate that there are no regulations that provide the legal basis for the post-marketing safety monitoring of medical devices. As Ukraine moves towards harmonization of regulatory requirements to be consistent with the EU, it is imperative to develop legislation to cover the gap in medical device regulations.

⁴⁷ Order of the Ministry of Health of Ukraine of 07.22.2009 No. 529 “Provision on Formulary Committees of Autonomous Republic of Crimea MoH, health care boards of oblast and Kyiv and Sevastopol municipal state administrations”

⁴⁸ Order of the Ministry of Health of Ukraine of 06.17.2005 No. 287 “On approval of the interaction between the State Service for Medicines and Health Products MoH of Ukraine and the State Pharmacological Center MoH of Ukraine in the sphere of medicines circulation”

⁴⁹ Order of the Ministry of Health of Ukraine of 11.22.2011 No. 809 “On approval of the procedure on establishment of prohibition (temporary prohibition) and renewal of circulation of medicinal products within the territory of Ukraine”

⁵⁰ Order of the Ministry of Health of Ukraine of 08.26.2005 No. 426 “Procedure for conducting expert evaluation of materials pertinent to medicinal products, which are submitted for state registration (re-registration) and expert evaluation of materials about introduction of changes to the registration documents during the validity period of registration certificate”

⁵¹ Order of the Ministry of Health of Ukraine of 01.26.2010 No. 55 “Procedure for conducting expert evaluation of materials pertinent to medicinal products of limited use which are submitted for state registration (re-registration)”

⁵² Order of the Ministry of Health of Ukraine of 08.17.2007 No. 190 “On approval of the procedure for conducting additional studies of medicinal products during expert evaluation of registration materials”

⁵³ Order of the Ministry of Health of Ukraine of 09.23.2009 No. 690 “Procedure for conducting clinical trials of medicinal products and expert evaluation of materials of clinical trials”

Implications of Lack of Policies and Legislation

The lack of relevant laws and regulations in a country signifies fundamental limitations for enforcing safety monitoring. Lack of provisions on pharmacovigilance in medicine laws that mandate post-marketing safety commitments of MAHs constrains the ability of NRAs to place responsibility for product stewardship on the license holder. Ukraine is already moving in the right direction in having most of the relevant regulations in place. The recent amendment to Order No 898 to include new and updated regulations that ensure comprehensive and proactive pharmacovigilance in tune with EU regulations are positive trends and can facilitate Ukraine's commitment to harmonize its pharmacovigilance regulations with that of the EU. The recent introduction of electronic reporting, inclusion of consumers in reporting, and adoption of transparency principles in managing ADR data are also positive developments. However, the lack of legal provisions that regulate post-marketing surveillance of medical devices means that the engagement of device manufacturers in device vigilance is often minimal.

Recommendations

- The MoH should develop Ukrainian Laws and Orders related to post-marketing surveillance of medical devices. The regulatory infrastructure for the regulation of medical devices should be based upon the GHTF Medical Devices Post Market Surveillance: Global Guidance for Adverse Event Reporting for Medical Devices.⁵⁴ Ukraine can follow future directions in the regulatory harmonization of medical device through the EU participation in the International Medical Device Regulators Forum.
- The MoH should update the Law “on Medicines” by incorporating the article on pharmacovigilance and taking into account the pharmacovigilance provisions in EU legislation, particularly the new pharmacovigilance legislation (Regulation 1235/2010 and Directive 2010/84/EU) that came into effect in July 2012. In addition, all other legislation regulating the circulation of medicinal products in Ukraine and their safety monitoring should be reviewed for their compliance with EU standards as pharmacovigilance regulations that are not similar with EU and are too demanding to meet can be an impediment to access to medicines while regulations that are too lax can expose patients to harm. The MoH should consider requesting support for this review. The MoH and SEC should include the following regulatory requirements into the Ukrainian legislation—
 - Require the regulated industry to conduct global safety literature scanning.
 - Require that market authorization applications for new chemical entities and applications for significant variations in the market authorization include a description of the pharmacovigilance system and where appropriate, the risk management system.
 - Require the regulated industry to report sales and prescription volume to the SEC.
- The SEC should implement pharmacovigilance provisions recently introduced into Ukrainian legislation to achieve equivalence with EU legislation—
 - Require the regulated industry to report any information that suggests changes in a products benefit/risk profile.

⁵⁴ Global Harmonization Task Force. 2006. Medical Devices Post Market Surveillance: Global Guidance for Adverse Event Reporting for Medical Devices. Available from <http://www.ghmf.org/documents/sg2/SG2-N54-R8-2006-Proposed.pdf>

- Require the regulated industry to document delegation of third parties responsible for pharmacovigilance through written policies, contracts, and procedures.
 - Require the regulated industry to inform the SEC before starting any post authorization safety study and require industry to provide periodic and final study report.
 - In accordance with EU guidelines, require the regulated industry to implement harmonized standards for RMPs as they have with the EMA and other European competent authorities. The RMP should include safety specifications and pharmacovigilance plans in accordance with ICH E2E and a risk minimization plan.
 - Require the industry to develop traceability to the patient level for adverse events of specific biologics.
-
- The MoH and the SEC should develop national pharmacovigilance guidelines. The guidelines should include government commitment to safeguard the safety of everyone exposed to all health products. It should expand the scope of pharmacovigilance to include medication errors, medical device vigilance, monitoring safety of blood products, and other emerging issues. The national guidelines should provide for governance instruments to guide the conduct of pharmacovigilance in Ukraine including involvement of civil societies, conflict of interest, declaration of assets, and confidential financial disclosure by committee members, policies, procedures, and guidelines guiding 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.
 - The SEC should develop relevant guidance documents to improve industry compliance to pharmacovigilance regulations. During the development of the guidance documents, the regulated industry should be invited to comment on them.
 - With the ascension of Ukraine as member of Pharmaceutical Inspection Convention and Pharmaceutical Inspection Co-operation Scheme (PIC/S) opportunities for sharing inspection and regulatory information should be maximized and other avenues for safety information sharing developed. Opportunities to promote information exchange among the key stakeholders assuring the safety of medicinal products in circulation in Ukraine should also be explored.
 - Further develop systems for adopting a proactive approach to pharmacovigilance. The SEC should define criteria and systems for conducting post-authorization active surveillance studies in the health system in Ukraine. The MoH and SEC should work together to implement risk management practices to reduce preventable adverse reactions identified through active surveillance. The SEC should also develop systems to use information generated from post-marketing surveillance activities for regulatory and treatment guidelines decision making.
 - The SEC should explore opportunities for submitting adverse event reports the SEC collects from MAH to the EMA who may include them in the Eudravigilance.
 - Develop needed tools, infrastructure, and human resources and implement pharmacovigilance audits of MAH pharmacovigilance systems.

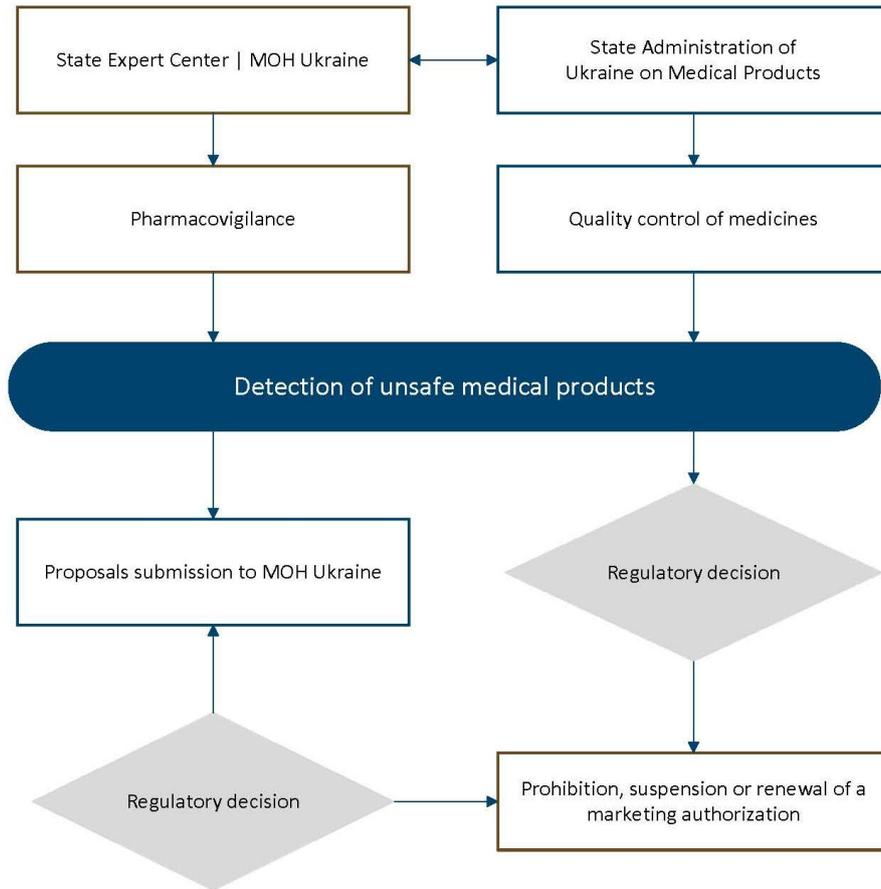
Systems, Structures, and Stakeholder Coordination

A comprehensive pharmacovigilance and medicine safety program requires the development of sustainable systems and structures that function effectively, and clearly defined roles and responsibilities for organizations and entities that are required to take appropriate action. These components enable and facilitate the effective use of staff, skills, and tools to perform critical functions of signal generation and data management, risk assessment and evaluation, and, risk management and communication. Effective stakeholder coordination and linkages between a country's national pharmacovigilance program and PHPs ensure that no gaps exist and that communication and opportunities for leveraging resources are exploited.

The MoH of Ukraine is the chief executive healthcare body in the country, and its functions include the registration and re-registration of medicinal products, temporary suspension of marketing authorization, and pharmacovigilance implementation. The MoH issues Orders on the registration or re-registration of individual medicinal products based on the conclusions and recommendations of the SEC, a MoH subordinate unit which conducts an expert evaluation of the registration materials. In terms of pharmacovigilance, the MoH entrusts the SEC with responsibility for conducting post marketing surveillance of adverse reactions to medicinal products (item 1.3 of MoH Order No 898 as amended in 2011). Alongside the MoH is the SAUMP which is also an executive body not subordinate to the MoH but directly to the Cabinet of Ministers of Ukraine. The SAUMP mandate includes registration of medical devices, quality control of medicinal products, licensing of pharmaceutical business entities (manufacturers, importers, exporters, wholesalers, and retailers), and temporary or permanent suspension of marketing authorization.

The SEC's mandate on pharmacovigilance is focused on ADRs and lack of efficacy of medicinal products (including medicinal immunobiological preparations [MIBPs]), and also medication errors, drug interactions, inappropriate use and overdose incidents, that is, adverse events that result from the use of medicines in clinical practice. SAUMP is responsible for the quality control of medicines and the registration of medical devices; however SAUMP does not conduct safety surveillance of medical devices. Therefore, the registration of medicines and the registration of medical devices are conducted by two separate institutions that are not linked administratively. While legislation to regulate for safety surveillance for medical devices is lacking, SAUMP does register and provide authorization for their use.

In Ukraine, both the MoH and the SAUMP can prohibit the use of medicines in the Ukraine market. The SAUMP issues a prohibition based on decisions about the quality of the medicine, while MoH decisions are based on the occurrence of a previously unknown adverse event that can cause serious harm or death, or changes in the risk/benefit ratio that increase the risk associated with use of a drug, especially where a safer alternative medicine is available. Another unique feature of the Ukrainian system for pharmacovigilance is that the SEC and the SAUMP exchange information in cases of death or unexpected adverse events where initial analysis indicates a link with a medicinal product. In such cases, the SEC informs the SAUMP which issues a temporary prohibition while quality control investigations are completed by the SAUMP. Figure 3 shows the respective roles of the state agencies for post-marketing surveillance of medicinal products.

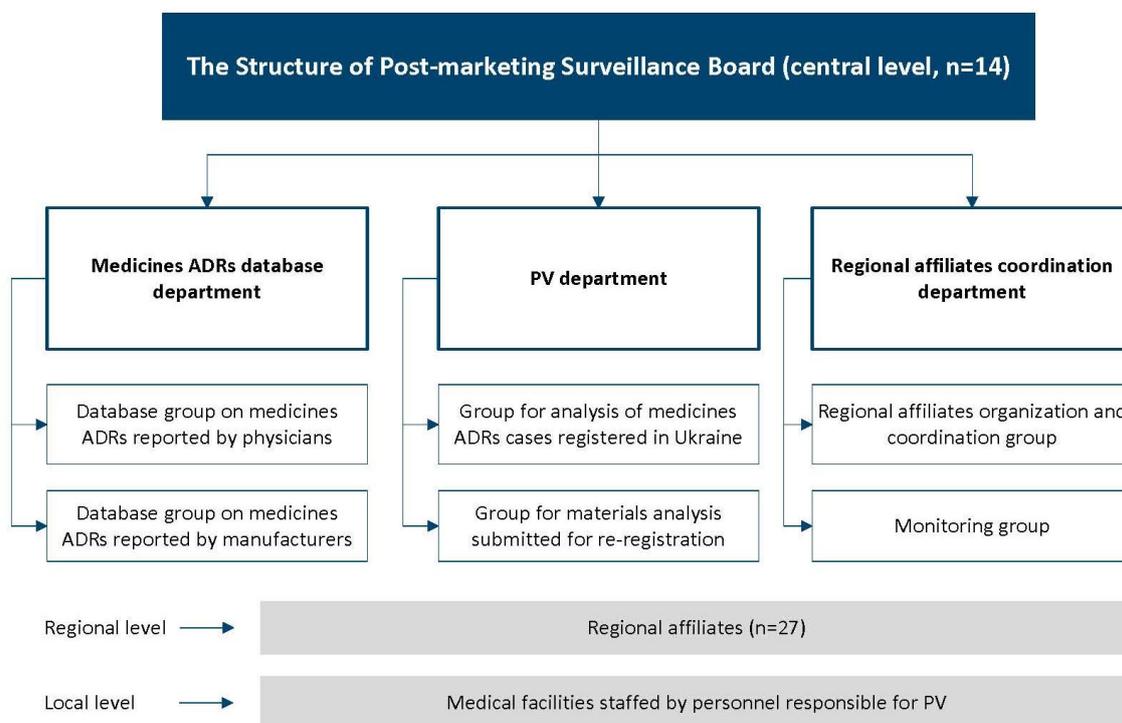


Source: SEC Presentation “Pharmacovigilance system in Ukraine: history, results, objectives” undated

Figure 3. State Agencies Responsible for Post-marketing Surveillance of Medicinal Products in Ukraine

Within SEC, the Post-Marketing Surveillance Board (the Board), a structural unit of the SEC is responsible for post-marketing safety surveillance of medicines. The Board’s primary pharmacovigilance activities are coordination of post-marketing surveillance of medicines safety (collecting and analyzing ADR/Lack of efficacy (LE) reports, and maintaining the national ADR data base); developing operational and organizational support for pharmacovigilance activities in Ukraine’s health care system and for MAHs; exchange of safety information with all organizations involved in regulating medicines in Ukraine and with relevant international agencies; coordinating SEC regional units’ pharmacovigilance activities; expert evaluation of renewal files submitted by MAHs; preparing proposals for the temporary prohibition of medicinal product use in the country for submission to the MoH; and, meeting Ukraine’s obligations with WHO as a country-member of the international medicines safety monitoring program. The structure of the Board is shown in figure 4. The Board consists of three departments, the Pharmacovigilance, the Database and the Coordination of Regional Service departments. The Board has 14 staff that work with regional affiliates and staff members who have designated responsibilities for pharmacovigilance at medical facilities to implement pharmacovigilance activities. Three staff members of SEC’s Department of Immunobiological Medicines and Immunophylaxis carry out relevant functions for vaccines and other MIBPs.

At the regional level, 27 regional affiliates have been appointed and are carrying out pharmacovigilance activities in all of Ukraine’s territorial administrative units (in oblasts and the cities of Kyiv and Sevastopol). As mentioned earlier, post-marketing quality control of medical devices is the responsibility of the SAUMP. The SAUMP has 30 staff at the central level that work with SAUMP territorial divisions to implement post-marketing quality control.



Source: SEC 2012

Figure 4. Structure of the SEC Post-Marketing Surveillance Board

Assessment findings regarding the central-level systems and structures that support medicinal product safety in Ukraine are summarized in table 3. The study identified significant achievements by the MoH and the SEC in establishing structures, systems, and processes at the central level for improving safety of medicines and MIBPs. National units specifically mandated to address pharmacovigilance⁵⁵ including medicine safety, vaccine and other MIBP safety, and for post-marketing quality surveillance, exist and have designated staff whose responsibilities are specified in their job descriptions. The units all have clear mandates, structures, and roles and responsibilities. Financing mechanisms for pharmacovigilance and quality surveillance activities differ between the SEC and the SAUMP. While SAUMP has a dedicated budget for activities, SEC activities are funded from fees received for registering medicines and other procedures. Responses from key informants indicate that a unit exists for quality control of medical devices but it is not known if the unit has a clear mandate for safety monitoring of products approved for use in Ukraine. As mentioned previously, a review of the legislation for post-marketing surveillance identified the lack of laws and bylaws to regulate post-marketing monitoring of medical devices safety.

⁵⁵ A pharmacovigilance system is used in this report to denote a system for the monitoring of safety of products including ADRs, medication errors, product quality, and therapeutic ineffectiveness.

Table 3. Pharmacovigilance Systems, Structures, and Procedures: National Level and Central State Agencies

National Level			
National PV guideline	Planned		
Forum for stakeholder coordination (including PHPs)	✓National Security and Defense Council of Ukraine		
Participation in international monitoring of medicines safety	✓full member of WHO Collaborating Centre for International Drug Monitoring since 2002		
Central State Agencies	Pharmacovigilance		Quality
	MoH of Ukraine		SAUMP
	SEC (Medicines)	SEC (MIBP)	
Unit designated for PV/quality surveillance activities	✓	✓	✓
Person specifically responsible for PV/quality surveillance and responsibilities are described in job description	✓	✓	✓
State financing for PV/quality surveillance			✓
National medicine/ vaccine safety advisory committee			
SOPs for PV/quality surveillance	✓		✓
Information service on PV in place	✓	✓	✓
Bulletin on PV topics, publications	✓publish Bulletin; contribute articles		✓contribute articles

Written and formally approved SOPs are in place at the SEC for post-registration monitoring of medicinal products (43 SOPs) and for quality control activities at the SAUMP, but have yet to be developed for MIBP surveillance. All three units have a query-response service that provides pharmacovigilance-related information. The SEC produces a subscription-based bulletin *Rational Pharmacotherapy* which is published monthly and SEC’s Post-Marketing Surveillance Board and the SAUMP regularly contribute articles to publications such as *Apteka*. The Department of Immunobiological Medicines and Immunoprophylaxis does not currently contribute articles to the SEC bulletin or other publications.

National security functions, in particular those connected with human health and life, are fulfilled by National Security and Defense Council of Ukraine (NSDCU); the Prime Minister and Minister of Health of Ukraine are members of this committee. According to respondents, a national safety advisory committee has not yet been constituted to provide technical advice and scientific opinions on issues related to the safety of medicinal products and/or medical devices. Expert councils and advisory groups exist at various levels and the expert council composed of leading experts of the MoH meets once a month to deliberate on medicine safety issues. Ukraine does not have a comprehensive national guideline for pharmacovigilance to help standardize the provision of pharmacovigilance services at all levels and coordinate stakeholder contributions to ensure effective communication and leverage resources. As mentioned earlier, the EU GVP Guidelines are currently pending EU approval and are also not in place in the EU. Those EU guideline modules that have already come into effect have been translated into Ukrainian and the process of establishing a national pharmacovigilance guideline has been initiated. Although procedures for interactions

between some stakeholders are in place, for example, between the SEC and the SAUMP, a platform that enables effective communications between all stakeholders, including PHPs, is not reportedly in place.

Key informants report that pharmacovigilance is integrated into the training curricula of medical and pharmacy schools but not nursing schools in Ukraine. The lack of pre-service pharmacovigilance training for nurses is mainly because nursing staff were not included in the group of ADR/LE reporters until the latest amendment to MoH Order No 898 came into force on April 4, 2012. Even in medical and pharmacy schools, pharmacovigilance is typically an elective module taught as part of the pharmacology course. Key topics including regulatory pharmacovigilance, risk identification and evaluation, and ensuring patient safety through risk management and communication were reported to be included in the clinical pharmacist curriculum at one university. Pharmacovigilance is not currently included in postgraduate medical educational programs.

At the local level interviews were conducted with six SEC regional affiliates and 32 health facilities⁵⁶ of six oblasts in Ukraine. Interviews revealed that responsibilities for pharmacovigilance at regional level are vested in the SEC regional affiliates and at health facilities, to persons responsible for pharmacovigilance as stipulated in Ukrainian legislation rather than to structural units. The duties of SEC regional affiliates are specified in a contract and, according to information from the central level SEC, are also included in their job descriptions. The interviews with health facility staff revealed that only one health facility had a pharmacovigilance unit consisting of several employees. Most of facilities visited had at least one person designated for pharmacovigilance (94 percent); exceptions were one TB dispensary and one AIDS center that lacked a designated person (figure 5). Duties of persons responsible for pharmacovigilance at health facilities are detailed in an internal health facility Order and half of the staff interviewed said that their responsibilities were also included in their job description. Numerous respondents emphasized the need to appoint clinical pharmacists at health facilities to assist in ADR reporting and active monitoring for adverse events.

The SEC provides an annual budget allocation towards the salaries of the regional affiliates and covers all travel expenses connected with the staff business trips in the region in compliance with Ukrainian financial legislation. No additional remuneration is paid to staff responsible for pharmacovigilance at health facilities. None of the health facilities visited receive a dedicated budget for pharmacovigilance activities.

Although some respondents reported that the Order issued by health facility heads or the oblast MoH includes basic instructions on how to complete and submit an ADR form, detailed SOPs for pharmacovigilance were said to be available in only one of six oblasts (17 percent) and three of 32 health facilities (9 percent). While the six SEC affiliates reported performing similar pharmacovigilance functions, the responses were very variable at health facility level. All except one facility (where nothing is done) receive and submit reports on adverse reactions to the SEC, and most identify safety signals from spontaneous reports. Reported involvement in determining seriousness, expectedness, and validity of the report and causality was inconsistent across types of facilities and regions.

⁵⁶ Interviews were held with staff from oblast-level hospitals (n=7), city/raion-level hospitals (n=7), polyclinics (n=6), TB dispensaries (n=6) and AIDS centers (n=6) in six regions

Informants asked about the availability of a medicine information service and a set of core information resources—reference materials, websites, and journals—(annex C) during the interviews. One of six regional affiliates (17 percent) and 11 of 32 health facilities (34 percent) reported the availability of the complete set of core information resources. All respondents said they routinely use MoH Order No 898 and the State Register of Medicinal Products in the performance of their pharmacovigilance duties. Two of the six regional affiliates had only the Law “On Medicines” and Order No 898 available, while three (50 percent) reported that they use all four key reference books/ documents. In addition, one regional affiliate had an extensive journals and resources available in addition to the basic set. 24 of 32 health facilities (75 percent) reported availability of all the four reference books/documents. SEC’s *Rational Pharmacotherapy* bulletin was reported to be available by only one of six regional affiliates (17 percent) and by 13 of 32 of health facilities (41 percent).

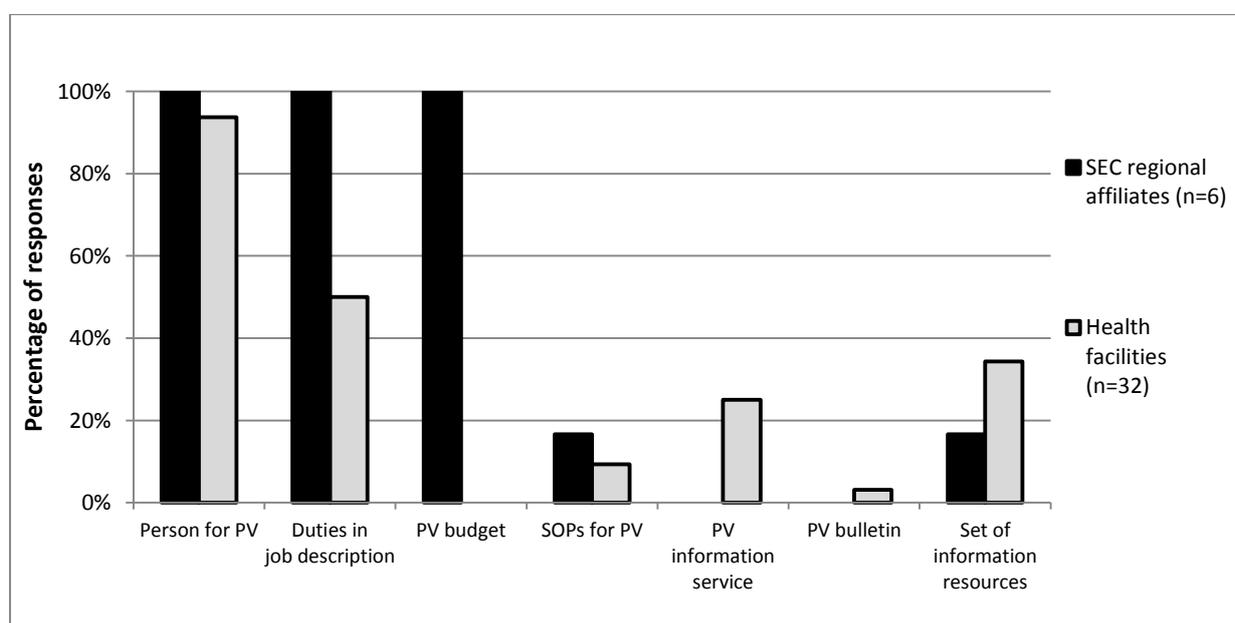


Figure 5. SEC regional affiliates and health facilities: systems and structures for pharmacovigilance

Efforts to measure continuing education training as an indicator are usually guided by a threshold. SPS used a threshold of five percent of health care workers (HCWs) trained and defined training as participation in a pharmacovigilance training course as opposed to a seminar. This target was achieved by only six (19 percent) of health facilities. However, all six regional affiliates reported that at least 5 percent of health professionals in the oblast had attended at least one lecture or seminar in the previous year. All regional affiliates participate in a pharmacovigilance training course annually.

Figure 6 illustrates the variability of three key indicators across different levels of facilities visited. While the availability of designated persons for pharmacovigilance whose duties are specified in job description was consistent across all (between 40 and 60 percent), the availability of a complete set of core information resources and trained staff varied significantly. The results indicate that AIDS centers are better equipped in terms of trained staff and information sources while TB dispensaries may require considerable investments in

both resources and training. In 2011-12, three training workshops were offered to physicians who prescribe ART (further described under the PHP chapter). Key informants at SEC reported that the training has resulted in an increase in ADR report submission from AIDS centers.

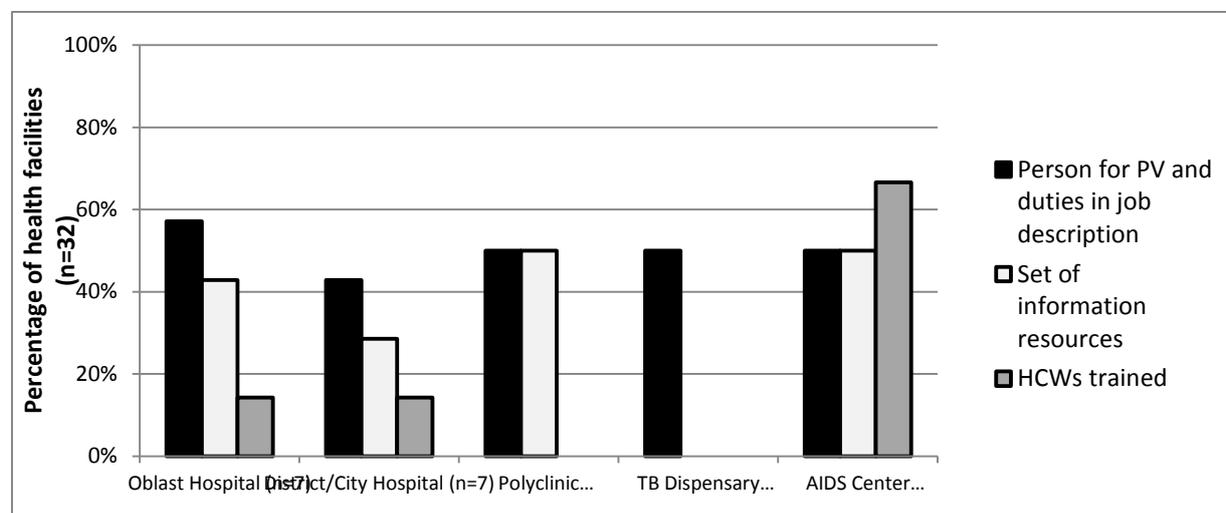


Figure 6. Availability of some systems and structures across different types of health facilities

Assessment findings regarding the systems and structures for SAUMP territorial subdivisions are summarized in figure 7. Interviews with SAUMP staff in four regions indicate that key systems and structures for quality monitoring are available in these four units with the exception of a set of core information resources.

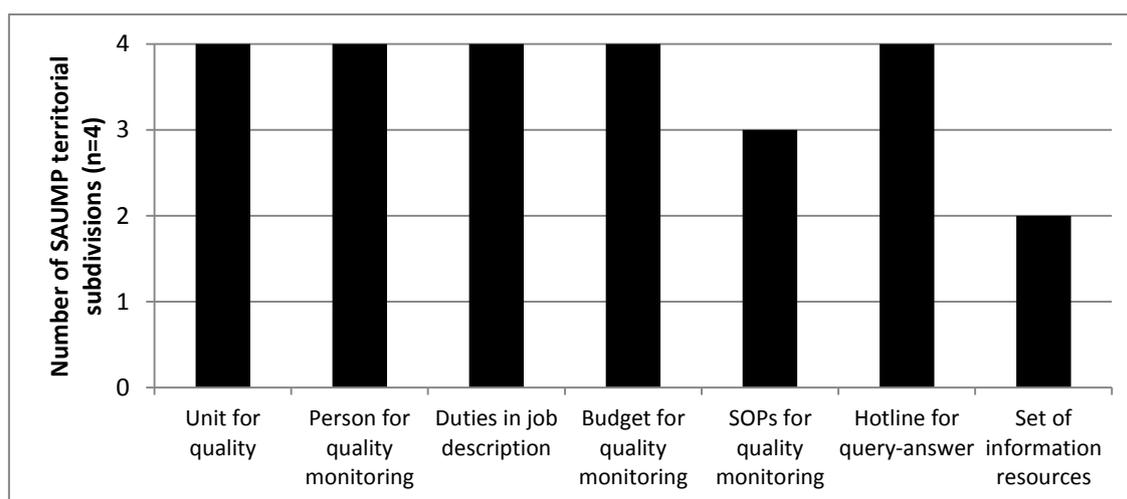


Figure 7. SAUMP territorial subdivisions: systems and structures for post-marketing quality surveillance

Implications of Weaknesses in Systems, Structures, and Stakeholder Coordination

In countries where regulatory functions are shared across two or more government institutions, it is important to ensure that their activities are carefully coordinated. In Ukraine, the assignment of responsibilities to executive bodies such as the MoH (the central executive authority in the health care system) and its subordinate units, and to SAUMP is regulated at the legislative level (provision on MoH and SAUMP in the Law of Ukraine “On Medicines” and MoH Orders No 157 and 898). These provisions when fully implemented can enable key processes to be optimized and assigned to relevant structures, as per the above mentioned legislative documents. In addition to effective legislation, national pharmacovigilance guidelines can serve as a basis for structured and coordinated actions by all stakeholders in medicines safety, including PHPs. Ukraine currently lacks a comprehensive guideline for health product safety surveillance, as does the EU which is just now finalizing its GVP guidelines. The development of such a guideline in Ukraine based on EU standards can encourage central agencies that implement PHPs such as the national TB program to strengthen pharmacovigilance activities. The absence of device safety surveillance, dedicated budgets for pharmacovigilance activities, and at regional and health facility levels, the lack of SOPs, postgraduate training courses in pharmacovigilance, trained human resources for pharmacovigilance (e.g. clinical pharmacists) and resources such as reference books and bulletins are issues that need to be addressed to strengthen medicine and device safety in Ukraine.

Recommendations

- Consider the necessity for setting up an advisory committee on medicines safety to provide technical advice and scientific opinions on safety issues related to medicinal products and medical devices, and provide strategic advice on strengthening national pharmacovigilance system and the quality of pharmacovigilance activities.
- Once EU GVP guidelines for the implementation of the 2010 pharmacovigilance legislation are in place, develop comprehensive national pharmacovigilance guidelines in Ukraine. The Ukrainian comprehensive national pharmacovigilance guidelines should be equivalent to the EU GVP guidelines. The proposed guidelines should discuss the scope of pharmacovigilance and medicine safety surveillance activities, stakeholders’ roles and responsibilities, the national notification system, approved methods for health product safety surveillance including spontaneous reporting and guidelines for conducting active surveillance studies, guidelines for the provision of medicine information, communicating safety and effectiveness and guidelines for ethical promotion of health products, guidelines and tools for benefit-risk assessment, guidelines for monitoring and evaluation of pharmacovigilance activities, and others.
- The SEC is advised to develop an Order for implementation of risk-based pharmacovigilance audits for approval by the MoH. In accordance with MoH Order No 898 (item 3.8) which requires that pharmacovigilance audits are conducted, develop guidance that spells out the details of its plans for pharmacovigilance audits and what companies need to know to be well prepared for those audits for example, documents to prepare for the auditor. Considering limited resources available and the

need for public health impact of pharmacovigilance activities the SEC will also need to develop a risk-based strategy or system for conducting audits.

- The MoH and the SEC are advised to consider setting up a medicines risk evaluation unit in the Post-Marketing Surveillance Board of the SEC. Some of the potential roles of this unit include determining research priorities on safety and quality of health products, identifying the need for post-authorization safety and effectiveness studies, exploring opportunities for establishing sentinel sites for active surveillance (example working with ART or TB programs to set up cohort event monitoring, working with rheumatologist to set up safety registries for biologics, etc), linkage to global safety surveillance networks like EMAs ENCePP, US OMOP, FDAs Sentinel Initiative. The medicines risk evaluation unit should also develop systems for registering ongoing and completed studies that have safety as an outcome of interest and develop steps for the use of information from safety studies for decision making.
- The MoH and the SAUMP should develop and implement the legislative base on medical device safety surveillance.
- The MoH, the SEC, and the SAUMP are advised to optimize coordination in the performance of pharmacovigilance activities. The timely exchange of information and collaboration in making regulatory decisions on medicinal product safety can facilitate better coordination of activities in post-marketing surveillance in Ukraine.
- Strengthen pharmacovigilance training in Ukraine.
 - The Government of Ukraine is advised to consider providing a dedicated budget for pharmacovigilance to support the development and conduct of training courses for medical workers, with an initial focus on priority national health programs.
 - The MoH of Ukraine should explore the possibility of financing and conducting advanced in-service training/refresher pharmacovigilance courses as needed.
 - The MoH and the SEC are advised to develop an Order on including pharmacovigilance into pre- and in-service medical and pharmaceutical education curricula.
 - The MoH should invite leading health care specialists to participate in the development of specialized training curricula on pharmacovigilance and medicines safety.
 - The SEC should develop postgraduate pharmacovigilance training programs and invite leading health care specialists to participate as trainers. The training programs should be accredited by the Kyiv Post-graduate Education Medical Academy. Priority should be given to developing a course in TB medicines safety.
 - The SEC, in cooperation with academic medical training institutions, should develop a pharmacovigilance in-service training program for pharmacy, nursing, and medical students to ensure that future health workers recognize the importance of pharmacovigilance in improving patient safety and treatment outcomes.
- Strengthen pharmacovigilance at the regional and health facility level. The SEC is advised to review the organizational structure of the pharmacovigilance system at

regional level to strengthen human resource capacity. Pharmacovigilance audit units should be established to facilitate the implementation of pharmacovigilance at the local level. Options for mobilizing resources to enhance post-marketing surveillance should be explored during the review.

- To standardize and improve pharmacovigilance operations at regional and local levels of the health care sector, the SEC should develop and/or update relevant instructions and SOPs for pharmacovigilance activities in accordance with updates to MoH Order No 898. Relevant SOPs should address the performance of pharmacovigilance activities by medical staff and processes for using information resources, and regular updating of information about pharmacovigilance and medicines safety on the MoH and SEC websites.
- The SEC should strengthen the coordination role of SEC regional affiliates at health facility level by improving planning and reporting on the work done and conducting audits to monitor activity implementation at all levels of the health care system.
- The Health Minister of the Autonomous Republic of Crimea, chiefs of health care oblast boards and municipal health care boards of Kyiv and Sevastopol should work with SEC to further enhance pharmacovigilance activities at the health facility level.
 - Develop and institutionalize SOPs for ADR/LE reporting by medical workers and implementing active surveillance activities at inpatient health care clinics. Requirements to support the implementation of active monitoring of medicine safety and effectiveness at health facilities include the development of appropriate information software by SEC and the appointment of clinical pharmacists at health facilities.
 - Establish clinical pharmacist positions into the health facility organization chart as per Order No 33 to help improve adverse events monitoring and reporting at the health facility, including medication error identification, analysis, and prevention as well as improving medicine and device information provision to medical workers. These specialists at health facilities will not only improve pharmacovigilance at the local level, but will also strengthen communication between all levels of the pharmacovigilance system (local, regional and central) as per the recommendations of Volume 9A of the rules governing medicinal products in the EU.
- Enhance access to medicines safety information for health care workers through better use of MoH and SEC resources.

Signal Generation and Data Management

The pharmacovigilance process involves signal detection, signal evaluation, and risk management. WHO defines a signal as “reported information on a possible causal relationship between an adverse event and a drug, the relationship being unknown or incompletely documented previously.”⁵⁷ A signal may be a new adverse effect or a change in the character or frequency of an ADR that is already known. A safety signal is defined as

⁵⁷ The Uppsala Monitoring Centre, WHO. 2000. Safety Monitoring of Medicinal Products: Guidelines for Setting Up and Running a Pharmacovigilance Center. <http://apps.who.int/medicinedocs/en/d/Jh2934e/>

“Information that arises from one or multiple sources (including observations and experiments), which suggests a new potentially causal association, or a new aspect of a known association, between an intervention and an event or set of related events, either adverse or beneficial, which would command regulatory, societal or clinical attention, and is judged to be of sufficient likelihood to justify verifiable, and when necessary, remedial actions.”⁵⁸ Pharmacovigilance includes monitoring for therapeutic ineffectiveness, medication errors, and product quality.⁵⁹ Ineffectiveness is a reportable event in pharmacovigilance.⁶⁰ Although an ADR form may be intended to capture all medicine-related adverse events, actual forms often do not have sections dedicated to reporting events such as medication errors, ineffectiveness, or poor product quality, or explicitly indicate that the form or other forms should be used to report such events.

In Ukraine, Form #137/o “ADR/LE form for medicinal products allowed for medical use,” a form annexed to MoH Order No 898⁶¹ is used by physicians to report information on suspected ADRs and lack of efficacy. The 2011 amendment to MoH Order No 898 expanded reporting to health care workers with medical and/or pharmaceutical education (physicians, pharmacists, and nurses) using Form #137/o. The amendment also authorizes the SEC to receive information on ADRs and lack of efficacy from patients or their representatives using the form “ADR/LE form filled by patient and/or his representative, by organizations representing the patients’ interests and dealing with drug ADR and/or lack of its efficacy when used for treatment.” As part of this latest amendment, Form #137/o has been revised to include a section for collecting additional information for suspected adverse events caused by vaccines or TB allergen. Included in this section is a check box option if the event is suspected to be due to a vaccine or TB allergen use error (program mistake).

Assessment findings show that Form #137/o is widely available at all types of health facilities and at all levels of the health care system. Of the 32 facilities visited, all but one AIDS center (97 percent) reported that the form was available, although one TB dispensary said they never used it. All SEC regional affiliates, SAUMP territorial subdivisions, and PHP program managers interviewed knew the form existed. Respondents said that there are no dedicated forms for reporting medication errors and product quality defects to the SEC and the SAUMP, respectively. Several staff reported that Form #137/o is also intended to capture suspected adverse events due to medication errors and poor product quality; however, the form lacks specific fields for reporting these events. To some extent, analysis of submitted ADRs and lack of efficacy reports at regional and/or central level may reveal that these events are related to medication errors or poor quality or even counterfeit products. However, dedicated forms offer opportunities for increasing the reporting of these events.

A signal can originate from many sources—spontaneous reports, literature, epidemiological study reports, patient records, registries, clinical trials, and cohort monitoring. Usually more than a single report is required to generate a signal depending upon the seriousness of the

⁵⁸ Hauben, M and Aronson, J. Defining ‘Signal’ and its Subtypes in Pharmacovigilance Based on a Systematic Review of Previous Definitions. *Drug Safety* 2009; 32 (2): 99-110

⁵⁹ Strengthening Pharmaceutical Systems (SPS). *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.

⁶⁰ Meyboom, R.H.B., M. Lindquist, A-K Flygare, C. Biriell, and I. R. Edwards. 2000. The Value of Reporting Therapeutic Ineffectiveness as an Adverse Drug Reaction. *Drug Safety* 23(2): 95-99.

⁶¹ Order of the Ministry of Health of Ukraine of 12.27.2006 No 898 “About Approval of Procedure for Surveillance over Adverse Reactions to Medicinal Products Permitted for Medical Use” (as amended by MoH Orders No 778 of September 14, 2010, No 568 of September 6, 2011, and No 1005 of December 29, 2011)

event and the quality of the information. A rigorous data management system is usually required for adverse event reporting and signal detection. The development of a unified data management system that receives and collates pharmacovigilance data from various sources in a country can help to improve synthesis, interpretation, and use of safety information.

The SEC maintains a database for medicines and MIBP safety reports that is the basis for generating signals and for regulatory decision making on medicinal product safety. The SEC uses a custom built database for receiving and collating data on medicine, vaccine, and other MIBP safety reports from multiple sources. Separate databases are maintained for medicines and MIBPs. At present, these two databases have different formats, however, SEC is moving forward with the development of a unified format for both medicines and MIBPs. When needed, summary data on ADRs for medicinal products used to treat or prevent specific diseases can be extracted from the database, for example, ADRs associated with the use of ARVs or anti-TB medicines. Summary reports are routinely generated for the National Program on Immunoprophylaxis and Prevention of Infectious Diseases, and on request for the HIV, oncology, and TB programs. The SEC ADR database can potentially be used to generate safety signals in Ukraine, if sufficient numbers of reports are entered. Between 2009 and 2011, six safety signals were confirmed, which provided information for revising medicine use instructions.

Currently all ADR reports are forwarded either electronically or in paper form to the SEC and entered into its database. Because the central database contains confidential information, access is restricted to employees of the SEC Post-marketing Surveillance Board. In addition to entering data, these employees are also authorized to view the data to correct errors. Other staff can only view information but not enter or change it. The SEC also maintains logs to track center workload and activities, for example, distribution of notices and dissemination of reports. SEC regional affiliates can maintain their own regional ADR database to assist in the performance of their duties, but are not required to do so. Three SEC regional affiliates (50 percent) maintain a manual or electronic log to track their pharmacovigilance activities. SEC regional affiliates receive quarterly reports electronically on information generated from reports submitted in their region and entered into the database; they can also request additional information as required to inform decision making. However, as SEC staff have signed non-disclosure agreements, they cannot provide confidential commercial information. With respect to publicly available information in Ukraine, the National Register of Medicines (the National Register) provides readers with unbiased information about medicines, their effectiveness, pharmacological properties, and safety. When the information on medicines safety is updated in the instructions for use, this information is also updated in the Register.

The SAUMP maintains a database of registered medical devices which is also available to the public. The agency also has a central database called Megapolis Laboratory System Universal System which is used by all SAUMP units to house all quality-related data for medicinal products, medical devices, and equipment and to track activities and workload. Information from respondents indicates that the SAUMP does not maintain a database that collects information on suspected post-marketing adverse events to medical devices. Such a database has not been established because safety surveillance of medical devices is not currently mandated by law in Ukraine, and therefore neither health workers nor patients can report adverse events that are suspected to be caused by such products. As mentioned earlier, Ukraine does not have a dedicated form or a field on an existing form for reporting product quality defects that are suspected to be associated with an adverse event, again because the reporting of such events is not required under current Ukrainian legislation.

Implications of Lack of Adequate Systems for Signal Generation and Data Management

Signal generation relies on sensitized health care workers and stakeholders who report suspected adverse events. The lack of a form or tool for reporting adverse events such as suspected medication errors and product quality problems can result in low reporting rates and late recognition of these problems. Opportunities to coordinate and collate data from different sources, for example, pre-marketing and post-marketing safety data are lost when separate unlinked databases are maintained. 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 utilizing the complementary roles of the pre-market and post-market safety data.⁶²

Recommendations

- The SAUMP in coordination with MoH and its structural units should improve the reporting of product quality problems and adverse events to medical devices from health workers and consumers through the development of specific reporting forms.
- The MoH and the SEC should develop a system for the reporting, collection, and evaluation of information on potential and actual medication errors to help identify strategies for minimizing their occurrence.
- The SEC and the lead institutions of the MoH and National Academy of Medical Sciences responsible for blood transfusion issues should develop forms for reporting of adverse events from use of blood products.
- The SEC should explore opportunities for using information technology to enhance adverse events reporting. The use of interactive PDF forms and cell phone text messaging are examples of strategies that can be explored to facilitate adverse events reporting by the health workers and the general public. Cell phones are widely deployed in Ukraine, with 118.66 mobile cellular subscriptions per 100 inhabitants in 2010; cell phones can be a good tool for post-marketing safety surveillance. Consumers can send reports of adverse events suspected to be related to medicines they used or reports of products of suspicious quality. These reports can be sent through prepaid lines. This type of system is currently being implemented in other countries.⁶³
- Improve health workers and consumers adverse events reporting and access to information. This recommendation is targeted at identifying new strategies to complement current reporting efforts that target health workers and consumers. The strategies should focus on improving reporting of medication errors, product quality concerns, and adverse events suspected to be related to the use of medical devices.
- The SEC should develop a unified central data warehouse and standard electronic tool for workload and activities tracking.

⁶² O'Neill R. 1998. Biostatistical considerations in pharmacovigilance and pharmacoepidemiology: linking quantitative risk assessment in pre-market licensure application safety data, post-market alert reports and formal epidemiological studies. *Statist. Med.* 17, 1851-1858.

⁶³ mPedigree. The use of SMS messaging to report fake medicines in Ghana. <http://mpedigree.net/>.

- In line with recent standards for the electronic transfer of regulatory information, the SEC should develop plans to upgrade its database for the electronic submission and exchange of reports using ICSR XML schema.

Risk Assessment and Evaluation

When a signal—particularly a potential signal that has significant public health importance—arises from one or more sources, it should be further investigated to evaluate the risk and benefit ratio. The procedure involves confirming the signal's validity, searching the appropriate literature and databases, gathering expert opinions, then making decisions, and taking appropriate actions to minimize the risks.⁶⁴ A spontaneous report can generate a qualitative signal that provides new and important data, if the quality, completeness, and case causality are sufficient. In contrast, a quantitative signal can only be detected when an increase in frequency of its occurrence is observed from epidemiological studies, clinical trials, or cohort event monitoring.⁶⁵ Active surveillance includes a wide range of 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.⁶⁶ The periodic review of the nature, severity, and specificity of adverse events through passive surveillance and evaluation of significant safety signals through active surveillance are fundamental to build a comprehensive and systematic pharmacovigilance and medicine safety system. Active approaches to surveillance are particularly valuable for PHPs, such as HIV/AIDS, TB, and malaria programs, and can provide useful information for evaluating new medicines for mass treatment and making evidence-based decisions involving revision of treatment guidelines and immunization protocols.

Reporting in Ukraine's Spontaneous Reporting System

Signals can be generated only when adverse events are reported. It may not be accurate to consider a pharmacovigilance system functional merely because one or two reports are sent in annually. The use of thresholds has been proposed to determine whether the number of reported adverse events meets that expected from a minimally functional system; however, at present, no consensus exists on the minimum acceptable number of reports per year from a country. According to the WHO International Drug Monitoring Program/Uppsala Monitoring Centre, optimal national pharmacovigilance centers should ideally send over 200 reports per million inhabitants per year.⁶⁷ Others propose a threshold of 100 reports per million inhabitants for functional pharmacovigilance systems in developing countries.⁶⁸ This

⁶⁴ Cobert, B. L. and P. Biron. 2002. *Pharmacovigilance from A to Z: Adverse Drug Event Surveillance*. Blackwell Science.

⁶⁵ Meyboom, R. H., A. C. Egberts, I. R. Edwards, et al. 1997. Principles of Signal Detection in Pharmacovigilance. *Drug Safety* 16(6):355-65.

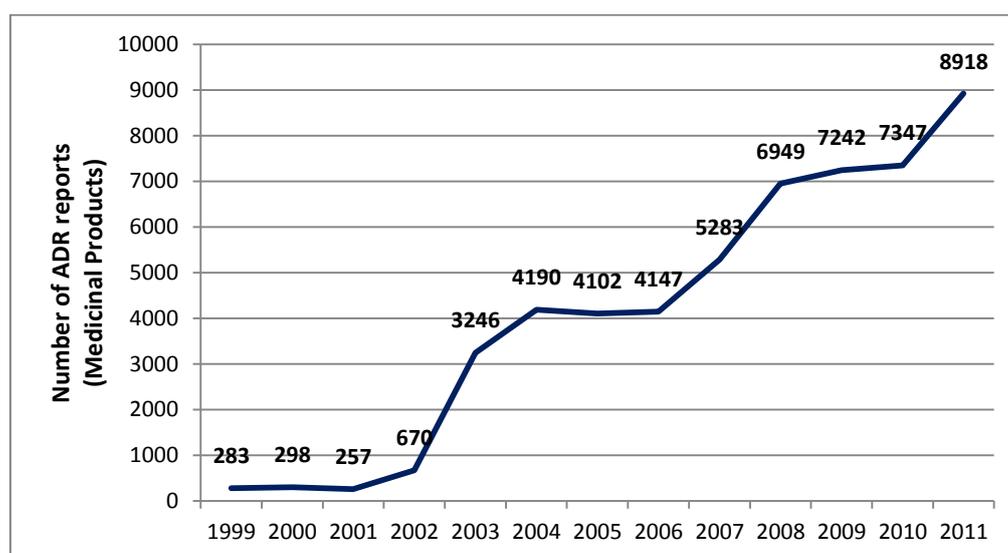
⁶⁶ European Medicines Agency. Pharmacovigilance Planning: Note for Guidance on Planning Pharmacovigilance Activities. 2006 CPMP/ICH/5716/03. Available at http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500002818.pdf

⁶⁷ WHO Uppsala Monitoring Centre <http://who-umc.org/DynPage.aspx?id=98082&mn1=7347&mn2=7252&mn3=7322&mn4=7326>

⁶⁸ Strengthening Pharmaceutical Systems (SPS) Program. 2009. Indicator-Based Pharmacovigilance Assessment Tool: Manual for Conducting Assessments in Developing Countries. Submitted to the U.S. Agency for International Development by the SPS Program. Arlington, VA: Management Sciences for Health. http://pdf.usaid.gov/pdf_docs/PNADS167.pdf

latter threshold may be mainly applicable to developing countries with comparatively few registered medicines and where most are products with established safety profiles or long history of use. Countries with tens of thousands of medicines registered including new chemical entities, biologics, and combination products with unresolved safety profile may be expected to have higher number of reports.

As can be seen from figure 8, Ukraine has made very good progress with regard to improving ADR reporting for medicinal products. Using the threshold of 100 reports per million inhabitants per year, Ukraine with its population of 45.8 million (January 1, 2011) would be expected to generate 4,518 adverse event reports per year. In 2011, the SEC received 11,347 adverse event reports to medicinal products of which 8,918 were entered into the national database,⁶⁹ equivalent to 195 reports per million inhabitants for this year. Twelve of the ADRs reported were serious events that resulted in fatalities where a cause and effect link was established. The number of reports received and entered into the database has been increasing steadily since 1996 when the Pharmacovigilance Center at the SEC was first established; in the last year alone reporting increased by 21 percent over 2010's figures. The SEC reported that at the end of 2011, 52,800 reports had been entered into the national database. Approximately 21 percent (2,429) of the reports submitted in the last year were not entered into the database because of inconsistent or incomplete reporting, duplicate reporting or lack of feedback from the reporter,⁷⁰ which represents a substantial loss of potentially useful data.



Sources: (1) SEC Presentation "Pharmacovigilance system in Ukraine: history, results, objectives" undated; (2) State Expert Center, Ministry of Health of Ukraine. 2012. *Major Performance Indicators of the Pharmacovigilance System in Ukraine in 2011*.

Figure 8. ADR spontaneous reporting in Ukraine—medicinal products (1996 to 2011)

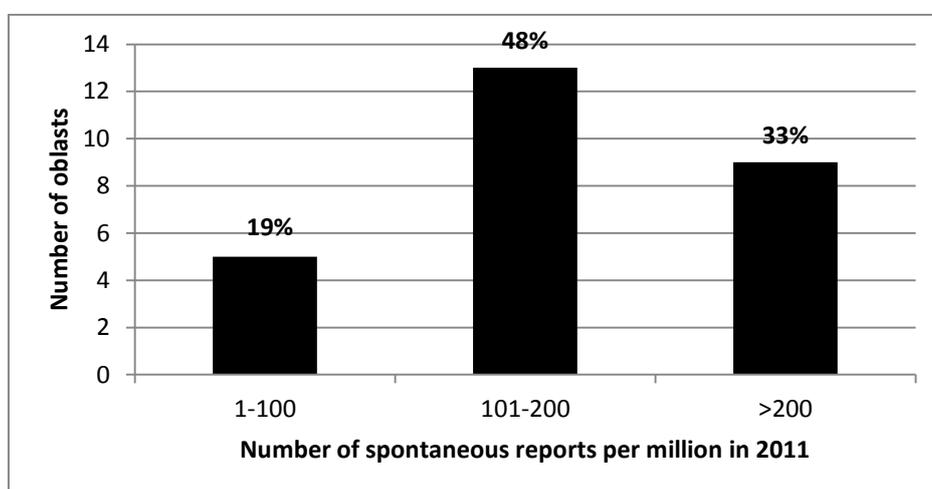
During 2011, SEC's Department of Immunobiological Medicines and Immunoprophylaxis received information on 34,213 adverse events following administration of MIBPs of which

⁶⁹ State Expert Center, Ministry of Health of Ukraine. 2012. *Major Performance Indicators of the Pharmacovigilance System in Ukraine in 2011*.

⁷⁰ Ibid

34,163 were entered into the national database, giving a total number of 1,040,974 reports in the database at the end of December 2011.⁷¹ Comparatively, in the United States, the vaccine adverse events reporting system (VAERS) receives around 30,000 reports annually.⁷²

In its annual report, the SEC also reports on ADR report submission by oblast.⁷³ In 2011, 22 of 27 oblasts (81 percent) exceeded the threshold of 100 reports per million inhabitants per year and reporting in nine oblasts (33 percent) exceeded 200 reports per million (figure 9). The SEC also reports annually on the percentage of health care institutions that submitted ADRs reports. In 2011, the SEC reported that 44 percent of institutions submitted at least one report, up from 27.2 percent in 2010.⁷⁴ While this is a substantial increase over 2010, it means that currently, over 50 percent of health institutions do not submit any ADR reports. Clearly Ukraine has greatly improved adverse event reporting but more needs to be done. According to the WHO individual case safety report global database for the period June 2007 to June 2012, all the Scandinavian countries and Cuba (a developing country) have more than 500 reports per million inhabitants per year.⁷⁵ The FDA received 758,890 reports in 2010.⁷⁶



Source of data: State Expert Center, Ministry of Health of Ukraine. 2012. *Major Performance Indicators of the Pharmacovigilance System in Ukraine in 2011*.

Figure 9. Number of spontaneous reports received in 2011 by oblast

For the SPS assessment, data was collected from health facilities in six oblasts. The reporting rate for these six oblasts in 2011 as calculated from data presented in the SEC 2011 annual report is presented in table 4. In 2011, two of the regions visited had a reporting rate of 100 or below, two between 101 and 200, and two above 200 reports per million.

⁷¹ State Expert Center, Ministry of Health of Ukraine. 2012. *Major Performance Indicators of the Pharmacovigilance System in Ukraine in 2011*

⁷² Vaccine Adverse Event Reporting System (VAERS) Program. <http://vaers.hhs.gov/about/index>

⁷³ State Expert Center, Ministry of Health of Ukraine. 2012. *Major Performance Indicators of the Pharmacovigilance System in Ukraine in 2011*.

⁷⁴ Ibid

⁷⁵ The Uppsala Monitoring Center. Active ICSRs in the WHO Global ICSR database per million inhabitants and year. <http://who-umc.org/DynPage.aspx?id=108476&mn1=7347&mn2=7252&mn3=7322&mn4=7558>

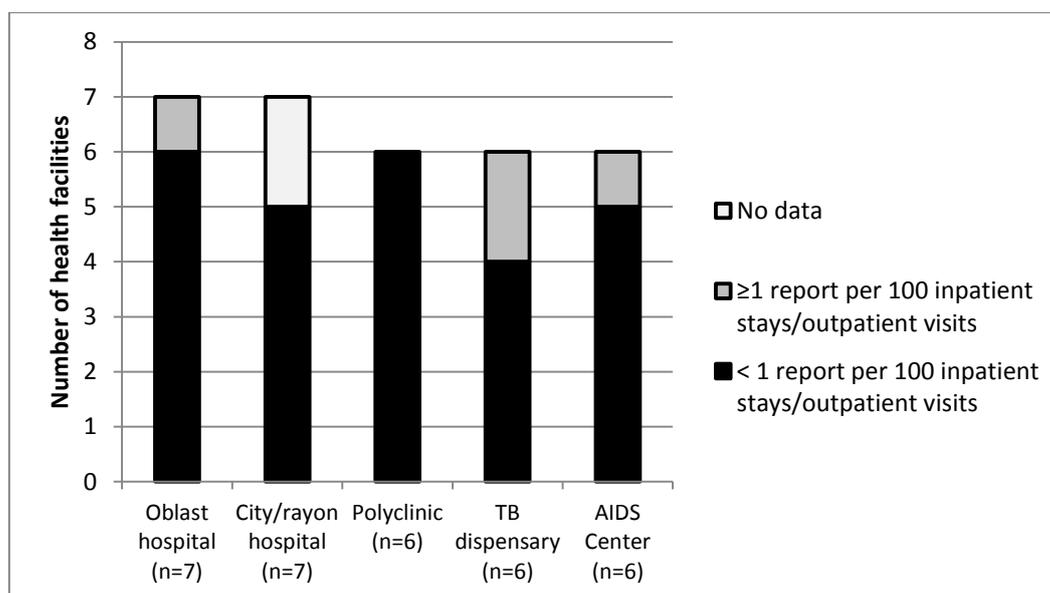
⁷⁶ USFDA. Reports Received and Reports Entered into AERS by Year. <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/ucm070434.htm>

Table 4. ADR Reporting Rate (2011) for Oblasts Visited in SPS Assessment

Oblast/Region	Number of ADR reports per million inhabitants
Kyiv city	187
Kyivska oblast	99
Kharkivska oblast	436
Khmelnitska oblast	408
Rivnenska oblast	78
Zhytomyrska oblast	133

Source of data: State Expert Center, Ministry of Health of Ukraine. 2012. *Major Performance Indicators of the Pharmacovigilance System in Ukraine in 2011.*

During the assessment, respondents in 32 facilities were asked about the number of ADR reports submitted by their facility in 2011. As data was not available on the population of the catchment area being served by each of the facilities, the number of ADR reports submitted per 100 outpatient visits or 100 inpatient stays in 2011 was used to assess reporting rates. Only four of the 32 facilities visited (13 percent) achieved a threshold of 1 report per 100 outpatient visits/inpatient stays— one oblast hospital, one TB dispensary, and two AIDS centers (figure 10). Two of the four facilities that achieved the threshold are located in Kharkiv oblast and two in Khmel'nitska oblast. Eight of the 32 facilities visited (25 percent) said they had not submitted any ADR reports in 2011.

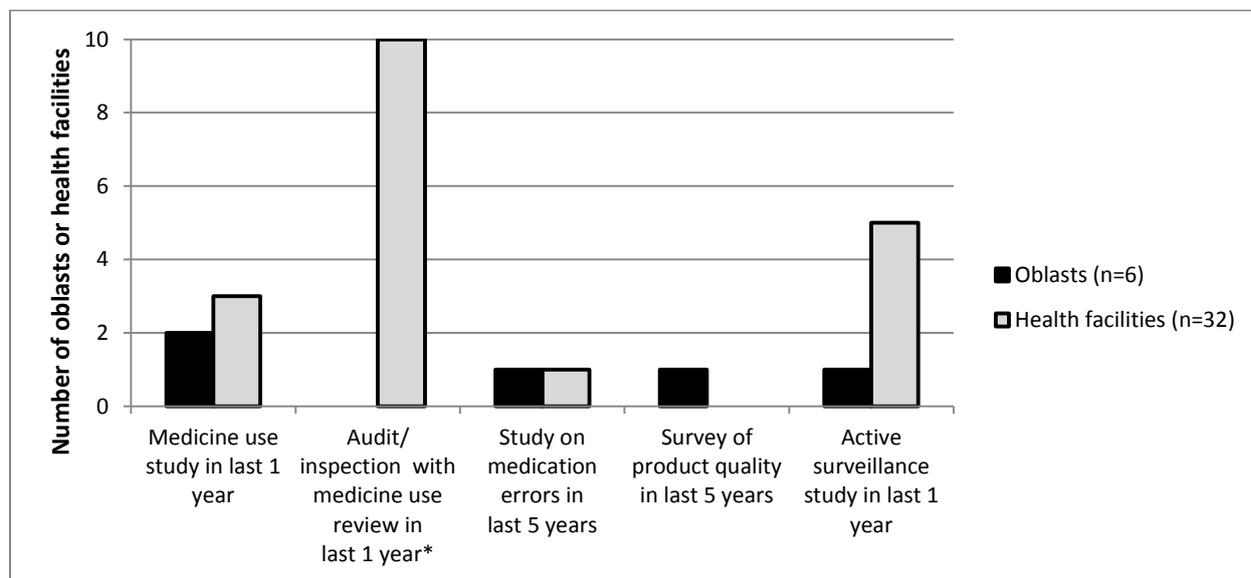


Oblast hospital: Reporting rates calculated using inpatient stays for six facilities and outpatient visits for one facility.
 City/rayon hospital: Reporting rates calculated using inpatient stays for four facilities and outpatient visits for one facility (data unavailable for two facilities).
 Polyclinic: Reporting rates calculated using inpatient stays for three facilities and outpatient visits for three facilities.
 TB dispensary: Reporting rates calculated using inpatient stays for four facilities and outpatient visits for two facilities.
 AIDS centers: Reporting rates calculated using outpatient visits for six facilities.

Figure 10. Analysis of ADR reports submitted in 2011 by the health facilities visited

Active Surveillance and Other Risk Evaluation Studies

As part of the review of risk assessment and evaluation, the SPS team also asked about medicine utilization review studies/drug use surveys, product quality surveys, and studies to determine the level of medication errors as well as active surveillance studies. The responses from the SEC regional affiliates and health facilities visited are presented in figure 11.



*Not relevant for oblast reporting

Figure 11. Risk evaluation activities conducted in oblasts and health facilities visited

Although very few oblasts and health facilities visited reported having conducted or participated in a medication use study in the last year, it is encouraging to note that 10 of the 32 facilities visited (31 percent) reported that an inspection or audit in the last year (usually by the formulary committee) had included some elements of rational medicine use review. These initial efforts, although currently limited in scope, are promising activities to build upon to improve medicine safety and rational use. Five of the facilities visited (16 percent) reported that they had participated in an active surveillance study in the last year. In 2009-10, the SEC and a local NGO in Zhytomyr supported a pilot project on monitoring the safety and effectiveness of medicines in hospitals in Zhytomyrska oblast. Study findings confirmed that the active collection of information on ADRs and adverse events of medicines was much more effective in gathering data than spontaneous reporting. The results were also valuable in evaluating the quality of medical care, identifying and minimizing medication errors, and conducting ABC and VEN analyses. The pilot demonstrated that active surveillance of medicines safety and effectiveness in hospitals is feasible in Ukraine.

The SPS team also looked for publications of pharmacovigilance and medicine safety studies that had been conducted in Ukraine. SPS searched MEDLINE with full text using the EBSCOhost search engine and the PubMed database using the following key words—Ukraine, active drug monitoring, active safety monitoring, active surveillance study, adverse drug reaction safety surveillance, active drug safety surveillance, adverse event, adverse event monitoring, cohort monitoring, cohort surveillance, drug reaction, drug safety monitoring, drug safety surveillance, drug toxicity, medicine safety, medicine safety

monitoring, medicine surveillance, post-marketing surveillance, and product surveillance post marketing, safety monitoring, safety surveillance, and surveillance monitoring. The *Google Scholar* database was also searched using the same terms.

A total of six publications were identified from the literature search and from respondents (annex D). Of the six studies conducted in Ukraine, two used active surveillance methodologies and four were based on passive (spontaneous) reporting (table 5). SPS also looked at clinical trials as part of the review of studies in Ukraine, specifically active Phase III and IV trials that had an outcome measure designated as a safety issue. SPS team members searched ClinicalTrials.gov, the clinical trials database⁷⁷ supported by the U.S. National Institutes of Health—this is a registry and results database of federally and privately supported clinical trials conducted in the United States and around the world. The search identified 124 ongoing clinical trials in Ukraine (annex E).

Table 5. Published Medicine Safety Studies Conducted and Ongoing Active Phase III/IV Clinical Trials that Have Safety as an Outcome Measure in Ukraine

	Study Methodology/ Trial Phase	Total Number	Public Health Program Area			
			Immunization/ Vaccination	HIV/AIDS	Antibiotics	Other
Published Medicine Safety Studies	Active surveillance	2	0	0	0	2
	Passive surveillance	4	0	0	0	4
	Total (published studies)	6	0	0	0	6
Active Phase III/IV Clinical	Phase II/III	8	0	0	0	8
	Phase III	106	1	0	9	96
	Phase III/IV	0	0	0	0	0
	Phase IV	6	0	1	0	5
	Total (trials)	120	1	1	9	109

The findings indicate that there are few active surveillance activities underway in Ukraine. Numerous clinical trials are currently ongoing in Ukraine; however, it is noteworthy how few of the clinical trials found that have safety as an outcome of interest address public health program areas.

Implications of Limitations in Risk Assessment and Evaluation

When efforts are not made to generate and evaluate signals of public health importance opportunities to learn about the safety and effectiveness of medicines during real-life use are lost. Assessment findings show that Ukraine has made very good progress with regard to improving ADR reporting for medicinal products. For the HIV program, summary reports of ARV ADR data generated from spontaneous reports are reviewed and used to inform treatment guideline revisions and the development of training programs. However, for the TB program, similar approaches are hindered by poor ADR reporting. Although the basic

⁷⁷ <http://www.clinicaltrials.gov/>

procedures for conducting active surveillance studies are provided by the MoH Order 898, the actual implementation of active surveillance studies and the development of systems for learning from the findings can be improved.

Recommendations

- The SEC should continue to develop strategies for strengthening adverse events reporting particularly at the health facility level. The overall reporting of suspected ADRs to medicines and vaccines is very good; however there are opportunities for improving reporting at the facility level. The SEC strategy for improving reporting may include the use of information technology to make reporting part of the normal clinical management of patients.
- The SEC should develop strategies for reducing incomplete and duplicate reports. According to the SEC 2011 annual report,⁷⁸ 21 percent of reports could not be entered because of incompleteness or duplication—this is a high number and strategies should be developed to reduce this percentage.
- The SEC should develop additional methodologies and tools to support risk assessment and data mining. As the number of reports in the SEC database increases, it provides an excellent opportunity for risk assessment.
- The SEC should develop strategies for improving active surveillance. The assessment identified few active surveillance activities in Ukraine. As in other countries, spontaneous reporting is the basic system for collecting information about ADRs. The two methods complement each other and are very useful for completing the pharmacovigilance process from risk identification to risk assessment and risk evaluation. The need for active surveillance for the evaluation of safety signals is more profound within the PHPs where spontaneous reporting does not have the capacity to uncover events of long latency. With the high burden of TB and HIV/AIDS, Ukraine should develop systems for active surveillance and 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.⁷⁹ An example of a HIV cohort collaboration that include safety surveillance is the National Institutes of Health-sponsored International Epidemiologic Database to Evaluate HIV/ AIDS cohort network. Another example of safety surveillance of new biologics is the Brazilian Biologic Registry.⁸⁰ The SEC should work with the PHPs and other stakeholders to immediately develop active safety surveillance activities in Ukraine. Consider options for engaging patient organizations in active surveillance activities.
- The SEC should work with consumer organizations to explore efforts to stimulate ADR reporting by consumers.

⁷⁸ State Expert Center, Ministry of Health of Ukraine. 2012. *Major Performance Indicators of the Pharmacovigilance System in Ukraine in 2011*.

⁷⁹ Miller, V., J. Nwokike, and A. Stergachis. 2012. Pharmacovigilance and global HIV/AIDS. *Curr Opin HIV AIDS*, 7:299–304

⁸⁰ Titton, D. et al. Brazilian Biologic Registry: BiobadaBrasil implementation process and preliminary results. *Rev Bras Reumatol* 2011;51(2):145-160]

Risk Management and Communication

The need to use pharmacovigilance data to improve the safe use of medicines is increasingly recognized and emphasized.^{81,82} Recently the focus is shifting to strengthen efforts at preventing or minimizing risk rather than merely identifying and managing harm after it has already occurred. The SPS IPAT tool has several indicators relating to risk management and communication that focus on recognizing the role of prevention in pharmacovigilance. If effectively implemented, such preventive approaches have significant potential to reduce the incidence of harm caused by medication use.

Use of Information from Outside Resources

Medicine safety issues of local relevance identified from outside sources, such as another country or regional or international organizations, can be used to prevent any possible harm in the local population. Those sources of information that countries can easily access and use to inform locally relevant decisions are safety newsletters from WHO,⁸³ publications such as Reaction Weekly,⁸⁴ and safety alerts from SRAs,⁸⁵ such as the FDA⁸⁶ and the EMA.⁸⁷ Countries without full capacity to generate signals and assess the risks can especially benefit from tracking, evaluating, and acting on safety information from countries with more regulatory capacity. The use of relevant regulatory intelligence and pharmacovigilance information from external source is an efficient strategy for timely regulatory action.

SEC's Post-Marketing Surveillance Board has a rigorous system in place for monitoring for new safety reports from outside sources. Staff members check websites daily and conduct literature searches using PubMed and the Guidelines International Network website.⁸⁸ In 2011, the SEC reported that 1973 amendments had been made to package inserts as a result of post-marketing activities, including the identification of reports from international sources that were acted upon.⁸⁹ SEC's Department of Immunobiological Medicines and Immunoprophylaxis relies primarily on communications from WHO for such information. In 2011, the Department identified and acted upon one safety issue and issued one safety alert letter about a separate concern.

⁸¹ U.S. Food and Drug Administration (FDA). FDA Safe Use Initiative: Collaborating to Reduce Preventable Harm from Medications. <http://www.fda.gov/Drugs/DrugSafety/ucm187806.htm>

⁸² 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.

⁸³ WHO. 2010. Pharmaceutical Newsletters, issues 1 to 6. Available at <http://www.who.int/medicines/publications/newsletter/en/>

⁸⁴ This journal provides a comprehensive update of published ADRs case reports, drug withdrawals due to safety issues, labeling changes, safety research, and other current issues related to drug safety; the content is sourced from journals, media releases, regulatory agency and pharmaceutical company websites, and bulletins from national centers. Available at <http://adisonline.com/reactions/pages/default.aspx>

⁸⁵ Members, observers, or associates of the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH). Available at www.ich.org

⁸⁶ FDA. 2010. Safety Alerts For Human Medical Products. Available at <http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm196258.htm>

⁸⁷ EMA. Monthly reports of the CHMP Pharmacovigilance Working Party. Available at http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/document_listing/document_listing_000198.jsp&mid=WC0b01ac0580033aa1

⁸⁸ <http://www.g-i-n.net/>

⁸⁹ State Expert Center, Ministry of Health of Ukraine. 2012. *Major Performance Indicators of the Pharmacovigilance System in Ukraine in 2011*.

The SAUMP receives information on alerts related to quality through the PIC/S⁹⁰ for products that are imported into Ukraine and other Commonwealth of Independent States countries. These alerts are communicated to the SAUMP territorial units through the Megapolis software.

Assessment findings show that SEC regional affiliates and health facilities rely mainly on communications from the SEC and the SAUMP for information on safety issues from other countries (figure 12). It is therefore important to ensure that these safety alerts reach health care facilities. Two of six SEC regional affiliates (33 percent) and four of 32 health facilities interviewed (13 percent) reported additional efforts to identify information through checking websites of the FDA, Medscape, or other organizations and/or reviewing publications. One SEC regional affiliate (17 percent) and key informants at ten health facilities (31 percent) reported that they were not aware of any system for such activities.

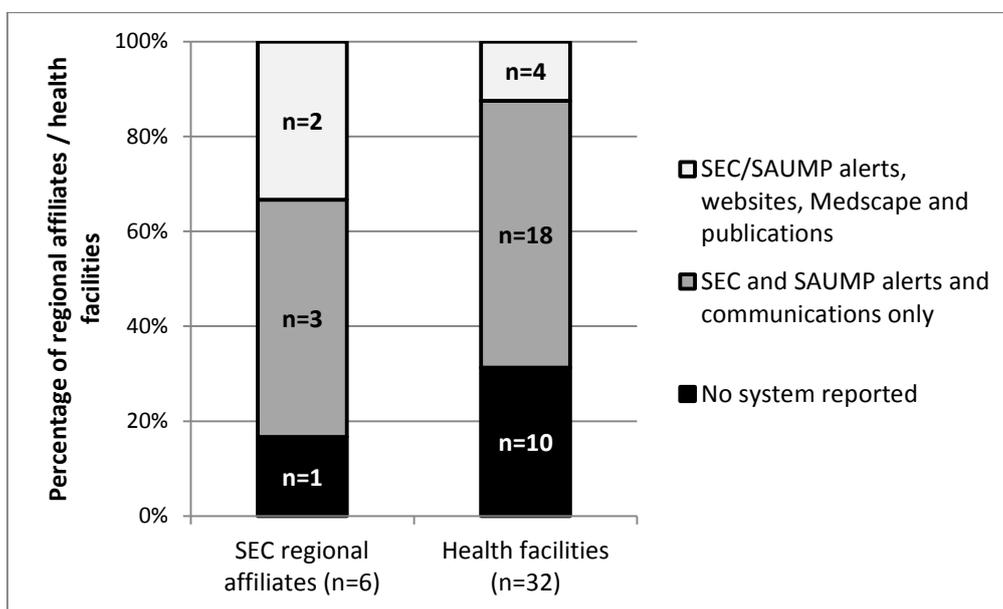


Figure 12. SEC regional affiliates and health facilities: systems for monitoring for new medicine and vaccine safety reports from outside sources

Risk Management

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

Routine pharmacovigilance activities include spontaneous reporting, collection of reports and feedback to reporters, signal detection, analysis of the obtained information and timely

⁹⁰ <http://www.picscheme.org/>

reporting, and for MAHs, PSUR development and submission. Interactions with health care workers, patients, and other information sources form the basis for routine activities.

Additional pharmacovigilance methods include—

- Enhanced passive (spontaneous) reporting through preparation of standard reporting forms for medicines that are identified as requiring additional surveillance and also stimulating the reporting of specific medicines.
- Active surveillance methods including intensive monitoring at sentinel sites, (of prescriptions or inpatient records), registries and electronic databases.
- Epidemiological studies, such as cohort event monitoring, cohort studies, cross sectional studies, medicine utilization studies, and exploration of existing databases.
- Clinical research such as phase 4 clinical trials

Risk minimization can be implemented using routine measures or through additional efforts.

Routine efforts involve—

- At the medicine development stage
 - Assigning a name to avoid confusion with other similarly named products
 - Product packaging requirements (size and design of the pack)
 - Formulating instructions for the use of the product (route of administration, dosage etc)
 - Product label information requirements such as boxed warnings on labels, or print size for patients with limited vision
 - Assigning a legal status for sale or dispensing of the product, based on risk of patient harm through inappropriate use
- During the product use process, several interventions to ensure safe and rational use of medicines can also be regarded as risk minimization practices or strategies to prevent known risk of a product. Examples include—
 - Safe injection practice guideline for immunization programs and hospitals to ensure safe use of injectable medicines, particularly to assure compatibilities of co-administered products
 - Prevention of accidental overdose or ingestion, for example, by children
 - Prevention or minimization of medication errors

Safety alerts and restrictions on product distribution are also important approaches to minimizing risk. A risk alert message is any information exchange concerning medicine access, or that describes the nature of the problem and risk to patient health or the environment. Information dissemination strategies to health care practitioners include training, issuing of Dear Health Care Professional letters or educational materials about medicine safety and its use (i.e., medication guide for patients, physician prescribing guide/checklists, or pharmacist dispensing guide/checklists). Informed patient consent forms to ensure patients understand the risk, package design or aids to assist correct administration, and special training programs or certification for health care professionals are other useful approaches.

Approaches to minimize risk during distribution and use include—

- Restricted distribution and use of the medicine in certain settings (i.e., dispensing the medicine only in a hospital) or to certain prescribers.
- Requiring dispensing records to be submitted when requesting further supplies.

- Checking patient records (for example to ensure the length of the treatment course is appropriate).
- Requirements for baseline and ongoing laboratory monitoring (for example for pregnancy prevention).

In the EU, risk management has three components— safety specification, pharmacovigilance plan, and evaluation. The new EU pharmacovigilance guidelines that came into effect on July 22, 2012, has provided for a new EU RMP structure; however all provisions under module V of the GVP guideline are not yet fully implemented. Module XVI of the GVP guideline “Risk-minimization measures: selection of tools and effectiveness indicators” was disseminated for discussion only in the second half of 2012. As a result, implementation of risk management practices is uneven across EU countries although some NRAs have practices whereby they publicly identify products that require risk management and publish their associated RMPs. For example, in the UK, the Medicines and Healthcare products Regulatory Agency provides a list of new drugs and vaccines under intensive surveillance every month.⁹¹

In Ukraine, some risk management elements are in place. Respondents from the SEC Board reported the use of risk management and minimization strategies such as physician prescribing guides, Dear Health Care Professional letters, publications in specialized medical journals, dissemination of new information on medicines safety on the MoH and SEC websites, and lectures for the medical community.

SPS used a list of products identified by the FDA that are required to have a risk evaluation and mitigation strategy⁹² to inquire about risk management activities at regional and facility level. SEC regional affiliates stated that risk minimization efforts are implemented locally and not at oblast level. Of the 32 health facilities visited, 24 (75 percent) kept at least one medicine on the FDA list and 18 of these 24 facilities (75 percent) reported some effort to control the use of these high-risk medicines (figure 13). Most commonly reported strategies included reminder or prompting systems for clinical or laboratory monitoring (for example hepatic monitoring for nevirapine), restricted distribution to tertiary specialist units, baseline and ongoing monitoring for ADRs, pregnancy prevention and monitoring, communication materials for patients and prescribers, and product label information requirements. Risk management strategies were absent in six of the 24 facilities (25 percent) that reported keeping high-risk medicines, including three of the six oblast hospitals, three of the five TB dispensaries that provided this information, and one of the six AIDS centers.

Schemes such as the WHO Certification Scheme on the Quality of Pharmaceutical Products Moving in International Commerce and PIC/S can provide some assurance about the quality of products based on inspection and certification of the manufacturing facilities for Good Manufacturing Practices (GMP). Ukraine joined the PIC/S in January 1, 2011 and as member of the Scheme can avail itself of opportunities for sharing inspection information. SPS inquired about the systems in place to prequalify suppliers or to consider prequalification reports from other countries that participate in PIC/S. Responses from key informants indicate that the MoH Procurement Department in Ukraine does not utilize prequalification of

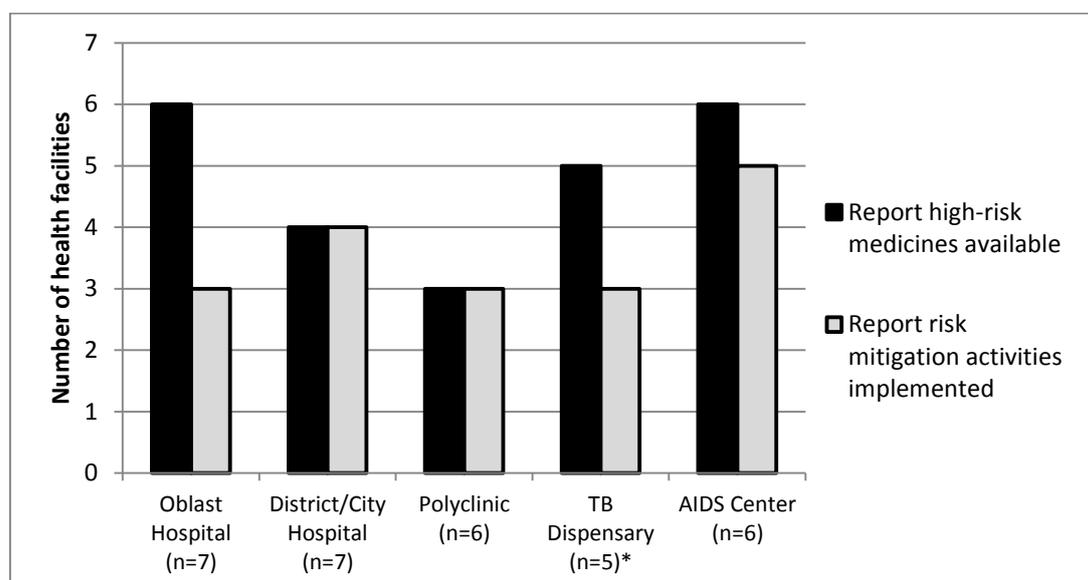
⁹¹ MRHA. The Black Triangle List June 2012 - UK marketed drugs under intensive surveillance.

<http://www.mhra.gov.uk/home/groups/pl-p/documents/websiteresources/con152736.pdf>

⁹² Available at

<http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm111350.htm>

suppliers or consider prequalification reports from WHO or other countries prior to procurement. The current procurement law does not stipulate criteria for quality assurance, such as WHO prequalification. GMP for tenders as well as WHO prequalification is currently not obligatory. However, if the source of funding is a grant from the Global Fund to Fight AIDS, Tuberculosis and Malaria (Global Fund), procurement processes require that supplier prequalification and WHO-prequalified products are used.



*Data not available for one of the six TB dispensaries visited

Figure 13. Health facilities: implementation of risk mitigation activities

Formulary Committees and Patient Safety

In health facilities, Formulary Committees (also known as in some countries as Drug and Therapeutics Committees) can ensure provision of cost-effective quality care to patients. The committee is typically responsible for adapting, developing, and implementing an efficient and cost-effective formulary and for monitoring all medicines prescribed and dispensed to patients to ensure that they are safe and of good quality. Formulary Committees can have a significant impact on preventing and managing medicines-related problems in patients by monitoring and addressing medication errors, ensuring medicine quality, and monitoring and addressing ADRs.⁹³

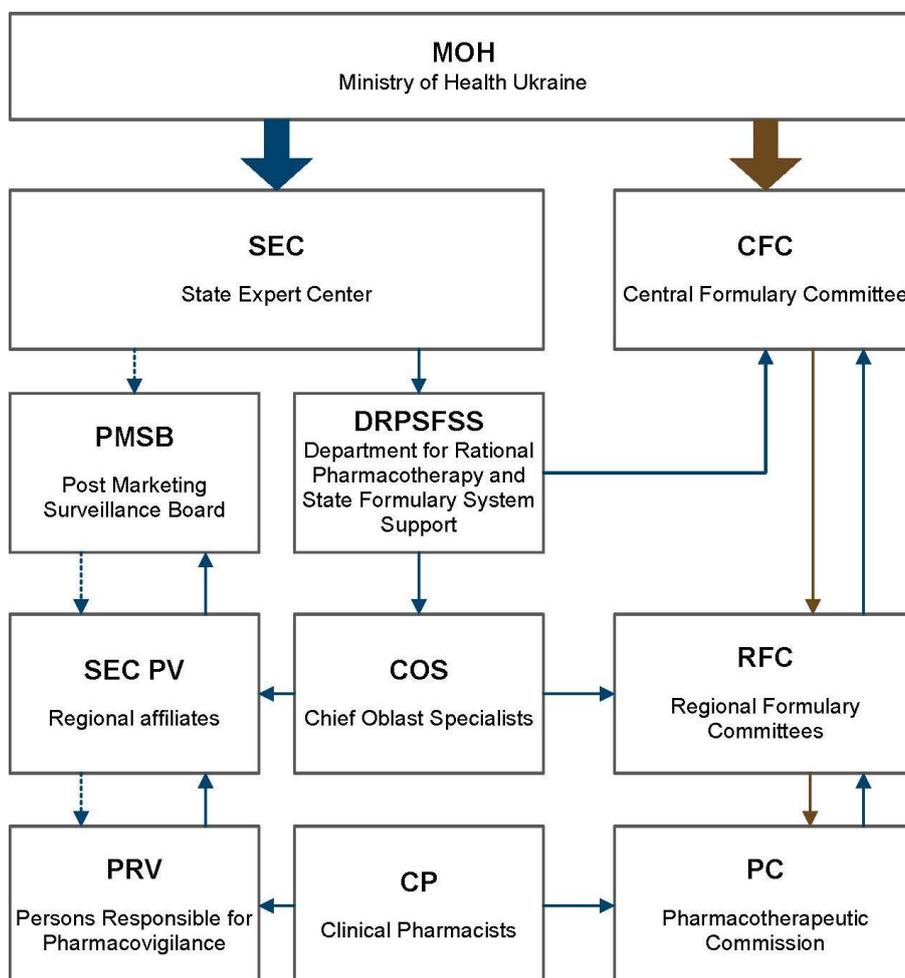
MoH Order of 07.22.2009 No 529⁹⁴ establishes and assigns responsibilities to Formulary Committees at all levels (national, regional and at health facilities). In addition to developing and updating formularies, these committees are responsible for contributing to post-marketing medicines monitoring. MoH Order of 09.01.2009 No 654⁹⁵ establishes mechanisms for

⁹³ Green, T. and K. Holloway. 2003. Drug and Therapeutic Committees: A Practical Guide. Geneva: WHO. <http://apps.who.int/medicinedocs/en/d/Js4882e/>

⁹⁴ Order of the Ministry of Health of Ukraine of 07.22.2009 № 529 “Provision on Formulary Committees of Autonomous Republic of Crimea MoH, health care boards of oblast and Kyiv and Sevastopol municipal state administrations”

⁹⁵ Order of the Ministry of Health of Ukraine of 09.01.2009 № 654 “On approval of plan of measures for improving post registration surveillance over safety and efficacy of medicinal products in hospitals”

cooperation between the SEC and Regional Formulary Committees and Pharmacotherapeutic Commissions in health facilities (figure 14). The SEC regional affiliates sit on Formulary Committees; clinical pharmacists from Pharmacotherapeutic Commissions, where appointed, are responsible for monitoring, analysis, and submission of ADR data to the SEC in addition to monitoring the rational use of medicines.



Source: SEC

Figure 14. Cooperation between the structures responsible for pharmacovigilance and the formulary system in Ukraine

During the assessment, SPS inquired about the existence of Formulary Committees at each level and their activities in addressing medicine safety issues in the last year. The SEC reports that the Central Formulary Committee exists and from time to time considers pharmacovigilance issues including ADRs and lack of efficacy. At regional level, five of the six SEC regional affiliates (83 percent) confirmed that the regional Formulary Committee existed and that three of the five committees have implemented at least one activity related to medicine safety in the last year. As these committees have been operational for only two years at most, they have focused their initial efforts on developing formularies and are only recently starting to consider pharmacovigilance issues.

Responses from key informants at health facilities indicate that 12 of 32 facilities (38 percent) visited have a Pharmacotherapeutic Commission that addresses formulary issues; however, only six of these 12 committees (all but one are in oblast or city/rayon hospitals) were reported to have engaged in any medicine safety activities in the last year. None of the TB dispensaries and only one of six AIDS centers visited reported having a committee.

It is encouraging to see that these committees are being established; some have developed formularies and are now implementing rational medicine use activities. Regional Formulary Committees and facility-level Pharmacotherapeutic Commissions can potentially be an effective mechanism for implementing activities to improve rational use, including medicine safety in Ukraine's health care system.

Communication and Actions

The immediate results of pharmacovigilance activities are preventative actions taken concerning medicine safety and quality, such as label change, changes or confirmation of safety of medicines in treatment guidelines, medicine formulary, essential medicines lists, product recalls, withdrawal of product licenses, and recommendations of risk management activities. These preventive actions should eventually lead to improved patient safety and better health outcomes.

Information from respondents and document review indicate that key risk communications and actions taken as a result of pharmacovigilance activities in 2011 in Ukraine at the national level include—

- Publication of all four planned issues of *Rational Pharmacotherapy*, the bulletin published by SEC's Post-Marketing Surveillance Board.
- Participation in five television and radio events that included vaccine safety issues by SEC's Department of Immunobiological Medicines and Immunoprophylaxis.
- Publication of 37 articles in medical journals and presentation at a national seminar with international participants.⁹⁶
- One hundred twenty-seven letters sent by the SEC to pharmaceutical company QPPVs regarding cases of unexpected ADRs, fatal outcomes as a result of ADRs, and cases of lack of efficacy of medicinal products.⁹⁷
- Four "Dear Doctor" letters sent— three issued by companies for medicinal products in agreement with SEC's Post-Marketing Surveillance Board and one by SEC's Department of Immunobiological Medicines and Immunoprophylaxis for a vaccine.
- For medicine products package inserts, 1,973 amendments made as a result of the SEC's pharmacovigilance activities and information identified from international sources.⁹⁸

⁹⁶ State Expert Center, Ministry of Health of Ukraine. 2012. *Major Performance Indicators of the Pharmacovigilance System in Ukraine in 2011*.

⁹⁷ Ibid

⁹⁸ Ibid

- One label change to a medicinal product.
- Five hundred and three temporary suspensions issued by the SAUMP in 2011 of which 110 were in connection with notifications on adverse reactions, 314 due to substandard products, and 80 suspected counterfeits.⁹⁹ There were no cases of suspension of drug registration due to substandard quality of products.
- No products were withdrawn from the market in 2011 because of safety concerns (two products were withdrawn in 2010 and three in 2009).

Almost all key informants at national, oblast, and facility levels reported that safety signals and significant safety issues are promptly communicated to health workers and the public, usually within 24 to 48 hours. One issue raised by a number of respondents from various levels during the assessment was the impact of suspensions on product availability. In some cases, only one or two batches of a product were available in the country and so the suspension precipitated shortages of important products.

The SEC regional affiliates' engagement in communication activities varied across the six regions visited. The estimated number of requests for pharmacovigilance-related information reportedly received in 2011 and addressed by each affiliate ranged from 8 to 240 per year. SPS used a threshold of 12 calls per year as an indication that a medicine information service on pharmacovigilance is functional, since any functioning center would be expected to receive at least one query per month. Four of the six affiliates (67 percent) received 12 or more pharmacovigilance-related calls in 2011. Only three of the six affiliates (50 percent) reported receiving and forwarding at least one "Dear Doctor" letter in the previous year. Four of the six regional affiliates (67 percent) reported carrying out one or more public and community education activity in 2011 on pharmacovigilance; activities included submitting articles to the local media and television/radio appearances. Key informants from all four SAUMP territorial subdivisions reported submission of at least one medicine safety-related article to the local media and/or a television appearance. A respondent reported that in the past the media appeared to be reluctant to publish unbiased information on medicine safety matters.

At the health facility level, assessment findings indicate that some initial communication efforts are underway in a few facilities. Records of these activities are rarely kept at health facilities so respondents were asked to provide some estimates. The number of pharmacovigilance-related queries received by the eight facilities that reported providing a medicine information service ranged from 2 to 70 queries per year, almost entirely from medical personnel. Five of 32 facilities visited (16 percent) said they had carried out at least one pharmacovigilance-related education activity for their patients or the public. The data on the number of "Dear Doctor" letters received and disseminated was not consistently collected; however, respondents from at least seven of the facilities visited said they had not received any such letters in 2011. Information on safety alerts is generally communicated to staff orally at daily or weekly meetings. Of the 23 facilities asked, 13 (57 percent) did not keep a register of letters received regarding suspensions, prohibitions, or letters that addresses product quality concerns.

⁹⁹ State Administration of Ukraine on Medicinal Products. January 10, 2012. *Major Indicators of Activities of Subdivisions of the State Administration of Ukraine on Medicinal Products, 2011.*

Implications of Limitations in Risk Management and Communication

Risk management and communication is a component of pharmacovigilance with high impact in preventing harm from medicinal products. The assessment findings indicate that in Ukraine, some risk management elements are in place; however opportunities for preventing harm from the use of medicines and vaccine need to be further exploited. Numerous products in the market require some sort of risk management and information that is already known about the safety of most medicines is not fully utilized to improve patient outcomes.

Recommendations

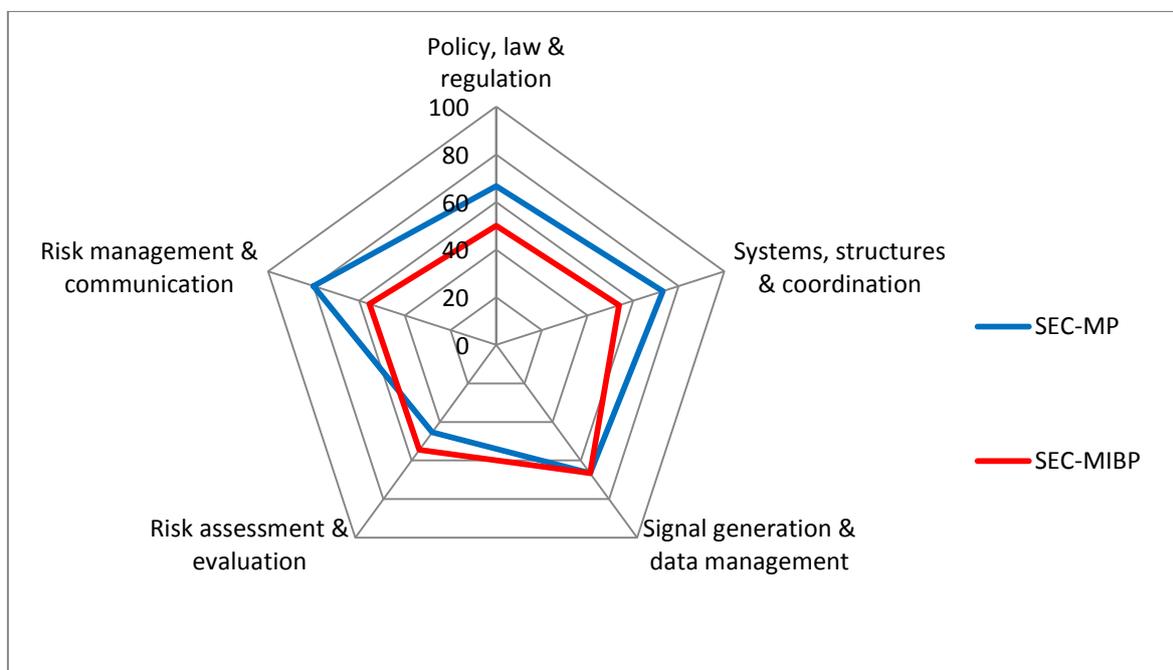
- The MoH and SEC should strengthen risk management practices to ensure safe use of medicines and prevent occurrences of preventable adverse reactions.
- Improve the distribution of safety communications and publications.
 - The MoH and the SEC should develop and implement an urgent medicines product safety warning and alert system.
 - MAHs and pharmaceutical manufacturers should improve the distribution of medicines safety information to the MoH, the SEC, and the health care staff.
 - The Health Minister of the Autonomous Republic of Crimea, chiefs of health care oblast boards and municipal health care boards of Kyiv and Sevastopol should ensure the timely dissemination of medicines safety information originating from the MoH, the SEC and other information sources such as MAHs to all health care facilities and health care staff in Ukraine.
- The MoH and the SEC should consider options to draw medical staff and consumer attention to selected medicines and medical devices (for example, that are considered high risk because they are more likely to cause significant patient harm when used in error) such as preparing lists of such medicines, special marking on packaging or updating instructions in the packet insert.
- The MoH and the SEC should improve the provision of medicines information to health care workers and the public as part of efforts to improve safe and rational use of medicinal products. Options for informing the public about the National Medicines Register which contains official information about medicines should be explored.
- The MoH and the SEC should develop software to assist health care workers in identifying and preventing drug interactions.
- The MoH, the SEC, and the Central Formulary Committee should ensure effective interactions between the pharmacovigilance and the formulary systems at all levels.
- The SAUMP and the SEC should fully utilize the opportunities presented by Ukraine's membership in the PIC/S to share GMP inspection and other regulatory intelligence reports. Through this membership Ukraine can reduce exposure to risky manufacturers and prevent some adverse events that would have occurred from using poor quality product from such manufacturers.
- The Government of Ukraine should assist the SEC to engage and communicate medicines safety information to the media.

Pictorial Representation of the Current Situation of Pharmacovigilance at National, Regional, and Health Facility Levels

When the current situation of the pharmacovigilance system is represented pictorially, (and subsequently tracked longitudinally), the visualization is anticipated to assist in recognizing improvements as they occur. Such representations are shown in figure 15, 16, and 17. These figures are constructed by converting the responses to the assessment questions and the indicators set out in annex A (disaggregated as core and supplementary) to “Yes/No” and using weighted scoring. For instance, the “Yes” responses to core indicators are scored 2 each and supplementary indicators scored 1. In addition to presenting information on the current status of pharmacovigilance in Ukraine, these charts provide a benchmark to measure future improvements.

Figure 15 shows the score for SEC’s Post-Marketing Surveillance Board at the central level (blue line) and for SEC’s Department of Immunobiological Medicines and Immunoprophylaxis (red line) as a radar chart. Figure 16 shows the overall score for these two central departments and the score for a sample of six regional affiliates. 25 core and 15 supplementary indicators were applicable for SEC’s Post-Marketing Surveillance Board and 25 core and 14 supplementary indicators for SEC’s Department of Immunobiological Medicines and Immunoprophylaxis. For the SEC regional affiliates, 20 core and 12 supplementary indicators were applicable.

Figure 16 shows the average scores for a sample of 32 facilities by type of facility. For health facilities, 17 core indicators and 11 supplementary indicators were applicable.



SEC-MP: SEC’s Post-Marketing Surveillance Board (medicinal products);
 SEC-MIBP: SEC’s Department of Immunobiological Medicines and Immunoprophylaxis (vaccines and other immunobiological products)

Figure 15. Radar chart of current situation of national pharmacovigilance systems

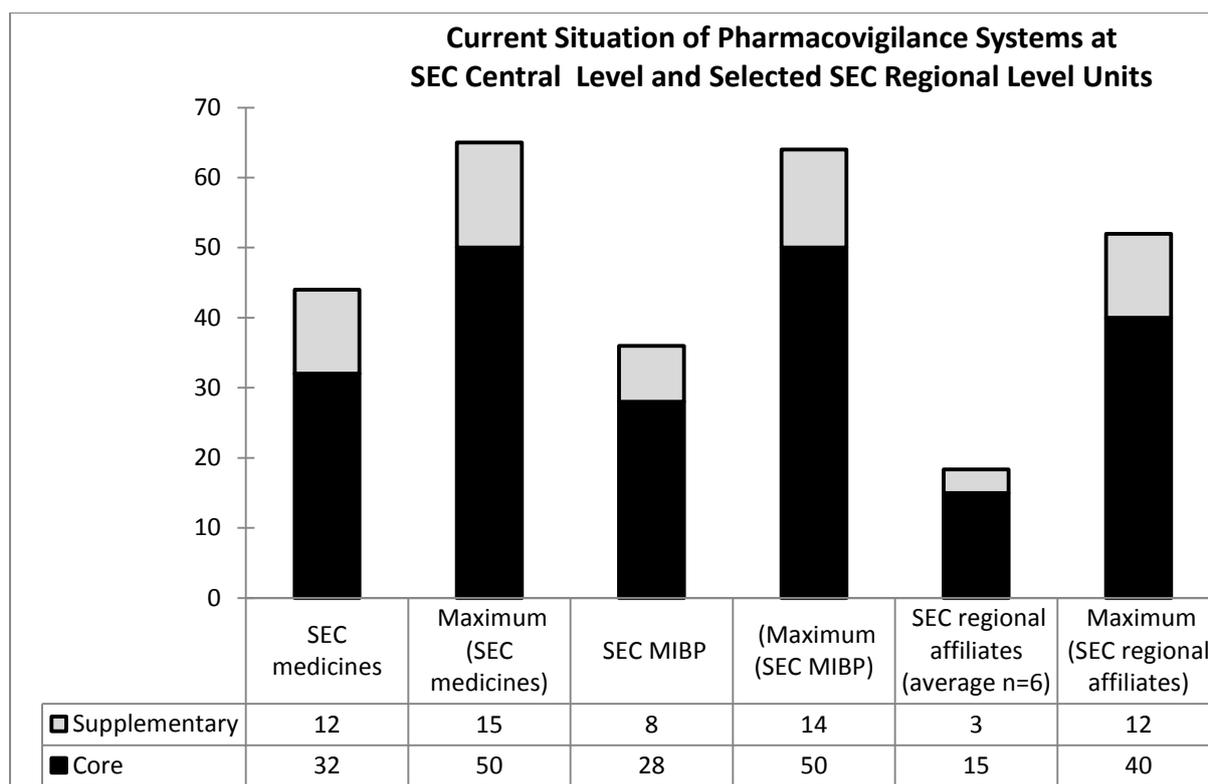


Figure 16. Current situation of pharmacovigilance systems: SEC (central levels) and a sample of six SEC regional level units

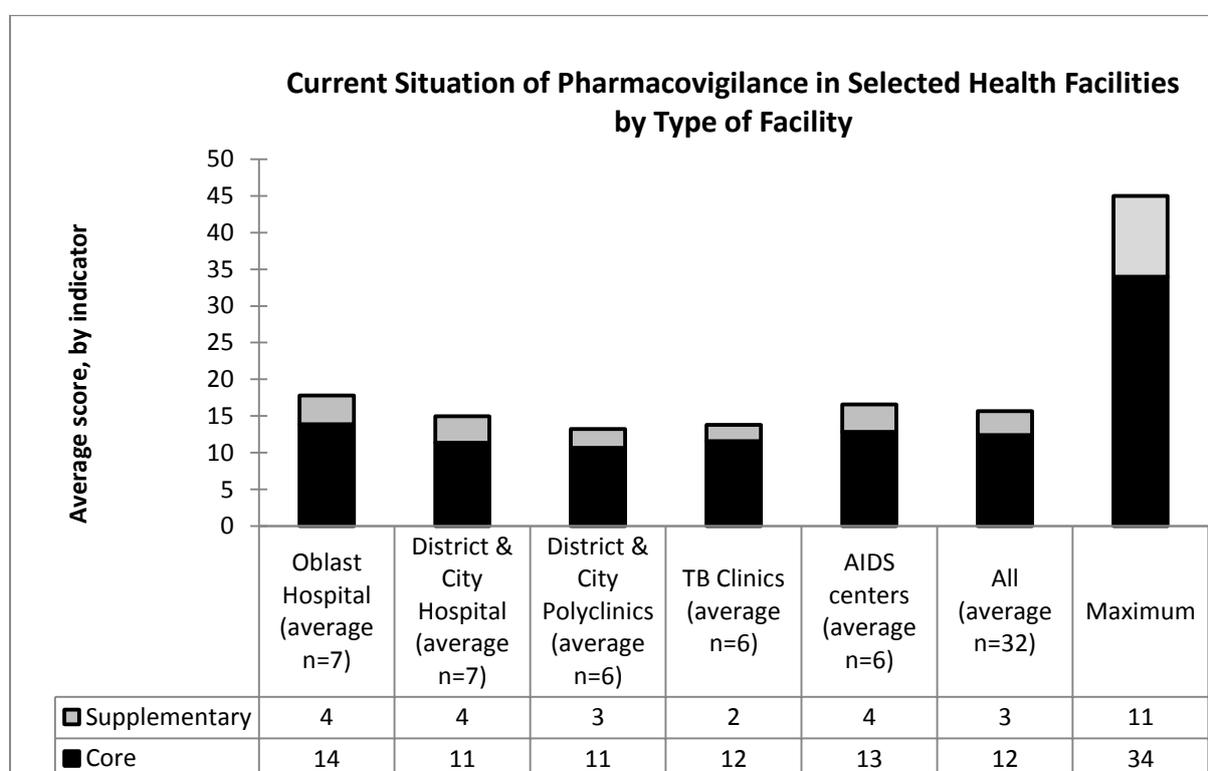


Figure 17. Current situation of pharmacovigilance systems in a sample of 32 health facilities by type of facility

For post-marketing quality surveillance, Figure 18 shows the score for SAUMP at the central unit and average scores for a sample of four SAUMP territorial sub-divisions. 17 core and 7 supplementary indicators were applicable at the central level. For the SAUMP territorial sub-division, 11 core and 7 supplementary indicators were applicable.

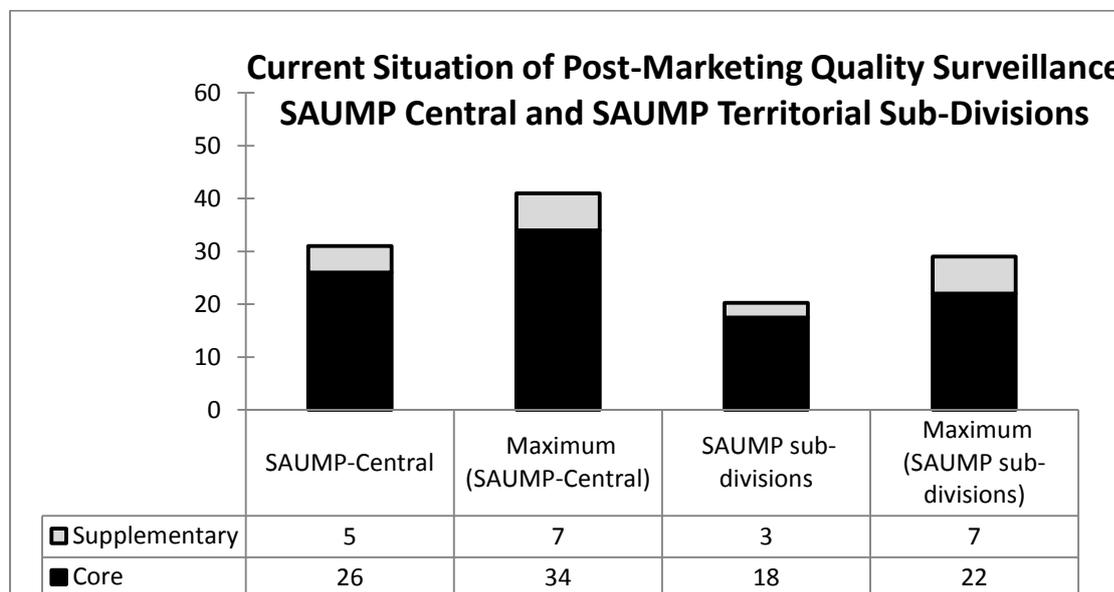


Figure 18. Current situation of post-marketing quality surveillance: SEC (central levels) and a sample of four SAUMP territorial sub-divisions

PHARMACOVIGILANCE IN UKRAINE'S PUBLIC HEALTH PROGRAMS

SPS collected data from the national immunization, HIV/AIDS, and TB programs in Ukraine to map out the extent to which these PHPs are involved in pharmacovigilance at the central level, and also interviewed staff at oblast-level TB dispensaries and AIDS Centers in the city of Kyiv and five oblasts. Data from these health facility interviews indicate the situation on implementation of medicine safety activities at the point of care. Many of the hospitals visited also provide immunization services but as these are one of many services delivered by these facilities, it was difficult to disaggregate the specific findings for the immunization program at this level. This chapter summarizes the key findings on pharmacovigilance in the HIV, TB, and immunization programs.

Findings

Policy and Guidelines

PHP policy documents and treatment guidelines that include a commitment to monitor the safety and effectiveness of pharmaceuticals such as vaccines, anti-TB, and ARV medicines, or set out adverse event reporting policies indicate that the country has given high-level attention and commitment to improving medicine and vaccine safety.

For the national TB, HIV, and immunization programs, SPS reviewed national treatment protocols to identify policy statements related to pharmacovigilance. The national protocols for treatment and management of drug-resistant TB,¹⁰⁰ HIV/TB coinfection,¹⁰¹ and AIDS¹⁰² include guidance on anti-TB and ARV drug toxicities and substitution, treatment failure and switching, and, clinical signs and management of ADRs and potential drug interactions. The 2006 instruction on TB treatment¹⁰³ provides direction on switching first-line regimens in case of drug resistance. Importantly, the ART guidelines for adults and adolescents specifically state the importance of providing information to patients on potential ADRs and drug interactions, monitoring for and reporting ADRs, and mention the procedure for submitting reports to the SEC according to MoH of Ukraine Order No. 898. The operational plans for the national TB¹⁰⁴ and HIV¹⁰⁵ programs do not, with the exception of anti-TB drug and ARV drug resistance, address pharmacovigilance directly.

For vaccines, antitoxins, and TB allergen, MoH Orders No. 898 and No. 595 “On the Procedure of Prophylactic Immunization in Ukraine and Control of Immunobiological

¹⁰⁰ “Standard of Medical Care Delivery to Patients with Drug-Resistant Tuberculosis” approved under MoH Order № 600 (2008) as amended by MoH Order № 108 (2012)

¹⁰¹ “Clinical Protocol for Provision of Health Care Services to Patients with TB/HIV co-infection” approved under MoH Order № 276 (2008)

¹⁰² “On Approval of Regulations of the Clinical Protocol for Antiretroviral Therapy of HIV Infection in Adults and Adolescents” approved under MoH Order № 551(2010)

¹⁰³ “On Approval of Instructions for Care Delivery to People with TB” approved under MoH Order № 385 (2006)

¹⁰⁴ National Programme Against Tuberculosis for 2007-2011.

¹⁰⁵ National Programme on HIV Prevention, Treatment, Care and Support for HIV-Infected and AIDS Patients for 2009–2013

Medicines Quality and Circulation” provide the regulatory basis for safety surveillance of these products when used for implementing the Law of Ukraine “On Ensuring Sanitary and Epidemic Population Safety,” and MoH Orders “On Approval of the National Program on Immunologic Prophylaxis and Population Protection from Infectious Diseases for 2009-2015 and “On Prophylactic Vaccinations in Ukraine and MIBP Quality and Circulation Control.”

Systems, Structures, and Stakeholder Coordination

WHO recommendations on integrating pharmacovigilance into PHPs advise that the model “should draw on the strengths of the national pharmacovigilance system and PHPs to avoiding duplication. The model should emphasize sharing of human resources and the expansion of knowledge on effectiveness/risk, collaboration, effective communication, integration, training and capacity building.”¹⁰⁶ Assessment findings indicate that in Ukraine, the TB and the HIV program do not have units designated for addressing pharmacovigilance issues or focal persons identified for pharmacovigilance whose responsibilities are specified in their job description (table 6). Primary responsibility for pharmacovigilance in Ukraine lies with the SEC, with the SAUMP supporting post-marketing quality surveillance. As reported earlier, all but one of the six TB dispensaries (83 percent) and one of six AIDS centers (83 percent) visited has a person that is specifically responsible for pharmacovigilance. Responsibilities for pharmacovigilance are described in the job description for three of five TB dispensaries and three of five AIDS centers visited.

In the immunization program, responsibility for post-marketing surveillance is assigned to SEC’s Department of Immunobiological Medicines and Immunoprophylaxis as set out in MoH Order No 595 whose staff work closely with the Department of Infectious Disease Prevention of the Administration of Public Health, MoH. Responsibility for vaccine surveillance has recently been relocated to the SEC.

Table 6. Pharmacovigilance Systems, Structures, and Procedures in TB, HIV and Immunization Programs

	TB	HIV	Immunization
Program has a budget allocation for PV			✓(MoH and SEC)
Communications technologies to facilitate safety reporting and provision of information	✓	✓	✓
Program has an information service for PV in place		✓	✓
Program produces a bulletin that features PV topics or regularly contributes articles			
Program has provided in-service training course in PV in last year		✓(with SEC)	

Of the three PHP programs, only the immunization program has an annual budget allocation for pharmacovigilance activities, although in 2011 the HIV program did receive both financial and technical support for conducting trainings on pharmacovigilance. In 2011, the All-Ukrainian Network of People Living with HIV (the Network) through the program

¹⁰⁶ WHO. 2006. *The Safety of Medicines in Public Health Programmes*. Geneva: WHO.

“HIV/AIDS prevention, support, treatment and care for the most vulnerable population of Ukraine” provided funds under the Global Fund Round 6 grant for the development of materials and two training workshops. The SEC, the Ukrainian National Training Center, ART specialists of L.V. Hromashevskiy Institute of Epidemiology and Infectious Diseases AIDS Clinic (the National Academy of Medical Sciences), and WHO provided technical support.

In accordance with MoH Order No 898, all ADR reports are forwarded directly by the medical staff providing TB and HIV treatment to the SEC Board through the SEC regional affiliates. For the national TB and HIV programs, the current legislation does not clearly identify mechanisms for interaction and coordination on pharmacovigilance activities between these national programs and the national agencies responsible for product safety and quality surveillance. As mentioned earlier, the immunization program is the exception where roles are clearly defined.

The MoH has a daytime telephone number that members of the public can call for general information and questions specific to the PHP programs are forwarded to program staff. The HIV program has a 24-hour toll-free hotline staffed by trained physicians that provides a question-and-answer service on HIV-related issues, including information on ADRs and medicines safety. For TB, the Fund of Development of Ukraine (FDU) has a 24-hour hotline for responding to queries from the public and patients that has been operational since December 2011. According to key informants, the range of topics that the FDU provides information on does not currently cover pharmacovigilance or ADRs, however, some of the 3,000 calls that they receive per month are regarding adverse events. Respondents at the TB dispensaries and AIDS centers visited said that patients are given information about ADRs and medicines as part of the treatment process consistent with the program guidelines. In addition, one of six AIDS center said that they had a “trust line” that members of the public can call to obtain information on HIV transmission, diagnosis, and treatment and on ADRs to ARVs. Two other AIDS centers reported that they had a specific person designated for responding to queries about ADRs.

None of the three PHPs produces a bulletin that regularly features pharmacovigilance topics or routinely contributes such articles to an existing publication, for example, SEC's *Rational Pharmacotherapy* bulletin. In 2011 and 2012, the HIV program, with financial support from Global Fund Round 6 grant and in collaboration with the SEC, ART specialists of L.V. Hromashevskiy Institute of Epidemiology and Infectious Diseases AIDS Clinic (the National Academy of Medical Sciences) and WHO, held three training workshops on pharmacovigilance which were attended by 72 specialists. The course “Pharmacovigilance: Control of ADRs and the effectiveness of antiretroviral medicines in treatment of patients with HIV” consists of 38 academic hours (plus one hour for testing). The course has been accredited by the P. L. Shupyk Academy of National Medical Post-Graduate Education. Four of the six AIDS centers visited (67 percent) reported that more than 5 percent of their physicians had attended one of the three training workshops. No pharmacovigilance trainings were organized by the TB program for central-level or dispensary staff in 2011, although the State Service expressed interest in introducing such activities. None of the six TB dispensaries visited reported that staff had attended any training that included pharmacovigilance. Two staff members from SEC's Department of Immunobiological Medicines and Immunoprophylaxis attended a seven-day WHO training in the previous year that included pharmacovigilance topics. Staff from the SEC and from the Department of

Infectious Disease Prevention of the Administration of Public Health, MoH, participate in MoH planned trainings and seminars to present on vaccine safety, when invited.

Signal Generation and Data Management

As the TB and HIV programs are not routinely involved in monitoring medicine safety, neither program has a database for collecting adverse event reports or for tracking pharmacovigilance activities and workload. The HIV program does, however, collect data on ARV substitutions due to ADRs and lack of efficacy which is analyzed and disseminated in its semiannual report. SEC's Department of Immunobiological Medicines and Immunoprophylaxis maintains the central database for PVAEs. Staff members of all three PHPs were aware of the existence of Form #137/o for spontaneous reporting of suspected adverse events and lack of efficacy as approved by MoH Order No. 898. The form was available in all six TB dispensaries (100 percent) and five of the six AIDS centers (83 percent) visited, although staff at one TB dispensary center said they never use it. None of the PHPs had a program-specific form for reporting medication errors or suspected poor product quality problems.

Risk Assessment and Evaluation

Without establishing robust mechanisms to monitor and assess the risks and benefits of new ARVs in disease programs in collaboration with national pharmacovigilance centers, the occurrence of serious adverse events in the context of a rapid scale-up of ART can significantly damage the credibility of the program.¹⁰⁷ Similar concerns can arise with the rollout of new medicines, for example, for MDR-TB and recently approved vaccines. PHPs should collate and document the proportion of patients who experienced drug-related adverse events among the total number of patients receiving the treatment.¹⁰⁸ This information can then be used to calculate rates of incidence of ADRs with a known denominator (number of patients treated) to identify or evaluate medicine safety issues.

In the HIV and TB programs, ADRs are recorded in individual patient files and an ADR report is submitted to the SEC's Post-Marketing Surveillance Board. The SEC Board provides information which can be found in its database on the number of ADR reports submitted for anti-TB and ARV medicines in 2011. The data presented in table 7 therefore includes reports submitted by physicians working in health facilities as well as TB dispensaries and AIDS centers. As can be seen in table 7, the current rate of reporting of ADRs for anti-TB medicines is very low, since it is known that adverse events to anti-TB medicines are common, ranging from 5.5 percent to 57.8 percent,¹⁰⁹ and can lead to a change in regimen in 43.42 percent of cases.¹¹⁰

¹⁰⁷ WHO. 2009. *A Practical Handbook on the Pharmacovigilance of Antiretroviral Medicines*. Available at http://whqlibdoc.who.int/publications/2009/9789241547949_eng.pdf

¹⁰⁸ WHO. 2006. *Safety of Medicines in Public Health Programs: Pharmacovigilance, an Essential Tool*. Available at http://www.who.int/medicines/areas/quality_safety/safety_efficacy/Pharmacovigilance_B.pdf

¹⁰⁹ Xia Y. et al Design of the Anti-tuberculosis Drugs induced Adverse Reactions in China National Tuberculosis Prevention and Control Scheme Study (ADACS). *BMC Public Health* 2010, 10:267 <http://www.biomedcentral.com/1471-2458/10/267>

¹¹⁰ Nikolaeva OD: [Side effects of chemotherapy in patients with pulmonary tuberculosis and concomitant diseases]. *Lik Sprava* 2003:74-78.

Table 7. Analysis of ADR Reports for Anti-TB and ARV Medicines and PVAE Reports Submitted to SEC, 2011

		Anti-TB medicines	ARVs	Vaccines, antitoxins, and TB allergen
Spontaneous ADR and PVAE reports (All)	No. of reports	281	387	34,286
	Estimated percentage	0.06%	1.45%	0.27%
	No. of reports per million	562	14,484	2,743
	Expected percentage	5.5 % ^{9,a}	8% ^b	Not available
Serious unknown ADR and PVAE reports	No. of reports	0	0	Not available
	Estimated percentage	0%	0%	Not available
	No. of reports per million	0	0	Not available
	Expected percentage	0 to 0.1% ^c	0 to 0.1% ^c	0 to 0.1% ^c

a = Minimum number of patients on anti-TB medicines experiencing adverse events. This varies depending on the population treated, definition of adverse event, and duration on treatment.

b = Source: MSF Antiretroviral therapy in primary health care: experience of the Khayelitsha programme in South Africa: case study. <http://www.who.int/hiv/amds/case8.pdf>. This data is only of patients needing to change an individual drug due to adverse events.

c = SPS Program. 2009. Indicator-Based Pharmacovigilance Assessment Tool: Manual for Conducting Assessments in Developing Countries. Submitted to the U.S. Agency for International Development by the SPS Program. Arlington, VA: Management Sciences for Health. http://pdf.usaid.gov/pdf_docs/PNADS167.pdf

Of the six TB dispensaries visited, two (33 percent) said they maintain a record of patients that experienced drug-related adverse events so they were able provide the percentage of patients treated that experienced an ADR or treatment failure. Five of the six AIDS centers visited (83 percent) maintain such records and were able to provide data on the percentage of ART patients treated that experienced an ADR (range from 0.35 to 13 percent), but only one had data on treatment failure.

Data on treatment modification and interruptions is routinely collected by the HIV program. Therefore, ADR reporting based on treatment modification/interruption can be one feasible approach to monitor ADRs in a large observational HIV cohort, as drug-related toxicity is often the most common cause of treatment modification/interruption in patients taking ART.^{111,112} Also, data collected by eTB Manager, the software currently being rolled out nationwide by the TB program with assistance from SPS, will enable better tracking of treatment modifications and interruptions in patients treated for both TB and MDR-TB. SEC's Department of Immunobiological Medicines and Immunoprophylaxis was able to provide data on the proportion of patients who experienced PVAEs among the total number of patients receiving vaccines, antitoxins, and TB allergens for 2011 (table 7). Since September 2011, the department has begun to collect and report suspected cases of

¹¹¹ d'Arminio Monforte A., A. C. Lepri, G. Rezza, et al. 2000. Insights into the reasons for discontinuation of the first highly active antiretroviral therapy (HAART) regimen in a cohort of antiretroviral naive patients. I.CO.N.A. Study Group. Italian Cohort of Antiretroviral-Naive Patients. *AIDS* 14(5): 499–507.

¹¹² Zhou et al. 2007. Experience with the use of a first-line regimen of stavudine, lamivudine and nevirapine in patients in the TREAT Asia HIV Observational Database. *HIV Medicine* 8: 8–16.

ineffectiveness as set out in MoH Order No. 595; 83 cases were reported from September to December 2011.

As part of the review of risk assessment and evaluation, the SPS team asked about existing efforts in the TB, HIV, and immunization programs to evaluate medicine and vaccine safety, quality, and rational use—current efforts are minimal (figure 19). In 2011, a few utilization studies were conducted, mainly by the immunization program which also conducted two medication error studies, including a survey of the level of errors associated with the administration of BCG vaccine. The TB program was preparing to conduct a study on prescribing practices at TB dispensaries with support from USAID at the time of this assessment. Ukraine was one of the countries included in a WHO multicountry survey on the quality of anti-TB medicines in circulation.¹¹³ Only the HIV program has engaged in active surveillance activities in the last five years; one WHO-supported study looked at the level of ARV drug resistance. In addition, one AIDS center participated in a regional active surveillance study that included different types of health facilities. A literature search did not reveal any additional studies to those reported.

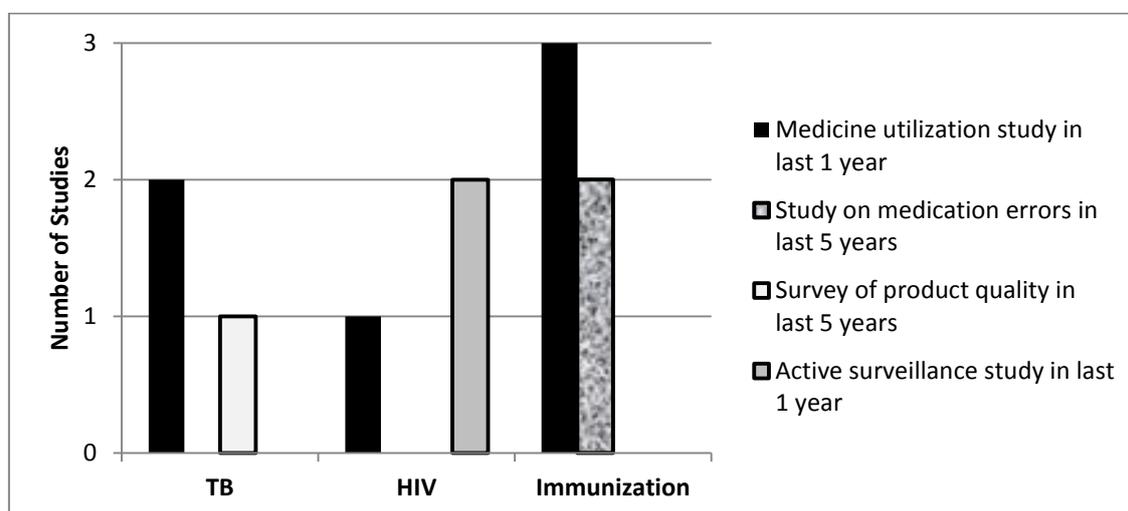


Figure 19. Risk evaluation activities conducted in TB, HIV, and immunization programs

Risk Management and Communication

Neither the TB or HIV programs are involved in routinely monitoring for new safety reports from other countries or communicating safety issues to health care workers—this is primarily the role of the SEC and the SAUMP who send alerts directly to health care facilities through their regional affiliates. PHP central-level staff forward any safety alerts they may receive to the relevant agency. It is not clear to what extent information is shared between these PHPs and the SEC and the SAUMP as the assessment noted that key informants were not able to provide information on the number of safety alert letters that were developed and distributed for TB or HIV-related pharmaceuticals in 2011.

¹¹³ WHO. 2011 *Survey of the quality of anti-tuberculosis medicines circulating in selected newly independent states of the former Soviet Union*. Geneva: WHO. Available at http://apps.who.int/prequal/info_applicants/qclabs/monitoring_documents/TBQuality-Survey_Nov2011.pdf

Neither program keeps a record of products quality withdrawals or concerns. However, there is no requirement to do so under current Ukrainian legislation because products that are suspected to be of poor quality are immediately withdrawn from the market and banned from medical use if a quality issue is confirmed. The withdrawal of products from the market because of poor quality concerns and maintaining records of such occurrences is the responsibility of the SAUMP. The standard should include a risk-based approach to safety monitoring of products used in the PHPs as pharmacovigilance requirements that are not streamlined or efficient can harm PHPs and become an impediment to access. During the assessment it was reported that when the SAUMP issued a prohibition for a batch of one vaccine before causality was established, administration of the vaccine stopped until the prohibition was cancelled, because there were only a few batches available in the country. As a result the immunization schedule was altered.

Key informants reported that there is incongruence between some provisions in the existing legislation, namely MoH Order No. 809¹¹⁴ and No. 898 that address interactions of the SEC and the SAUMP when an ADR is detected. A provision of Order No. 809 states a report from the MoH and a SAUMP territorial subdivision of an unsuspected serious ADR and/or death as a result of one or several batches of a medicine is grounds for a temporary suspension of the product while the medicine or MIBP quality is investigated. Order No. 809 states that one of the grounds for prohibiting the circulation of medicinal products is the confirmed notification of a report of an unsuspected serious ADR and/or death as a result of one or several batches of a medicine, but does not specify who should provide the confirmation, although this process is specified in Order No. 898. Section 9 of Order No. 898 designates SEC as responsible for assessing a causal association between an adverse event and use of the suspected medicinal product once information is presented to the SEC. As a result, there is a lack of clarity about the process of suspending a product which can lead to products being suspended before causality is established. Also reported was the need for additional provisions in Order No. 809 that specify the place for sampling the suspected product as well as procedures to enable the batch(es) of medicinal products, including MIBPs, to be returned to use where no cause and effect relationship has been detected between their use and the ADR or PVAE.

Responses from key informants indicate that the engagement of TB central-level program staff in risk management is mainly confined to reviewing treatment protocols in line with international recommendations and local experience on medication safety, and providing guidance on clinical management of ADRs. National guidelines restrict the provision of treatment for MDR-TB to tertiary antituberculosis facilities¹¹⁵ and the TB program will soon require that physicians are trained before they can treat patients with second-line anti-TB medicines to comply with conditions of a recently awarded Global Drug Facility grant. In addition to periodically reviewing treatment protocols and advising on ADR case management, HIV program risk management activities include requiring that all physicians complete a certification course before they can prescribe ARVs. Topics covered include specific guidance on contraindications to ARV use and requirements for baseline and

¹¹⁴ Order of the Ministry of Health of Ukraine of 11.22.2011 No 809 "On approval of the procedure on establishment of prohibition (temporary prohibition) and renewal of circulation of medicinal products within the territory of Ukraine"

¹¹⁵ "Standard of Medical Care Delivery to Patients with Drug-Resistant Tuberculosis" approved under MoH Order № 600 (2008) as amended by MoH Order № 108 (2012)

ongoing monitoring to monitor for potential ADRs, for example, hepatic monitoring with nevirapine.

For the immunization program, SEC's Department of Immunobiological Medicines and Immunoprophylaxis directly supports the Department of Infectious Disease Prevention of the Administration of Public Health, MoH, in risk management and communication activities. In addition to reviewing immunization protocols, the SEC assists the MoH in trainings on safety issues and sends letters to oblast and local levels to request that specific trainings are given. The SEC Department also helps to identify and promote the introduction of technologies such as self-blocking syringes that decrease risks.

Although the HIV and TB programs have 24-hour hotlines, both reportedly received few pharmacovigilance-related requests in 2011. The HIV program was engaged in several public and community education activities in 2011, but only one dealt specifically with medicines safety (an article on medicines that may be harmful during pregnancy). SPS inquired about public and community education efforts of three local NGOs supporting TB and HIV programs in Ukraine. None of them reported engaging in any such activities in 2011. SEC's Department of Immunobiological Medicines and Immunoprophylaxis received approximately 600 calls in 2011, however, not all requests were safety related as many pertained to doses and indications. The SEC and the Department of Infectious Disease Prevention of the Administration of Public Health, MoH gave approximately 15 radio and television interviews in 2011, however, these events did not deal specifically with vaccine safety.

Recommendations

- The MoH should define minimum requirements for PHP pharmacovigilance activities. Such criteria may require that PHPs that expose a certain number of the population to medicines including mass drug administration programs should develop pharmacovigilance plans before the introduction of new medicines (like medicines for MDR-TB), have a focal person for pharmacovigilance who is a liaison with the SEC, and include pharmacovigilance indicators (for example; rates of ADR/toxicity-related switches) as part of program indicators.
- The State Service on HIV and Other Socially Dangerous Diseases (the State Service) should emphasize pharmacovigilance and the importance of monitoring safety of medicines in the National Program for HIV Prevention, Care and Support and in the National Program on TB Control.
- Improve adverse event reporting and data management across all the PHPs.
 - In accordance with existing Ukrainian legislation concerning the integration pharmacovigilance into TB and HIV PHPs, the heads of health care facilities that use anti-TB and ARV medicines, should encourage health care workers to report ADRs.
 - To improve ADR reporting, the MoH and the State Service should explore opportunities for embedding Form #137/o in the electronic records in eTB Manager.
- The MoH, the SEC, and the State Service should develop a legislative basis and implement mechanisms for stakeholder interaction and coordination (the MoH, the SEC, the SAUMP, and their regional affiliates/territorial sub-divisions, the State Service of

Ukraine, health care facilities, and pharmacies) on issues related to information exchange, risk assessment, and risk management.

- The experiences in PVAE monitoring and the systems for communication and coordination between the stakeholders in the immunization program should be used as a model to strengthen pharmacovigilance in other PHPs.
- The MoH, the SEC, and the SAUMP should take measures to immediately address incongruences and gaps in the provisions of the existing legislation regulating medicine registration and safety controls that relate to interactions and regulatory decision-making connected with medicines safety in particular, for TB- and ART-related medicinal products and MIBPs.
- Training on pharmacovigilance in PHP programs should be improved.
 - The SEC and the State Service should develop training materials for the provision of pharmacovigilance trainings for TB program staff members.
 - The MoH, the SEC, and the State Service should ensure that pharmacovigilance training is provided to health care workers in the TB program on a regular basis using the developed training materials.
 - The SEC should develop a training curriculum on pharmacovigilance and MIBP adverse events.
- The MoH, the SEC, and the State Service should—
 - Disseminate information on medicines safety to health care workers and patients using a range of approaches such as hot telephone lines, bulletins, and publications in specialized medical periodicals;
 - Develop SOPs to standardize practices across all the health-related toll-free hotlines being implemented in Ukraine to ensure that calls related to adverse events and safety information request are addressed in a standard manner;
 - Ensure that health information-related toll-free lines at all levels are used to advance safe medicines use. Phone line operators should document the type of questions posed by the caller and how it was addressed. The information should be analyzed to study the priority safety concerns of patients, and to inform the development of educational activities to improve patient adherence and enhance the reputation of PHPs.
- The MoH, the SEC, and State Service should consider highlighting anti-TB and ARV medicines safety issues and the reporting activities of relevant health facilities on ADRs and/or lack of efficacy in their periodic reports (bulletins). This strategy can help to motivate health care workers to report ADRs and/or lack of efficacy and the data obtained can be used to assess medicines safety and inform discussions on how to study the priority safety concerns that are identified.
- The MoH, SEC, and the State Service should develop active approaches to TB and ARV medicines safety and efficacy monitoring in health facilities inpatient departments to quantify and characterize the incidence and the risk of short- and long-term toxicities experienced by patients on treatment.

PHARMACOVIGILANCE AND MEDICAL DEVICE SAFETY IN THE PHARMACEUTICAL INDUSTRY

Introduction

The pharmaceutical industry is one of the multiple stakeholders that share the responsibility for ensuring pharmacovigilance and device safety within a country. A MAH must establish appropriate medicine and device safety systems to ensure responsibility and liability for its products, and should also monitor and report adverse events related to the use of its products wherever they are marketed. SRAs such as the EMA and the FDA require MAHs to report drug or device-related adverse events that occur in all countries where their products are marketed. These agencies also require companies to conduct post-marketing safety studies or risk minimization activities for high-risk medicines and products with unresolved safety concerns,^{116,117} according to ICH guidelines.

Although Ukraine has long had legal provisions that require MAHs to report all serious ADRs to the SEC, the requirement for MAHs to conduct post-marketing surveillance activities was introduced only recently under MoH Order No. 898 as amended by MoH of 12.29.2011 Order No. 1005. Currently, there are no legal provisions that establish similar requirements for medical devices. The assessment findings of pharmacovigilance and medicines safety in Ukraine's pharmaceutical industry reflect the country's until recent limited legal mandate to regulate the industry for medicines safety and the continuing absence of regulations for device safety.

Selection of Study Sites

A web search identified that in 2007, there were over 600 pharmaceutical companies in Ukraine.¹¹⁸ The total pharmaceutical market size estimated from the sales figure of leading corporations was about USD 3.3 billion in 2011.¹¹⁹ Medicines consumed at the hospital level account for 14 percent of these. About 72 percent of products used in the retail sector in Ukraine are imported. There are 13,272 medicines¹²⁰ registered in Ukraine and approximately 80 percent of the medicines registered are generic products.¹²¹

SPS interviewed representatives from 11 pharmaceutical companies from December 12 to 22, 2011. This included five multinational innovator pharmaceutical companies (MICs), two

¹¹⁶ EU. Legislation Volume 9: Guidelines for pharmacovigilance for medicinal products for human and veterinary use. Available at http://ec.europa.eu/health/files/eudralex/vol-9/pdf/vol9_10-2004_en.pdf

¹¹⁷ FDA. Draft guidance for industry: post-marketing safety reporting for human drug and biological products including vaccine. 2001. Available at <http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Vaccines/ucm074850.htm#INTRODUCTION>

¹¹⁸ Roland Berger Strategy Consultants. 2009. *New investment opportunities in the Ukrainian pharmaceutical industry*. Available at

http://www.rolandberger.ua/media/pdf/Roland_Berger_PharmaInvestmentOpportunities_Eng_20090223.pdf

¹¹⁹ MedPharmConnect. Available at

http://medpharmconnect.com/Ukrainian_market/Ukrainian_Pharmaceutical_Market.htm

¹²⁰ Ministry of Health of Ukraine State Expert Center website 06.13.2012. <http://www.pharma-center.kiev.ua/view/index>

¹²¹ Data of the Department of Regulatory Policy, Ministry of Health, Ukraine. March 12, 2012

multinational generic pharmaceutical companies (MGCs), and four local pharmaceutical manufacturers (LMs). All of the medicinal products marketed by MICs and MGCs in Ukraine are manufactured elsewhere and imported for sale in the country. Three of the four local manufacturers are locally owned and the fourth is part of a multinational corporation which has manufacturing plants in India in addition to Ukraine. Table 8 provides information on the number of products marketed by each company interviewed in Ukraine.

Table 8. Pharmaceutical Companies Surveyed: Number of Medicinal Products in Ukraine Market

Number of medicinal products in Ukraine market	Pharmaceutical Companies		
	MIC	MGC	LM
1–50	2	1	
51–100	1	1	2
101–150			
151–200	1		1
201–250	1		1

In April and May 2012, SPS interviewed two companies that market medical devices in Ukraine to assess their systems to monitor device safety and minimize risk from these products. Medical devices account for approximately 30 percent of the pharmaceutical market size in 2011.¹²² The small sample surveyed included—

- One multinational device company (MDC) with one Class III device (insulin pen) on Ukraine market
- One local device manufacturer (LDM) with eight Class I, IIa, IIb, III products on Ukraine market

None of the CROs based in Ukraine agreed to be interviewed for this assessment.

Caveats and Limitations

Several pharmaceutical manufacturers were unwilling to participate in the assessment and ultimately SPS completed only 11 out of 20 planned interviews, including four of the intended seven interviews with local manufacturers. As a result, some bias may have been introduced as the companies, particularly the local manufacturers that agreed to be interviewed, are likely to have more advanced pharmacovigilance systems in place. Only two medical device manufacturers agreed to be interviewed (one of which only markets one product in Ukraine) and so the findings of these interviews cannot be considered to be representative and may only indicate trends. SPS also approached a number of CROs to request interviews but all refused, mostly citing confidentiality clauses with their clients as a concern.

Where possible, SPS tried to verify the responses reported by key informants, for example by requesting to see copies of policies, SOPs, and forms to confirm their existence. However, in several cases companies did not share these documents due to concerns about confidentiality.

¹²² MedPharmConnect. Available at http://medpharmconnect.com/Ukrainian_market/Ukrainian_Pharmaceutical_Market.htm

It should be noted, however, that most of the documents SPS requested were documents that should be publicly available, uncompleted forms, and aggregate data from registers. Documents with patient identifiers or obvious confidential information were not requested.

Findings

Policy, Law, and Regulation

Pharmaceutical Companies

Figure 20 depicts the key findings with regard to pharmaceutical industry pharmacovigilance policies and compliance with applicable national legal provisions and standards in Ukraine. Seven (64 percent) of the 11 companies surveyed, including most MICs, both MGCs, but only one of four LMs report the existence of internal policies that contain essential statements on pharmacovigilance or medicine safety monitoring that have been updated in the last five years. Three companies that reported the absence of statements in policies indicated that they were included in SOPs; one LM lacked such statements in both policies and SOPs. All but one company (one LM) reported that the quality systems of their companies include pharmacovigilance procedures that are in compliance with Ukrainian legal provisions set out in MoH Order 898. Similarly, with the exception of one LM, companies have SOPs for expedited reporting of serious ADRs and all 11 companies reported submitting PSURs as per the national regulatory requirements (eight companies shared their PSUR report or form with SPS). Of the ten companies that perform or contract other companies to conduct clinical trials, all said they submit development safety update reports as per national requirements.

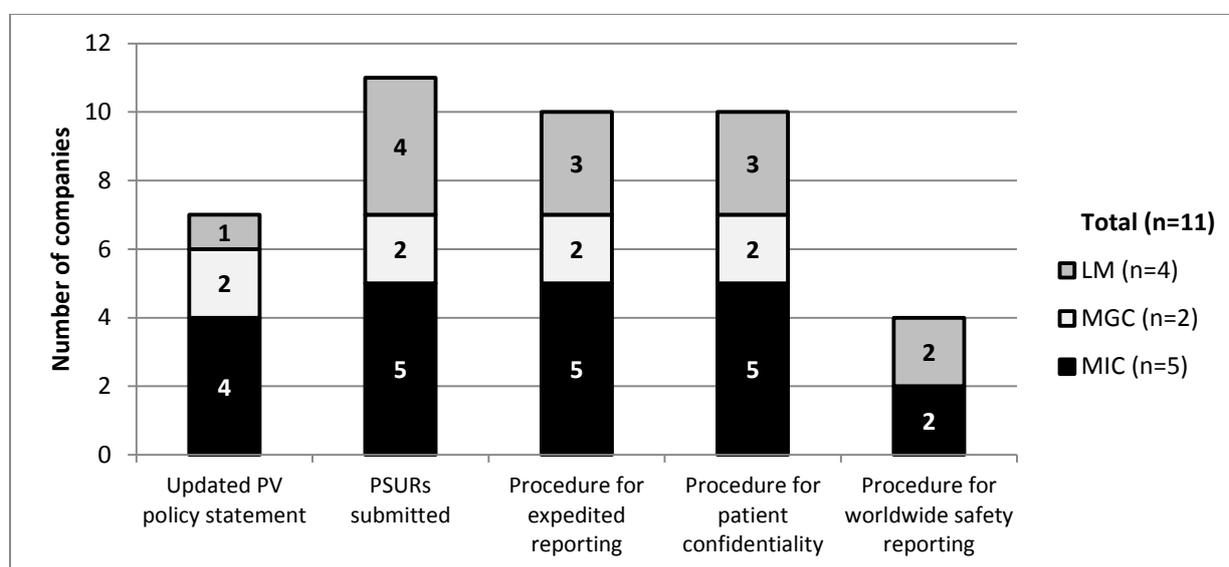


Figure 20. Pharmaceutical companies: existence of pharmacovigilance policies and procedures as per applicable legal provisions

As can be seen in figure 20, with the exception of one LM, most companies have internal policies or procedures on maintaining patient confidentiality in reporting that comply with national regulatory provisions. However, only four companies (36 percent) reported the

existence of procedures for reporting global safety experiences (for example, ADRs from other countries involving a product they hold marketing authorization for in Ukraine) to the Ukrainian regulatory authority at the time of the assessment.

Medical Device Companies

Table 9 shows the existence of policies and procedures for device safety at the two device companies interviewed. The multinational device company said that updated internal policies that contain essential statements on device safety monitoring and procedures addressing device safety are included in the company’s quality system. The local device company’s policy and procedures pertain to the monitoring of quality only and primarily concern device manufacture and registration, rather than post-marketing safety surveillance. One company has a corrective and preventative action procedure which sets out step by step the process for completing and documenting such actions. Currently, Ukraine does not have legal provisions requiring MAHs to report adverse events to medical devices or to conduct post-marketing surveillance activities so neither company has procedures that address adverse event reporting or the reporting of worldwide safety experience to authorities in Ukraine. However, the multinational device company has procedures that comply with global guidance issued by the GHTF¹²³ at the central office of the company for reporting to regulatory bodies such as the EMA and FDA. According to respondents, neither company has internal policies and procedures in place for maintaining patient confidentiality in reporting that comply with national regulatory provisions; however one company is in the process of developing such a policy.

Table 9. Medical Device Companies in Ukraine: Existence of Device Safety Policies and Procedures

	MDC (1)	LMC (1)
Updated policy statement on device safety (within last 5 years)	✓	
Procedures addressing device safety in quality system	✓	
Corrective and preventative action procedure	✓	
Procedures comply with Global Guidance for Adverse Event Reporting for Medical Devices (GHTF/SG2/N54R8:2006)	Head office level	
Compliance with GHTF guidance on timing of adverse event reporting (GHTF N21R8 and GHTF/SG2/N33)	Head office level	
Policy on compliance with national clauses and standards on patient confidentiality		
Procedure for mandatory reporting of worldwide safety experience		

¹²³ Global Harmonization Task Force (GHTF) SG2-N54R8:2006. Medical Devices Post Market Surveillance: Global Guidance for Adverse Event Reporting for Medical Devices. <http://www.ghtf.org/documents/>

System, Structure, and Stakeholder Coordination

Pharmaceutical Companies

Most of the companies surveyed have the basic structures for conducting pharmacovigilance activities in place (figure 21). All companies have established a pharmacovigilance unit, although it physically exists in only eight of 11 offices (64 percent). With the exception of one LM, all units have a clear mandate, reporting lines, and roles and responsibilities. Ten companies (91 percent) have a dedicated budget allocation for pharmacovigilance activities. All companies have a person that is specifically responsible for medicines safety (a qualified person for pharmacovigilance—QPPV) and, with the exception of one LM, QPPV responsibilities for medicines safety are described in their job description. Although the position is part time in six companies (55 percent), three of the five MICs and two of four LMs have one or several full-time staff for pharmacovigilance.

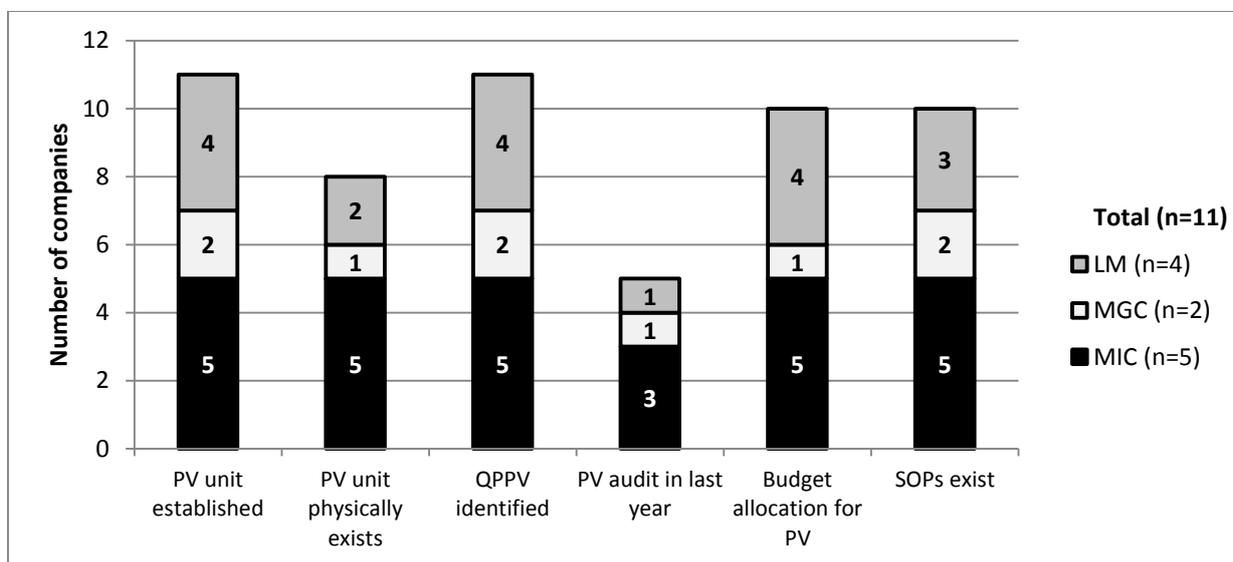


Figure 21. Pharmaceutical companies: systems and structures for pharmacovigilance

Written, authorized SOPs for pharmacovigilance were reported to be in place by 10 of the 11 companies surveyed (and were seen for 7 companies); one LM has yet to develop SOPs. All MICs and most MGC and LMs routinely perform the pharmacovigilance activities listed below either locally or for multinational companies, at the global or parent office or jointly between the local and global office. The exceptions are noted in parentheses.

- Collection of adverse events occurring in Ukraine
- Identification of safety signals from spontaneous reports in Ukraine and reports from other countries (not done at one MGC and one LM)
- Determination of seriousness and expectedness of the report using international guidelines and terminologies (MedDRA coding) (not done by two LMs)
- Determination of the validity of the report
- Determination of causality between an adverse event and a product
- Preparation and submission of expedited ADR reports
- Preparation and submission of PSUR

- Risk-benefit assessment of the medicinal product (not done by one LM)
- Decision making and taking preventive actions to minimize known risk of marketed products (not done by two LMs)
- Communication with the SEC and the SAUMP
- Management of database or archive of information (not done by one LM)
- Performance of internal pharmacovigilance audits (not done by one MGC and two LMs)

Nine of 11 companies (82 percent) have procedures for internal pharmacovigilance audits; however, only five companies (45 percent) have been audited in the last year. The frequency of audits average 2–3 years for most companies (range from semiannual to four years). As the SEC does not currently perform pharmacovigilance audits, none of the companies had procedures in place for external audits.

All companies said they provide a medicine information service and all have well-functioning communication technologies in place. However, medicine information services are typically not well developed or utilized and the compilation of queries is poorly coordinated in most cases. Five of 11 companies (45 percent) estimated that they received less than 20 pharmacovigilance -related information requests in the last year, and only one received more than 100 requests. Five companies (45 percent) including only one of four LMs, have a hotline or dedicated telephone number that operates 24 hours per day and two have a medical information or advice department. Although two companies have staff members who are trained to respond to questions related to medicines safety, in most cases these queries are forwarded to the QPPV. The availability of pharmacovigilance-related information resources for providing ADR and medicine information varied considerably across companies. Some companies reported access to a wide variety of journals (national and international) and use of search engines such as PubMed with several multinational companies accessing these resources through the global or parent office. Others (mostly local) relied on local publications and the SEC website as primary sources of information.

Eight companies (73 percent), including all five MICs, both MGCs, and one of the four LMs said they had formal pharmacovigilance training programs in place for staff that included induction trainings for new staff and update training for others at least annually. Most keep formal records of staff trainings, some of which are reviewed as part of internal audits. Two companies have web-based training. Less formal systems appear to be in place for the four LMs interviewed with only one LM requiring mandatory trainings for staff and maintaining training records.

Device Companies

The availability of systems and structures for device safety varied considerably between the two device companies interviewed (table 10) with the local company lacking all but communications technology. Even though the MDC has a part-time staff member designated for device safety and SOPs for device safety, the unit's activities mainly involve the monitoring of product quality at the local level as per parent company procedures. Activities include addressing complaints regarding product quality, ensuring procedures to monitor and assure quality are followed within the company, and checking that distributors comply with quality requirements indicated in their contract. One of the two companies (the MDC) has processes in place for evaluating device information queries to detect adverse events, assessing causality, or for reporting trends of adverse events in compliance with

GHTF/SG2/N36 at the global office but not in Ukraine; at the moment of the assessment such procedures are not required under the legal provisions in Ukraine.

Table 10. Medical Device Companies in Ukraine: Systems and Structures for Pharmacovigilance

	MDC (1)	LMC (1)
Device safety unit established and physically exists	✓	
Unit has clear mandate, organizational structure, and reporting lines	✓	
Person responsible for device safety	✓	
Budget allocation for device safety	✓	
SOPs exist for device safety	✓	
Procedures for device safety audit exist	Head office level	
Device safety audit performed in last year		
Communications technologies to facilitate safety reporting and provision of device information	✓	✓
Information service on device safety in place		
Staff trained in device safety		

Signal Generation and Data Management

Pharmaceutical Manufacturers

All companies have a central database for archiving and storing medical safety documents and collating pharmacovigilance data (figure 22); however, for two of the four LMs it contains only spontaneous ADR reports. In four companies (three of five MICs and one of

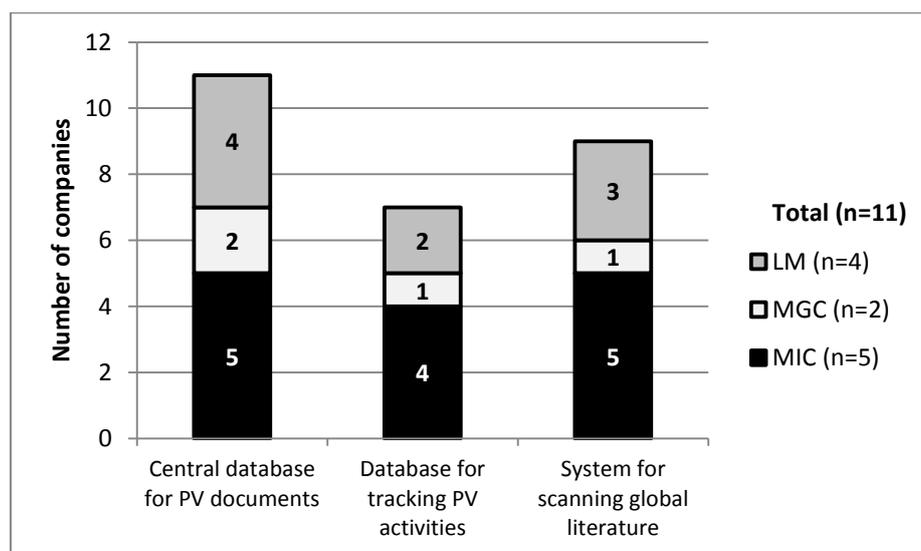


Figure 22. Pharmaceutical companies: existence of pharmacovigilance databases and systems for scanning global literature for relevant safety issues

two MGCs), this database is located at the global level; the local office send information to the database but cannot always access it directly. Seven companies (64 percent) also have a database that uses ICH E2B standards to track center activities and workload.

Most of companies surveyed (82 percent) claimed to have a standardized system to scan global literature to identify medicine safety issues of local relevance and almost all said they regularly monitored these resources to identify new safety reports for their products. All the multinational companies are assisted by their global office in this task. Limited access to references and resources indicate that LM efforts may be less formal.

Figure 23 shows the availability of forms for reporting suspected medicine safety concerns at the companies surveyed. All companies have forms for spontaneous reporting of ADRs that can be received in both paper and electronic formats and, for all but one LM, the form met E2B standards (seen for 9 of 11 companies). For most companies, the ADR form was also used to report lack of efficacy in line with the SEC form included in Order 898. Eight companies (73 percent) also had a form for reporting poor product quality issues; three of the forms were for a company’s internal use. One company had a form with a specific field for reporting medication errors to their global office.

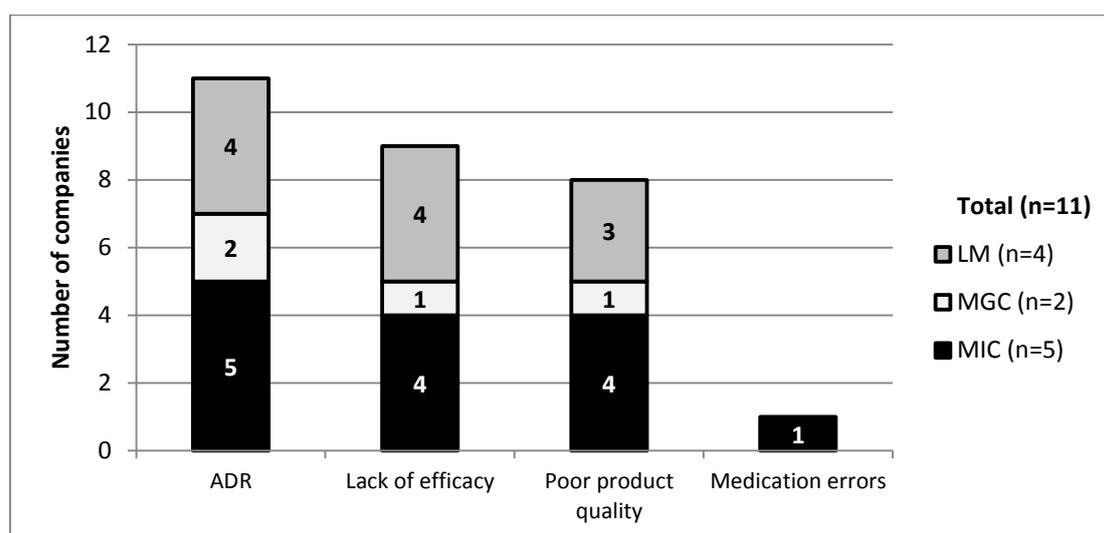


Figure 23. Pharmaceutical companies: existence of forms for reporting suspected medicine safety concerns

Device Companies

Of the two device companies interviewed, one (the MDC) has a database for storing device safety documents and collating data including complaints received and pre- and post-registration data. A system for scanning global literature to identify safety issues of local relevance is in place at the global level for the MDC while the LDM reported using PubMed for this purpose. However, neither company routinely reviews resources to identify new safety reports from outside sources. One of the two companies had a form for spontaneous reporting of suspected device-related adverse events or errors in use in Ukraine for reporting to their global office.

Risk Assessment and Evaluation

Pharmaceutical Companies

Pharmaceutical industry efforts to identify safety signals and evaluate the risks are insufficient across all types of companies interviewed. The SPS team inquired about ADR reporting in the last year. The number of ADR reports received in Ukraine ranged from zero to 644 per company with eight of the 10 companies (80 percent) that shared data receiving an average of less than one ADR report per product in the last year (table 11). The number of serious and unknown adverse events received in the last year ranged from zero to 40 per company; five companies received no such reports.

Table 11. Number of ADR Reports Received and Committed to ADR Database per Registered Product in Last Year

Number of ADR reports received per registered product	Number of Companies		
	MIC	MGC	LM
None	1	1	0
Less than 1 report per product	3	0	3
1 to 5 reports per product	0	1	1
Data not shared	1	0	0

Ten of the 11 companies (91 percent) said they maintain paper or electronic records of the number of patients that experience drug-related adverse events (one MGC did not). Five companies were able to estimate that the percentage of patients that used their products and experienced an adverse event in the last year was less than 0.02 percent. Six (55 percent) of the surveyed companies, including only one of four LMs, have statistical or mathematical tools for data mining either at the local or central level. The methods used are Bayesian confidence propagation neural network, odds ratio, and Empirical Bayes Geometric Mean, each used by one company. Three of the six companies could not name the tool used.

The SPS team inquired about active surveillance activities, medication error, and utilization studies (table 12). Active surveillance activities were lacking across all companies surveyed, and very few other studies or surveys had been conducted or were underway.

Table 12. Number of Risk Assessment and Evaluation Studies/Surveys Conducted

	Number of studies or surveys conducted		
	MIC (n=5)	MGC (n=2)	LM (n=4)
Medicine utilization review study/drug use survey in the last year	1	0	0
Active surveillance study initiated or carried out in the last 5 years	0	0	0
Survey to determine level of medication errors in the last year	1	0	1

Device Companies

No activities to identify safety signals and evaluate the risks associated with device use are currently performed by the two companies interviewed. The companies do not collect suspected device adverse event reports in Ukraine so no reports were received by them in the last year and no cases were documented. No active surveillance activities, utilization studies, or efforts to determine the level of user errors have been conducted by the companies in Ukraine.

Risk Management and Communication

Pharmaceutical Companies

At the time of the assessment, there were no legal provisions in Ukraine requiring MAHs to prepare and submit RMPs or to implement risk minimization activities. Encouragingly, most companies surveyed were familiar with EMA and FDA requirements regarding risk management. The assessment found that eight companies marketed at least one product in Ukraine for which the FDA requires an RMP. However, only four companies (35 percent)—three MIC and one LM—had implemented such a plan and some type of risk mitigation activities in Ukraine (figure 24). Most of the companies interviewed do not implement risk mitigation activities but engage medical providers through marketing presentations, training, and disseminating articles and letters. RMPs and activities were rarely implemented by the two MGCs (mainly because of the lack of perceived need for generic products) and most LMs.

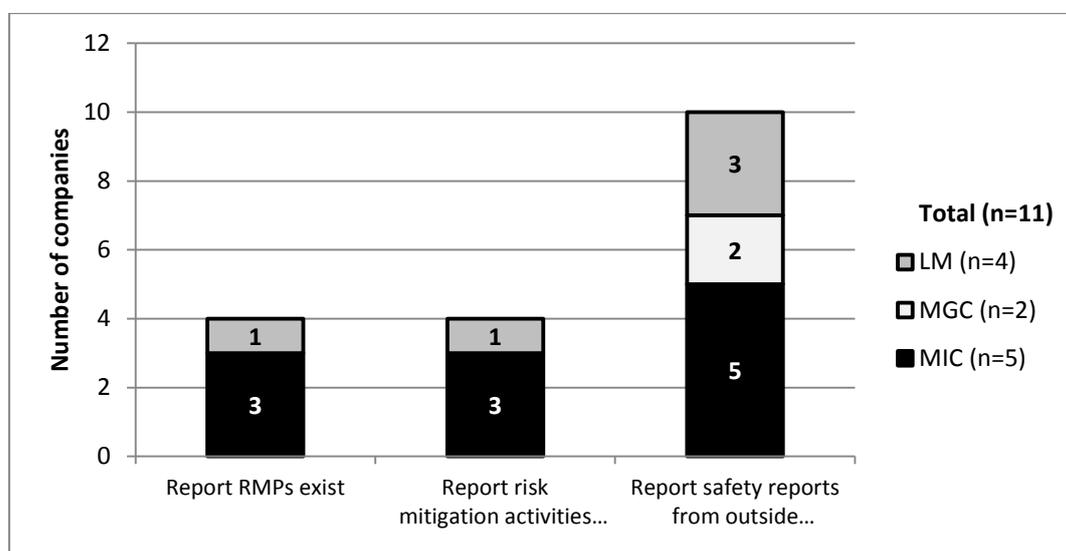


Figure 24. Pharmaceutical companies: implementation of RMPs, risk mitigation activities and monitoring of safety issues from outside sources

Communication activities were minimal in most pharmaceutical companies at the time of the assessment. In Ukraine, the SEC and the SAUMP take the lead on ensuring that significant safety issues and signals are promptly communicated to health workers and the public, and post safety communications and announcements on their respective websites and in the mass

media. In the last year, only three of the companies interviewed (27 percent)—one MIC and two LMs—had worked with the SEC to develop and distribute one or more “Dear Health Care Professional” letter.

Device Companies

Neither of the two device manufacturers had RMPs for any of their products or implemented any risk mitigation or communication activities in Ukraine. Nor is there any legal requirement for them to do so. The MDC said that they inform health workers and public about poor quality issues as soon as they get confirmation and approval from head office, however, there had not been any need to do so in the last year.

Summary of Findings: Current Situation of Pharmacovigilance Systems in Pharmaceutical Industry in Ukraine

Pharmaceutical Companies

The assessment findings for the situation of pharmacovigilance systems in the 11 pharmaceutical companies sampled are presented pictorially in figures 25 and 26. Of the 43 IPAT indicators, 30 were relevant to the pharmaceutical industry—19 core and 11 supplementary. These figures are constructed by converting the responses to the assessment questions and the indicators (disaggregated as core and supplementary) to “Yes/No” and using weighted scoring. For instance, the “Yes” responses to core indicators are scored 2 each and supplementary indicators scored 1. Figure 25 shows the average score for all 11 companies and figure 26, the average score for 5 MICs (green line), 2 MGCs (blue line), and 4 LMs (red line).

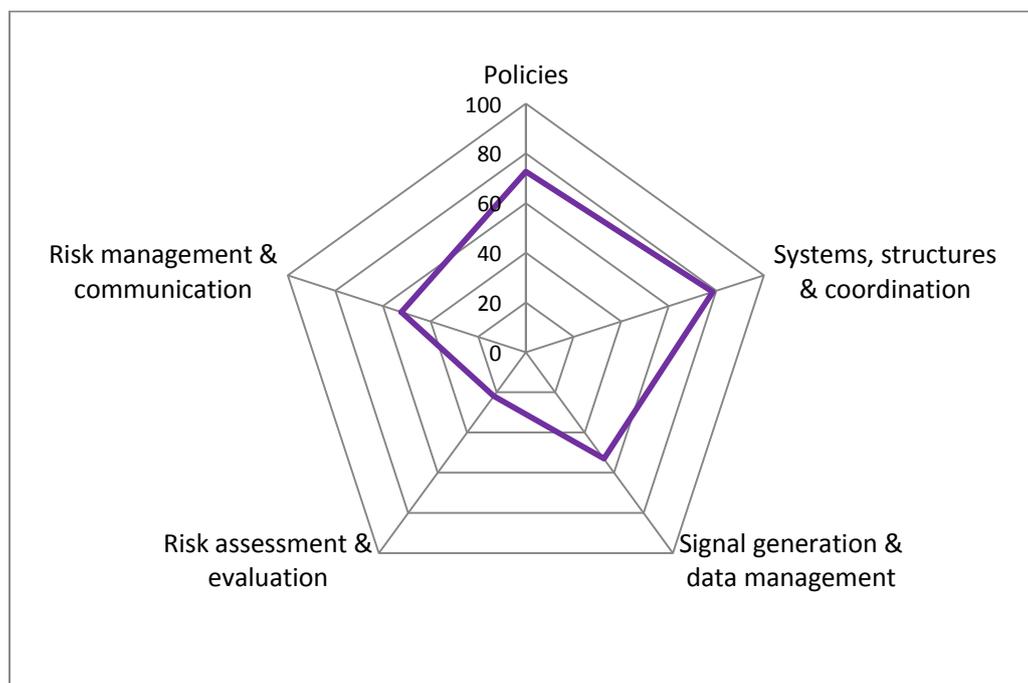


Figure 25. Pharmaceutical companies: current situation of pharmacovigilance system in sample of 11 companies (average of 5 MICs, 2 MGCs, and 4 LMs)

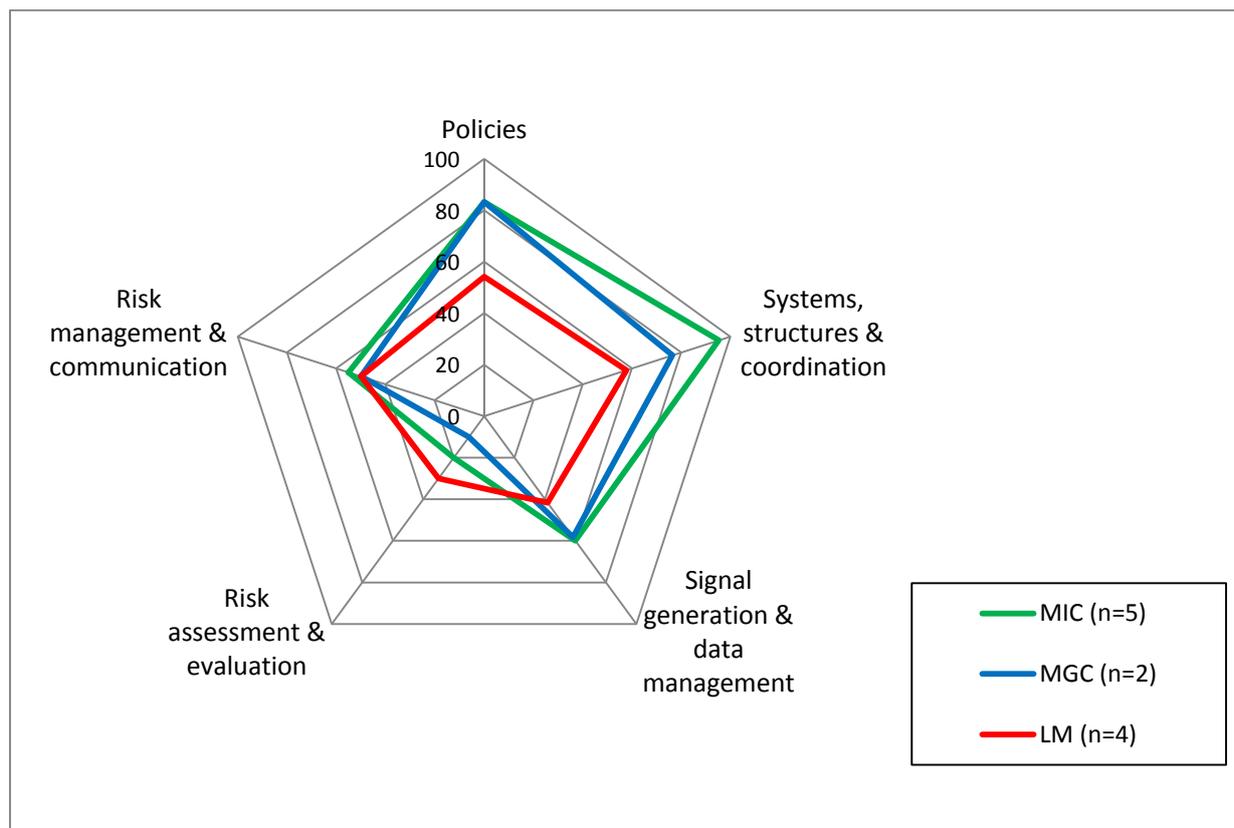


Figure 26. Pharmaceutical companies: current situation of pharmacovigilance system in a sample of five MICs, two MGCs, and four LMs

Overall, the findings related to pharmacovigilance policies and systems, structures, and coordination for the 11 pharmaceutical companies sampled are encouraging although there are some differences between local manufacturers and the multinational companies. With regard to industry pharmacovigilance policies and compliance with national legal provisions and standards, at the time of the assessment, the companies interviewed complied with existing national legal requirements. Although, local manufacturers in contrast to most multinational companies did not have certain pharmacovigilance policies included as part of their corporate policies, this was not then a requirement under Ukrainian legislation. Most of the multinational companies (MICs and MGCs) have systems and structures in place for pharmacovigilance in accordance with international standards. Across all companies, medicine information services are not well developed and appear to be poorly utilized at present. For LMs, three of the four companies have many procedures and systems in place, however the lack of pharmacovigilance-related information resources and formal mandatory training programs for staff are common weaknesses. All companies lack procedures for external audits as the SEC was not performing these audits at the time of the assessment.

In terms of signal generation and data management, although all companies have a central database for archiving medical safety documents and collating pharmacovigilance data, the local offices for four of the seven multinational companies interviewed cannot access it directly. Also for two of the four LMs, the database contains only spontaneous reports. Systems for tracking pharmacovigilance activities and for scanning the global literature are other areas where the findings indicate LMs can improve. The lack of forms for reporting

suspected medication errors and poor quality products are other potential areas that could be strengthened for all companies. Assessment findings indicate the greatest weaknesses lie in risk assessment and evaluation and also in risk management and communication. ADR reporting is low and none of the companies interviewed had conducted any active surveillance activities in the last five years. Similarly, RMPs and risk mitigation activities are absent in most MGCs and LMs interviewed and communication activities are minimal across all types of companies sampled.

Device Companies

Figure 27 shows the assessment findings for the small sample of device companies interviewed. The MDC has some policies and procedures, and systems and structures in place for device vigilance but these are mostly related to monitoring product quality at the local level. The findings for risk assessment and evaluation, and for risk management and communication indicate the absence of any such activities by the two companies interviewed.

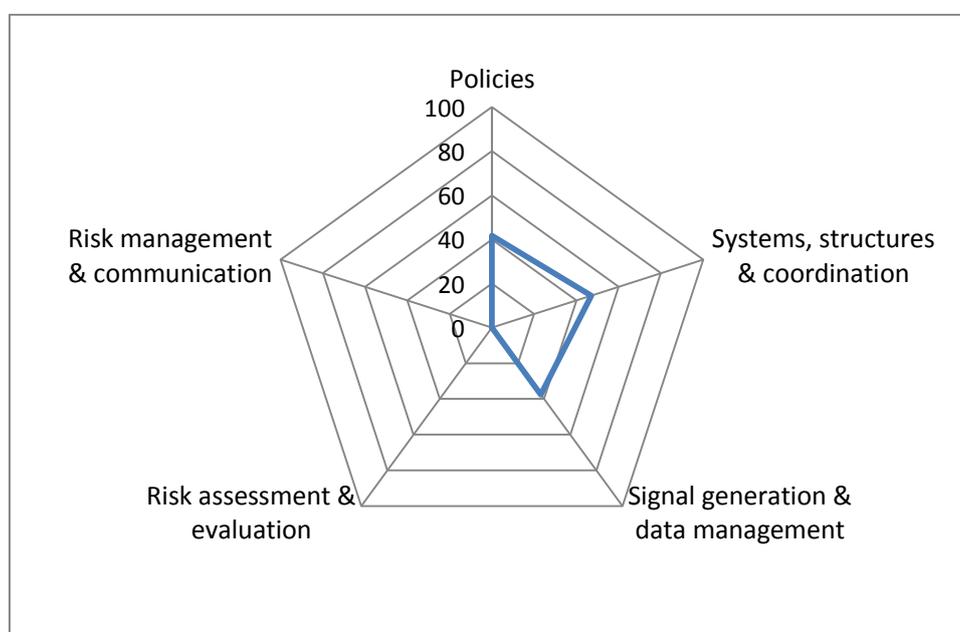


Figure 27. Medical device companies: current situation of pharmacovigilance system in sample of two companies (one MDC and one LDM)

Recommendations

- The regulated industry (also referred to as companies) should immediately develop or further enhance their policies, systems, and structures to facilitate their ability to fully comply to local regulations on pharmacovigilance. The industry should aim for high standards to safeguard the health of the patients and should commit to working closely with the SEC and the MoH to implement EU harmonized standards on pharmacovigilance within Ukraine.
- The industry should identify aspects of the current pharmacovigilance regulations that they are unclear about and seek clarifications from the SEC. There should be an

opportunity for dialogue between the SEC and industry in a neutral forum to discuss how the industry can better comply with pharmacovigilance legislations.

- Local pharmaceutical industries should strengthen their systems to meet regulatory standards. Although only four LMs participated in the assessment, taking that those four may be the very responsive companies it could be suspected that LMs are lagging behind in compliance to meeting pharmacovigilance responsibilities of the industry. The SEC should provide more support to LMs to develop their pharmacovigilance system including policy statements.
- Industry should improve all aspects of compliance to pharmacovigilance particularly for risk assessment and evaluation and risk management and communication.
- Industry should immediately strengthen their system for worldwide safety report scanning including the purchase of relevant resources to ensure that safety issues identified from outside sources for a product that is registered and in use in Ukraine, is promptly communicated to the SEC, health workers, and consumers.
- Industry, including the MGCs and LMs should immediately develop systems for internal pharmacovigilance audits.
- Industry should ensure that all safety data should be kept at one central location within the country and easily retrieved when needed by the SEC, health workers, or patients. The assessment found that in four companies (three of five MICs and one of two MGCs) the adverse events database is located at the global level and the local office sends information to it but cannot always access it directly themselves. That is not a good practice. The safety data should be readily available in Ukraine.
- Industry should develop minimum standards to guide the provision of medicine information service. These standards should identify minimum infrastructure and resources required for delivering medicines information services that will meet the expectations of the regulatory authority.
- Strengthen product quality reporting by ensuring that reporting forms are available electronically and everywhere the product is available to enable health workers and consumers to report on suspected product quality issues.
- Industry should implement active surveillance activities. The assessment found that the industry hardly conducts active surveillance studies in Ukraine. The SEC, industry, academia, and development organizations should develop a relationship to build the infrastructure to support pooling resources to study safety concerns of public health importance.
- Industry should work with the SEC to conduct risk management practices. RMPs should be consistent with similar requirements by the EMA and other competent authorities in the EU.
- Industry should collaborate with the SEC to improve safety communication to health workers and consumers. The industry should ensure that “Dear Health Care Professional”

letters approved by the SEC are actively disseminated and confirmed to have reached the target audience.

- Industry should submit sales and utilization data on their products to the SEC. Consistent with the Volume 9A requirements under the roles and responsibilities of market authorization holders, “The marketing authorization holder is also responsible for on-going pharmacovigilance evaluation during the post-authorization period and for ensuring that any request from the competent authorities for the provision of additional information necessary for the evaluation of the benefits and the risks afforded by a medicinal product is answered fully and promptly, including the provision of information about the volume of sales or prescriptions of the medicinal product concerned.”
- Industry should support the conduct of regulatory impact assessment for products placed on the market for which the SEC took a regulatory decision. For instance, companies should study if changes in indications as a result of recent regulatory decisions are seen in prescription patterns. Also companies should report off label use and their plans to limit that.
- Industry should support the SEC to establish legislations, regulations, and guidance documents for the medical devices industry. These regulations can be adapted from the GHTF guidelines. Ukraine currently does not have legal provisions requiring MAHs to report adverse events to medical devices or to conduct post-marketing surveillance activities. The industry, particularly those marketing high risk devices, should implement GHTF vigilance guidelines as they would in countries with stringent regulatory systems.

SUMMARY OF RECOMMENDATIONS

Policy, Law, and Regulation

- The MoH should update the Law “on Medicines” by incorporating articles on pharmacovigilance and taking into account the pharmacovigilance provisions in the EU legislation particularly the new pharmacovigilance legislation (Regulation 1235/2010 and Directive 2010/84/EU). The proposed addition to the legislation may include statutory powers for the SEC to require post-authorization studies from the MAH, risk management, and monitoring of utilization of health products in Ukraine.
- The MoH, the SEC, and the SAUMP should take measures to immediately address incongruences and gaps in the provisions of the existing legislation regulating medicine registration and safety controls that relate to interactions and regulatory decision-making connected with medicines safety in particular, for anti-TB- and ART-related medicinal products and MIBPs.
- The MoH working together with the SAUMP should develop and implement Ukrainian Laws and Orders related to post-marketing surveillance of medical devices. The regulatory infrastructure should be based upon the GHTF Medical Devices Post Market Surveillance: Global Guidance for Adverse Event Reporting for Medical Devices.
- The SEC should facilitate the implementation of the pharmacovigilance provisions recently introduced into Ukrainian legislation as provided for by MoH Order No. 898 approved 27.12.2006 with amendments of MoH Order No. 1005 approved 29.12.2011 requiring greater compliance from the industry and health care sector. Requirements in some key areas in the industry include PSUR and product benefit/risk profile, compliance with post-authorization safety study requirements, and enhance adverse events reporting and traceability of specific biologics.
- Once EU GVP guidelines for the implementation of the 2010 pharmacovigilance legislation are in place, the MoH and the SEC should develop comprehensive national pharmacovigilance guidelines in Ukraine. The guidelines should be equivalent to the EU GVP guidelines. The SEC with input from all relevant stakeholders should develop and implement the guidelines which will facilitate implementation and adherence to the provisions of national legislation in pharmacovigilance and development of the pharmacovigilance system.
- The SEC should develop and obtain MoH approval for a plan of action to implement the provisions on the newly developed legislation in pharmacovigilance.

Systems, Structures, and Stakeholder Coordination

- The MoH should consider the necessity for setting up the advisory committee on medicines safety to provide technical advice and scientific opinions on safety issues related to medicinal products and medical devices, and provide strategic advice on strengthening national pharmacovigilance system and the quality of pharmacovigilance activities.

- The MoH should define minimum requirements for PHP pharmacovigilance activities. Such requirements may include the condition that PHPs that expose a certain number of the population to medicines should develop pharmacovigilance plans before the introduction of new medicines (like medicines for MDR-TB), have a focal person for pharmacovigilance who is a liaison with the SEC, and include pharmacovigilance indicators (for example; rates of ADR/toxicity-related switches) as part of program indicators.
- The Government of Ukraine is advised to consider providing a dedicated budget for pharmacovigilance to support the development and conduct of training courses for medical workers, with an initial focus on priority national health programs. To promote effective coordination in post-marketing surveillance, the MoH, the SEC, the SAUMP, and the PHPs are advised to ensure that all staff engaged in product safety monitoring are trained and are aware of procedures set out in relevant regulations. The MoH and the SEC are advised to develop an Order on including pharmacovigilance into pre- and in-service medical and pharmaceutical education curricula.
- The SEC with the agreement of the MoH should develop relevant guidance documents for implementation of post-marketing surveillance in health care facilities and industry. The SAUMP with the agreement of the MoH should develop relevant guidance documents for implementation of post-marketing surveillance for medical devices in health care facilities and industry.
- Strengthen pharmacovigilance at the regional and health facility level. The SEC is advised to review the organizational structure of the pharmacovigilance system at regional level to strengthen human resource capacity and establish pharmacovigilance audit units to facilitate the implementation of pharmacovigilance at the local level. Options for mobilizing resources to enhance post-marketing surveillance should be explored during the review. The SEC and the MoH should also establish clinical pharmacists into the organizational structure as per Order No. 33, develop appropriate information software to enable active surveillance within hospitals on medicine safety and effectiveness, and provide information systems on drug interactions as part of the interventions to strengthen pharmacovigilance at the regional and health facility level.
- The pharmaceutical industry (including medical device companies) should immediately develop or further enhance their policies, systems, and structures to facilitate their ability to comply with local regulations on pharmacovigilance. The industry should aim for high standards to safeguard the health of the patients and should commit to working closely with the SEC and the MoH to implement EU harmonized standards on pharmacovigilance within Ukraine.
- The industry should identify aspects of the current pharmacovigilance regulations that they are unclear about and seek clarifications from the SEC, the MoH and the SAMP.
- Industry should ensure that all safety data is kept at one central location within the country and easily retrieved when needed by the SEC, health workers, or patients.

Signal Generation and Data Management

- The SEC should explore the necessity and opportunities for exchange of suspected ADR data with the EMA through Eudravigilance.
- The SAUMP in coordination with MoH and its structural units should improve the reporting of product quality problems and adverse events to medical devices from health workers and consumers through the development of specific reporting forms.
- The MoH and the SEC should develop a system for the reporting, collection, and evaluation of information on potential and actual medication errors to help identify strategies for minimizing their occurrence.
- The SEC and the lead institutions of the MoH and National Academy of Medical Sciences responsible for blood transfusion issues should develop forms for reporting of adverse events from use of blood products.
- The SEC should develop tools for the enhancement of adverse events reporting and access to information. SEC should explore opportunities for using information technology (including embedding of the ADR form in the electronic medical records and other electronic health records such as the eTB Manager, use of cell phones for consumer reporting, etc.) to enhance adverse events reporting. Opportunities for increasing the submission of reports electronically to the SEC should also be explored. These efforts will automate reporting, facilitate submission, reduce the burden on reporters, and improve the quality of reports.
- The SEC should ensure public access to safety information through improved dissemination, publication and communications regarding ADRs of medicinal products.
- The MoH should require health facilities and PHPs to improve adverse events reporting. The MoH, SEC and the State Services responsible for HIV/AIDS and TB PHPs should develop approaches to TB and ARV medicines safety and efficacy monitoring in health facility inpatient departments to quantify and characterize the incidence and the risk of short- and long-term toxicities experienced by patients on treatment as well as the rational use of medicines.
- The SEC should develop strategies for reducing incomplete and duplicate reports. The SEC should develop a unified central data warehouse and standard electronic tool for workload and activities tracking.
- The SEC should develop additional methodologies and tools to support risk assessment and data mining. As the number of reports in the SEC database increases, it provides a great opportunity for risk assessment. The SEC should undertake a review to determine if it is getting maximum results from the huge number of reports available through the medicines adverse events database and the vaccine reports available through the SEC's Department of Immunobiological Medicines and Immunoprophylaxis.

- In line with recent standards for the electronic transfer of regulatory information, the SEC should develop plans to upgrade its database for the electronic submission and exchange of reports using ICSR XML schema.

Risk Assessment and Evaluation

- The MoH and the SEC are advised to consider setting up a risk evaluation unit in the Post-Marketing Surveillance Board. Some of the potential roles of this unit are to develop systems for active surveillance in Ukraine, determine research priorities on safety and quality of health products, define criteria and need for post-authorization safety and effectiveness studies, establish sentinel sites for active surveillance, and link Ukraine to global safety surveillance networks. The unit should also develop systems for registering ongoing and completed studies that have safety as an outcome of interest and develop steps for the use of information from safety studies for regulatory and treatment guidelines decision making.
- The SEC should develop strategies for improving active surveillance. The need for active surveillance for the evaluation of safety signals is more profound within the PHPs where spontaneous reporting does not have the capacity to uncover events of long latency. With the high burden of TB and HIV, Ukraine should develop systems for active surveillance and participate in cohort event monitoring collaborations. Observational cohorts based at health facilities are potentially valuable sources of information regarding medicine use, treatment effectiveness, and adverse events.
- The SEC should develop an electronic tool that can be used as a sustainable platform for active surveillance activities across PHPs and several chronic disease medicines and vaccines. The MoH should use these platforms to implement active surveillance studies in PHPs to facilitate the quantification and characterization of the incidence and the risk of short- and long-term toxicities experienced by patients on treatment. The information collected from these active surveillance activities can be used for revising the treatment guidelines, preventing adverse events, improving adherence, and improving treatment outcomes. It is important to develop a sustainable system rather than ad hoc engagement in individual studies that are not addressing priority safety concerns and data generated that are not reviewed for policy decisions.
- All stakeholders should improve all aspects of compliance to pharmacovigilance particularly for risk assessment, evaluation, and minimization as this is an emerging area that can have significant results. Stakeholders, including the industry should implement active surveillance activities. The SEC, industry, academia, and development organizations should develop a relationship to build the infrastructure to support pooling of resources to study safety concerns of public health importance.

Risk Management and Communication

- The SEC should strengthen risk management practices to ensure safe use of medicines and prevent occurrences of preventable adverse reactions.

- The SEC should improve the provision of medicines information to health care workers and the public as part of efforts to improve safe and rational use of medicines, vaccines and other medicinal products.
- The SEC should improve the provision of information to health care workers and the public as part of efforts to improve safe and rational use of medical devices.
- The SAUMP and the SEC should explore opportunities for improving information sharing amongst themselves and the public on the safety and quality of health products in Ukraine. With the ascension of Ukraine as member of PIC/S opportunities for sharing inspection and regulatory information should be maximized and other avenues for safety information sharing developed. Through this membership Ukraine can reduce exposure to risky manufacturers and prevent some adverse events that would have occurred from using poor quality product from such manufacturers.
- The SEC should collaborate with and strengthen Formulary Committees to ensure effective interactions between the pharmacovigilance and the formulary systems at all levels and monitor adherence of institutions to standard treatment guidelines which is a key strategy for managing risk.
- The Health Minister of the Autonomous Republic of Crimea, chiefs of health care oblast boards and municipal health care boards of Kyiv and Sevastopol should ensure the timely dissemination of medicines safety information originating from the MoH, the SEC and other information sources such as MAHs to all health care facilities and health care staff in Ukraine.
- The SEC should improve the active distribution of safety communications and publications by implementing an urgent medicines product safety warning and alert system. The SEC should develop a system for tracking the distribution and readership of its risk communication materials. The SEC should develop SOPs to standardize practices across all the health-related toll-free hotlines being implemented in Ukraine to ensure that calls related to adverse events and safety information requests are addressed in a standard manner.
- Industry should immediately strengthen their system for worldwide safety report scanning including the purchase of relevant resources to ensure that safety issues identified from outside sources for a product that is registered and in use in Ukraine, is promptly communicated to the SEC, health workers, and consumers.
- The industry should improve the distribution of medicines safety information to the MoH, the SEC, and the health care staff.
- Industry should develop minimum standards to guide the provision of medicine information service. These standards should identify minimum infrastructure and resources required for delivering medicines information services that will meet the expectations of the regulatory authority.
- Industry should collaborate with the SEC to improve safety communication to health workers and consumers. The industry should ensure that “Dear Health Care Professional”

letters approved by the SEC are actively disseminated and confirmed to have reached the target audience.

CONCLUSION

This assessment of the pharmacovigilance system in Ukraine identified major achievements by the MoH and the SEC in establishing basic structures, systems, and processes for improving safety of medicines and MIBPs. Ukraine has achieved the best overall results so far in 40 pharmacovigilance systems country assessments conducted with the IPAT to date. However, weaknesses exist in systems and processes particularly with regard to post-marketing surveillance of medical devices, implementation of pharmacovigilance activities at the local levels, and active surveillance. The assessment and analysis of the pharmacovigilance system has highlighted those limitations and made recommendations for improvement. Further efforts are required to link existing activities together for a comprehensive and robust pharmacovigilance system.

Incorporating active approaches while strengthening the passive surveillance system, implementing risk management, coordinating all stakeholders and their contributions, and developing a legislative base for surveillance of medical devices can further enhance the impact of pharmacovigilance and medicine safety systems, and ultimately, improve quality of care and patient safety. Opportunities should be exploited by all stakeholders to implement the recommendations set out in this report.

ANNEX A. SUMMARY OF IPAT INDICATORS¹²⁴

Indicator Number	Indicator	Core/ Supplementary	Type of Indicator	Data Collection Level	Recommended Frequency of Measurement
Component 1. Policy, Law, and Regulation					
1.1	Existence of a policy document that contains essential statements on pharmacovigilance or medicine safety (stand alone or as a part of some other policy document)	Core	Structural	MoH, PHP	Every 5 years
1.2	Existence of specific legal provisions for pharmacovigilance in the national medicines legislation or similar legislation	Core	Structural	MoH	Every 5 years
1.3	Legal provisions require that the marketing authorization holder mandatorily report all serious ADRs to the national drug regulatory authority	Supplementary	Structural	MoH	Every 5 years
1.4	Legal provisions require the marketing authorization holder to conduct the same or similar post-marketing surveillance activities for products as required by stringent regulatory authorities	Supplementary	Structural	MoH	Every 5 years
Component 2. Systems, Structures, and Stakeholder Coordination					
2.1	Existence of a pharmacovigilance center or unit	Core	Structural	MoH, PHP, HF	Every 5 years
2.2	Pharmacovigilance center or unit has a clear mandate, structure, roles, and responsibilities	Core	Structural	MoH, PHP, HF	Every 5 years

¹²⁴ SPS Program. 2009. *Indicator-Based Pharmacovigilance Assessment Tool: Manual for Conducting Assessments in Developing Countries*. Submitted to the U.S. Agency for International Development by the SPS Program. Arlington, VA: Management Sciences for Health.

Indicator Number	Indicator	Core/ Supplementary	Type of Indicator	Data Collection Level	Recommended Frequency of Measurement
2.3	Existence of a medicine information or pharmacovigilance service that provides ADR and drug safety-related question-and-answer services	Core	Structural	MoH, PHP, HF	Annually
2.4	A designated staff responsible for pharmacovigilance or medicine safety activities	Core	Structural	MoH, PHP, HF	Annually
2.5	Dedicated budget available for pharmacovigilance-related activities	Core	Structural	MoH, PHP, HF	Annually
2.6	Existence of a national medicine safety advisory committee or a subcommittee with similar functions that has met at least once in the last year	Core	Structural	MoH	Annually
2.7	Existence of national pharmacovigilance guidelines updated within the last five years	Core	Structural	MoH	Every 5 years
2.8	Existence of protocols or SOPs for improving patient safety relating to medicine use	Core	Structural	MoH, PHP, HF	Annually
2.9	Existence of a minimum core list of communication technologies to improve access to safety reporting and provision of medicine information	Core	Structural	MoH, PHP, HF	Annually
2.10	Existence of an ADR or medicine safety bulletin (or any other health-related newsletter that routinely features ADR or medicine safety issues) published in the last six months	Core	Structural	MoH, PHP, HF	Annually
2.11	Percentage of predefined core reference materials available in the medicine information or pharmacovigilance center	Supplementary	Process	MoH, PHP, HF	Annually

Indicator Number	Indicator	Core/ Supplementary	Type of Indicator	Data Collection Level	Recommended Frequency of Measurement
2.12	Percentage of predefined core pharmacovigilance topics present in the preservice training curricula (disaggregated by medicine, pharmacy, nursing, and public health curricula)	Supplementary	Process	Universities, health profession council	Annually
2.13	Number of health care providers trained on pharmacovigilance and medicine safety in the last year	Supplementary	Process	MoH, PHP, HF	Annually
2.14	Platform or strategy exists for the coordination of pharmacovigilance activities at the national level	Core	Process	MoH	Annually
2.15	National pharmacovigilance center is a full or associate member of the WHO Programme for International Drug Monitoring	Supplementary	Structural	MoH	Every 5 years
Component 3. Signal Generation and Data Management					
3.1	Existence of a system for coordination and collation of pharmacovigilance data from all sources in the country (e.g., health programs, immunization program, active surveillance studies)	Core	Process	MoH	Annually
3.2	Existence of a database for tracking pharmacovigilance activities	Core	Process	MoH	Annually
3.3	Existence of a form for reporting suspected ADRs	Core	Process	MoH, PHP, HF	Annually
3.4	Existence of a form for reporting suspected product quality issues (as a subset in the ADR form or as a separate form)	Core	Process	MoH, PHP, HF	Annually

Indicator Number	Indicator	Core/ Supplementary	Type of Indicator	Data Collection Level	Recommended Frequency of Measurement
3.5	Existence of a form for reporting suspected medication errors (as a subset in the ADR form or as a separate form)	Core	Process	MoH, PHP, HF	Annually
3.6	Existence of a form for reporting suspected treatment failure (as a subset in the ADR form or as a separate form)	Core	Process	MoH, PHP, HF	Annually
Component 4. Risk Assessment and Evaluation					
4.1	Number of medicine utilization reviews carried out in the last year	Supplementary	Process	MoH, PHP, HF	Annually
4.2	Pharmaceutical product quality survey conducted within the last five years	Supplementary	Process	MoH	Every 5 years
4.3	Incidence of medication errors quantified in the last year	Supplementary	Process	MoH, PHP, HF	Annually
4.4	Number of ADR reports received in the last year	Core	Process	MoH, PHP, HF	Annually
4.5	Number of active surveillance activities currently ongoing or carried out in the last five years	Core	Process	MoH, PHP, HF	Every 5 years
4.6	Percentage of patients in public health programs for whom drug-related adverse events were reported in the last year (disaggregated by type of adverse event, drug, severity, outcomes, and demographics)	Core	Process	MoH, PHP, HF	Annually
4.7	Percentage of patients undergoing treatment within a public health program whose treatment was modified because of treatment failure or ADRs in the last year (disaggregated by treatment failure and ADRs)	Core	Process	MoH, PHP, HF	Annually

Indicator Number	Indicator	Core/ Supplementary	Type of Indicator	Data Collection Level	Recommended Frequency of Measurement
4.8	Percentage of patients in public health programs for whom drug-related, serious “unexpected adverse events” were reported in the last year	Supplementary	Process	MoH, PHP, HF	Annually
Component 5. Risk Management and Communication					
5.1	Risk mitigation plans currently in place that are targeted at high-risk medicines	Supplementary	Outcome	MoH, PHP, HF	Annually
5.2	Prequalification schemes (e.g., WHO prequalification program and Pharmaceutical Inspection Co-operation Scheme) used in medicine procurement decisions	Supplementary	Outcome	MoH, PHP	Annually
5.3	Number of medicine safety information requests received and addressed in the last year	Supplementary	Outcome	MoH, PHP, HF	Annually
5.4	Percentage of planned issues of the medicine safety bulletin (or any other health-related newsletter that routinely features ADR or medicine safety issues) published in the last year	Supplementary	Outcome	MoH, PHP, HF	Annually
5.5	Number of medicine safety issues of local relevance identified from outside sources (e.g., from another country, or from regional or international sources) and acted on locally in the last year	Supplementary	Outcome	MoH, PHP, HF	Annually
5.6	Number of “Dear Health Care Professional” letters or other safety alerts developed and distributed in the last year	Supplementary	Outcome	MoH, PHP, HF	Annually

Indicator Number	Indicator	Core/ Supplementary	Type of Indicator	Data Collection Level	Recommended Frequency of Measurement
5.7	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	Core	Outcome	MoH, PHP, HF	Annually
5.8	Percentage of the sampled Drug and Therapeutics Committees that have carried out pharmacovigilance activities or addressed medicine safety issues in the last year	Core	Outcome	MoH, HF	Annually
5.9	Number of public or community education activities relating to medicine safety carried out in the last year	Supplementary	Outcome	MoH, PHP, HF	Annually
5.10	Percentage of medicines sampled in the last year that passed product quality tests	Core	Outcome	MoH, PHP, HF	Annually

ANNEX B. LIST OF DOCUMENTS REVIEWED

Laws and Regulatory Documents

Law of Ukraine “On Medicines” (as amended) of April 4, 1996, No. 124/96-VR

Cabinet of Ministers of Ukraine Decree of 05.26.2005 No. 376 “On approval of the procedure for state registration (re-registration) of medicinal products and amounts of fees for their state registration (re-registration).”

Decree of the President of Ukraine of 04.08.2011 No. 440 “On approval of regulations on State Service of Ukraine on Medicines and Health Products.”

Order of the Ministry of Health of Ukraine of 06.17.2005 No. 287 “On approval of the interaction between the State Service for Medicines and Health Products MoH of Ukraine and the State Pharmacological Center MoH of Ukraine in the sphere of medicines circulation.”

Order of the Ministry of Health of Ukraine of 08.26.2005 No. 426 “Procedure for conducting expert evaluation of materials pertinent to medicinal products, which are submitted for state registration (re-registration) and expert evaluation of materials about introduction of changes to the registration documents during the validity period.”

Order of the Ministry of Health of Ukraine of 12.27.2006 No. 898 “About approval of procedure for surveillance over adverse reactions to medicinal products permitted for medical use”

Order of the Ministry of Health of Ukraine of 08.17.2007 No. 190 “On approval of the procedure for conducting additional studies of medicinal products during expert evaluation of registration materials.”

Order of the Ministry of Health of Ukraine of 04.06.2009 No. 406 “On measures to make safe medical application in the territory of Ukraine of co-formulated non-steroidal anti-inflammatory medicinal products.”

Order of the Ministry of Health of Ukraine of 07.22.2009 No. 529 “Provision on Formulary Committees of Autonomous Republic of Crimea MoH, health care boards of oblast and Kyiv and Sevastopol municipal state administrations.”

Order of the Ministry of Health of Ukraine of 07.24.2009 No. 531 “On approving the Order of medicines safety and efficacy monitoring and inpatient health care facilities.”

Order of the Ministry of Health of Ukraine of 09.01.2009 No. 654 “On approval of plan of measures for improving post registration surveillance over safety and efficacy of medicinal products in hospitals.”

Order of the Ministry of Health of Ukraine of 09.23.2009 No. 690 “procedure for conducting clinical trials of medicinal products and expert evaluation of materials of clinical trials.”

Order of the Ministry of Health of Ukraine of 12.14.2009 No. 944 “Procedure for Conducting Pre-clinical Study of Medicinal Products and Expert Evaluation of Materials of Pre-clinical Study.”

Order of the Ministry of Health of Ukraine of 01.26.2010 No. 55 “Procedure for conducting expert evaluation of materials pertinent to medicinal products of limited use which are submitted for State Registration (Re-registration).”

Order of the Ministry of Health of Ukraine of 03.17.2010 No. 236 “Procedure for inspecting manufacturing site for medicinal products submitted for state registration.”

Order of the Ministry of Health of Ukraine of 04.15.2010 No. 334 “On the temporary prohibition of use of medicines that contain active substance sibutramine.”

Order of the Ministry of Health of Ukraine of 08.31.2010 No. 736 “On measures for implementation of monitoring of safety and efficacy of medicinal products in hospitals.”

Order of the Ministry of Health of Ukraine of 10.28.2010 No. 917 “On the temporary prohibition to use medicines that contain active substance rozyhlitazon.”

Order of the Ministry of Health of Ukraine of 08.16.2011 No. 595 “On the procedure of prophylactic immunization in Ukraine and control of immunobiological medicines quality and circulation.”

Order of the Ministry of Health of Ukraine of 11.22.2011 No. 809 “On approval of the procedure on establishment of prohibition (temporary prohibition) and renewal of circulation of medicinal products within the territory of Ukraine.”

Order of the Ministry of Health of Ukraine of 12.29.2011 No. 1005 “On making changes to the MoH of Ukraine Order No. 898 of 12.27.2006.”

Public Health Program Operational Plans and Standard Treatment Guidelines

National Programme Against Tuberculosis for 2007-2011

“On Approval of Instructions for Care Delivery to People with TB” approved under MoH Order No. 385 (2006)

“Standard of Medical Care Delivery to Patients with Drug-Resistant Tuberculosis” approved under MoH Order No. 600 (2008) as amended by MoH Order No. 108 (2012)

“Clinical Protocol for Provision of Health Care Services to Patients with TB/HIV co-infection” approved under MoH Order No. 276 (2008).

National Programme on HIV Prevention, Treatment, Care and Support for HIV-Infected and AIDS Patients for 2009–2013.

"On Approval of Regulations of the Clinical Protocol for Antiretroviral Therapy of HIV Infection in Adults and Adolescents" approved under MoH Order No. 551(2010)

Documents and Presentations and State Expert Centre and State Administration of Ukraine on Medicinal Products

State Expert Center, Ministry of Health of Ukraine. 2012. *Major performance indicators of the pharmacovigilance system in Ukraine in 2011.*

State Expert Centre, Ministry of Health of Ukraine (undated) presentation
Pharmacovigilance system in Ukraine: history, results, objectives.

Matvieieva, O. State Expert Centre, Ministry of Health of Ukraine. 2010 presentation
Pharmacovigilance in Ukraine: Formation and Challenges.

Matvieieva, O. State Expert Centre, Ministry of Health of Ukraine. 2010 presentation
Pharmacovigilance in Ukraine: focus on ARV treatment.

State Administration of Ukraine on Medicinal Products. January 10, 2012. *Major indicators of activities of subdivisions of the State Administration of Ukraine on Medicinal Products, 2011.*

Other Documents

Joint Evaluation Mission WHO/EURO, Delegation of EU Commission in Ukraine and USAID Regional Mission for Ukraine, Belarus and Moldova. July 2008. *Procurement and Supply Management of HIV/AIDS and Tuberculosis Medicines and Related Commodities in Ukraine.*

Perehinets I., WHO Country Office in Ukraine: *Pharmacovigilance (PV) in HIV treatment in Ukraine: Situation Analysis.* Presentation in Dar es Salaam (November 23-28, 2009).
Available at: <http://www.who.int/hiv/topics/pharmacovigilance/ukraine.pdf>

Stefanov, O., M. Sharayeva and V. Jajtchenja. 2004. Development of pharmacovigilance system in Ukraine: first results. *Pharmacoepidemiol Drug Saf* 13(3):197–199.

Vaidya, S. S., J. J. Guo, P. C. Heaton, and M. Steinbuch. 2010. Overview and comparison of post-marketing drug safety surveillance in selected developing and well-developed countries. *Drug Information Journal*, 44(5), p.519-533. Available at:
http://www.diahome.org/DIAHome/resources/content.aspx?type=eopdf&file=/productfiles/8357/diaj_36875.pdf

ANNEX C. REFERENCE LISTS FOR DATA COLLECTION

List of Basic Reference Materials and Resources for Pharmacovigilance

PHPs, SEC Regional Affiliates, and Health Facilities

- Law of Ukraine “On Medicines” (as amended) # 124/96BP of April 4, 1996
- Order of the Ministry of Health of Ukraine of 12.27.2006 No. 898 “About approval of procedure for surveillance over adverse reactions to medicinal products permitted for medical use”
- Register of medicinal products registered in Ukraine
- The State Formulary of Medicinal Products
- State Expert Center, Ministry of Health, Ukraine website <http://www.pharma-center.kiev.ua/view/index>
- *Apteka*
- *Rational Pharmacotherapy*

SAUMP Territorial Subdivisions

- Law of Ukraine “On Medicines” (as amended) # 124/96BP of April 4, 1996
- Order of the Ministry of Health of Ukraine of 12.27.2006 No. 898 “About approval of procedure for surveillance over adverse reactions to medicinal products permitted for medical use”
- Register of medicinal products registered in Ukraine
- State Expert Center, Ministry of Health, Ukraine website <http://www.pharma-center.kiev.ua/view/index>
- *Apteka*

Pharmaceutical Companies

- Law of Ukraine “On Medicines” (as amended) # 124/96BP of April 4, 1996
- Order of the Ministry of Health of Ukraine of 12.27.2006 No. 898 “About approval of procedure for surveillance over adverse reactions to medicinal products permitted for medical use”
- Register of medicinal products registered in Ukraine
- The State Formulary of Medicinal Products
- State Expert Center, Ministry of Health, Ukraine website <http://www.pharma-center.kiev.ua/view/index>
- *Apteka*
- *Rational Pharmacotherapy*

ANNEX D. LIST OF PUBLISHED PHARMACOVIGILANCE AND MEDICINE SAFETY STUDIES CONDUCTED IN UKRAINE

Khalangot M, Tronko M, Kravchenko V, Kovtun V. 2009. Glibenclamide-related excess in total and cardiovascular mortality risks: data from large Ukrainian observational cohort study. *Diabetes Res Clin Pract* 86(3):247-53. Epub 2009.

Khalangot M, Kravchenko V, Tronko M, Gurianov V. 2009. Glibenclamide-related excess in total and cardiovascular mortality risks: data from large Ukrainian observational cohort study. *Eur J Intern Med* 20(6):611-5. Epub 2009 May 24.

Likhonosov PN, Khalangot ND. 2007. [Levels of some auto-antibodies and C-peptide in insulin-treated patients with diabetes mellitus (DM) depending on gender of the patients and disease duration]. *Lik Sprava* 2007 5-6:50-5. Russian.

Tronko ND, Khalangot ND, Kravchenko VI, Kulchinskaia IaB, Gurianov VG, Misko LA. 2004. [Incidence of proliferative retinopathy and sex-related differences in death rate among patients with diabetes mellitus and sight impairment treated with insulin (according to the data from national diabetic registry)]. *Lik Sprava* 7:29-32. Russian.

Khalangot, ND, Koka MA, Latypova GA, Bakhtiarova AA. 2004. [Insulin edema in patients with diabetes mellitus and recent diabetic ketoacidosis (epidemiology and case reports)]. *Lik Sprava* 8:39-43. Russian.

Tronko ND, Khalangot ND, Kravchenko VI, Kulchinskaia IaB, Gurianov VG, Misko LA. 2004. [Incidence of proliferative retinopathy and sex-related differences in death rate among patients with diabetes mellitus and sight impairment treated with insulin (according to the data from national diabetic registry)]. *Lik Sprava* 7:29-32. Russian.

Chumak VT, Morozov AM, Matveyeva OV, Viktorov OP, Pushkar LO, Yaychenya VP, Yevko OI, Logvina OI, Pariy VD, Myshkovskiy VS, Tolstanov OK, Yakovleva LV. *Experience of introducing the new method of collecting information on adverse drug effects of medicinal products*. (unpublished document) State Enterprise (State Pharmacological Center) of the Ministry of Health Care of Ukraine, n.d.

**ANNEX E. LIST OF PHASE III/IV CLINICAL TRIALS ONGOING IN UKRAINE
THAT HAVE SAFETY AS AN OUTCOME OF INTEREST**

NCT¹²⁵ No.	Title	Sponsor	Phase	Status
00042088	A Randomized, Open-label, Multi-center, Phase II/III Study on Treatment With ABR-217620 Combined With IFN-alpha vs. IFN-alpha Alone in Patients With Advanced Renal Cell Carcinoma.	Active Biotech AB	II/III	Ongoing
00941616	An Open-label, Multi-centre Study to Assess the Pharmacokinetics, Efficacy and Safety of Biostate® in Subjects With Von Willebrand Disease.	CSL Behring/Parexel	II/III	Ongoing
01129674	A Long-Term, Open-Label, Multicenter Study of LY2140023 Compared to Atypical Antipsychotic Standard of Care in Patients With DSM-IV-TR Schizophrenia	Eli Lilly and Company	II/III	Ongoing
00420888	A Randomized, Open-label, Multi-center, Phase II/III Study on Treatment With ABR-217620 Combined With IFN-alpha vs. IFN-alpha Alone in Patients With Advanced Renal Cell Carcinoma.	Active Biotech AB	II/III	Ongoing
01283594	A Double-blind, Randomized, Placebo-controlled Study of the Safety and Efficacy of SYN115 as Adjunctive Therapy in Levodopa-treated Parkinson's Subjects With End of Dose Wearing Off	Biotie Therapies Inc	II/III	Ongoing
01521143	A Randomized, Double-Blinded, Placebo-Controlled Trial of Cvac as Maintenance Treatment in Patients With EOC in CR Following First-Line Chemotherapy	Prima BioMed Ltd	II/III	Ongoing
01129674	A Long-Term, Open-Label, Multicenter Study of LY2140023 Compared to Atypical Antipsychotic Standard of Care in Patients With DSM-IV-TR Schizophrenia	Eli Lilly and Company	II & III	Ongoing
00413699	A Long-Term, Open-Label Follow-Up Study Of Tasocitinib (CP-690,550) For Treatment Of Rheumatoid Arthritis	Pfizer	II & III	Ongoing
00324155	A Multi-center, Randomized, Double-Blind, Two-Arm, Phase III Study in Patients With Untreated Stage III (Unresectable) or IV Melanoma Receiving Dacarbazine Plus 10 mg/kg Ipilimumab (MDX-010) vs. Dacarbazine With Placebo	Bristol-Myers Squibb	III	Ongoing
01230775	A Phase III, Randomized, Multicenter, Subject and Sponsor-blinded, Placebo Controlled Study to Compare the Efficacy and Safety of "Anagrelide Retard" Versus Placebo in "at Risk" Subjects With Essential Thrombocythaemia	AOP Orphan Pharmaceuticals AG	III	Ongoing
01500694	A Phase 3, Open-label, Multicentre Study to Provide Access to Guanfacine Hydrochloride Extended-release for European Subjects With Attention-deficit/Hyperactivity Disorder (ADHD) Who Participated in Study SPD503-315 or SPD503-316	SHIRE	III	Ongoing
01290783	Randomized Double-blind Phase III Trial of FOLF(HA)Iri vs FOLFIRI for Second or Third Line Therapy in Irinotecan-naïve Patients With Metastatic Colorectal Cancer	Alchemia Oncology	III	Ongoing
01154140	Randomized, Open-Label Study Of The Efficacy And Safety Of Crizotinib Versus Pemetrexed/Cisplatin Or Pemetrexed/Carboplatin In Previously Untreated Patients With Non-Squamous Carcinoma Of The Lung Harboring A Translocation Or Inversion Event Involving The Anaplastic Lymphoma Kinase (ALK) Gene Locus	Pfizer	III	Ongoing
01160211	Ph III Trial to Compare Safety and Efficacy of Lapatinib Plus Trastuzumab Plus Aromatase Inhibitor (AI) vs. Trastuzumab Plus AI vs. Lapatinib Plus AI as 1st Line in Postmenopausal Subjects With Hormone Receptor+ HER2+ MBC Who Received	GlaxoSmith-Kline	III	Ongoing

¹²⁵ National Clinical Trial (NCT) number <http://www.clinicaltrials.gov/>

NCT¹²⁵ No.	Title	Sponsor	Phase	Status
	Trastuzumab and Endocrine Therapy in Neo- and/or Adjuvant Setting			
01499277	A Phase III, Multicentre, Randomised, Double-Blind Comparative Study to Evaluate the Efficacy and Safety of Ceftaroline Fosamil (600 mg Every 8 Hours) Versus Vancomycin Plus Aztreonam in the Treatment of Patients With Complicated Bacterial Skin and Soft Tissue Infections With Evidence of Systemic Inflammatory Response or Underlying Comorbidities	Astrazeneca/ Cerexa, Inc	III	Ongoing
00858364	A Randomized, Double-blind, Placebo-controlled Study to Evaluate the Long-term Safety and Efficacy of Darbepoetin Alfa Administered at 500 µg Once-Every-3-Weeks in Anemic Subjects With Advanced Stage Non-small Cell Lung Cancer Receiving Multi-cycle Chemotherapy	Amgen	III	Ongoing
01499277	A Phase III, Multicentre, Randomised, Double-Blind Comparative Study to Evaluate the Efficacy and Safety of Ceftaroline Fosamil (600 mg Every 8 Hours) Versus Vancomycin Plus Aztreonam in the Treatment of Patients With Complicated Bacterial Skin and Soft Tissue Infections With Evidence of Systemic Inflammatory Response or Underlying Comorbidities	Astrazeneca/ Cerexa, Inc	III	Ongoing
01244490	A Phase 3, Randomised, Double-blind, Multicentre, Parallel-group, Placebo- and Active-reference, Dose-optimisation Efficacy and Safety Study of Extended-release Guanfacine Hydrochloride in Children and Adolescents Aged 6-17 Years With Attention-Deficit/Hyperactivity Disorder	Shire Development LLC	III	Ongoing
01069900	A Randomized, Double-blind, Multicenter Trial to Evaluate the Safety and Efficacy of Sequential (Intravenous, Oral) Moxifloxacin Versus Comparator in Pediatric Subjects With Complicated Intra-abdominal Infection	Bayer	III	Ongoing
01285323	A 12-Month, Double-Blind, Placebo-Controlled, Parallel-Group Study to Evaluate the Efficacy and Safety of Reslizumab (3.0 mg/kg) in the Reduction of Clinical Asthma Exacerbations in Patients (12-75 Years of Age) With Eosinophilic Asthma	Teva Pharmaceuticals (Cephalon)	III	Ongoing
01339091	A Phase 3, Randomized, Double-Blind, Double-Dummy Study to Compare the Efficacy and Safety of Dalbavancin to a Comparator Regimen (Vancomycin and Linezolid) for the Treatment of Acute Bacterial Skin and Skin Structure Infections	Drata Therapeutics, Inc,	III	Ongoing
01500239	A Phase III, Randomized, Multicenter, Double Blind, Double-Dummy, Parallel-Group, Comparative Study to Determine the Efficacy, Safety, and Tolerability of Ceftazidime Avibactam Plus Metronidazole Versus Meropenem in the Treatment of Complicated Intra-Abdominal Infections In Hospitalized Adults	Astrazeneca/ Cerexa, Inc	III	Ongoing
01085136	Phase III Randomized Trial of BIBW 2992 Plus Weekly Paclitaxel Versus Investigator's Choice of Chemotherapy Following BIBW 2992 Monotherapy in Non-small Lung Cancer Patients Failing Erlotinib or Gefitinib	Boehringer Ingelheim Pharmaceuticals	III	Ongoing
01154140	Phase 3, Randomized, Open-Label Study Of The Efficacy And Safety Of Crizotinib Versus Pemetrexed/Cisplatin Or Pemetrexed/Carboplatin In Previously Untreated Patients With Non-Squamous Carcinoma Of The Lung Harboring A Translocation Or Inversion Event Involving The Anaplastic Lymphoma Kinase (ALK) Gene Locus	Pfizer	III	Ongoing
00561470	A Multinational, Randomized, Double-blind Study, Comparing the Efficacy of Aflibercept Once Every 2 Weeks Versus Placebo in Patients With Metastatic Colorectal Cancer (MCRC) Treated With Irinotecan / 5-FU Combination (FOLFIRI) After Failure of an Oxaliplatin Based Regimen	Sanofi-Aventis/ Regeneron Pharmaceuticals /National Surgical Adjuvant Breast And Bowel	III	Ongoing

Annex E. List of Phase III/IV Clinical Trials Ongoing in Ukraine That Have Safety As An Outcome of Interest

NCT¹²⁵ No.	Title	Sponsor	Phase	Status
		Project (NSABP)		
01500694	A Phase 3, Open-label, Multicentre Study to Provide Access to Guanfacine Hydrochloride Extended-release for European Subjects With Attention-deficit/Hyperactivity Disorder (ADHD) Who Participated in Study SPD503-315 or SPD503-316	Shire Development	III	Ongoing
01232556	An Open-Label, Randomized, Phase 3 Study Of Inotuzumab Ozogamicin Administered In Combination With Rituximab Compared To Defined Investigator's Choice Therapy In Subjects With Relapsed Or Refractory CD22-Positive Aggressive Non-Hodgkin Lymphoma Who Are Not Candidates For Intensive High-Dose Chemotherapy	Pfizer/UCB, Inc.	III	Ongoing
01289990	A Phase III Double-blind, Extension, Placebo-controlled Parallel Group Safety and Efficacy Trial of BI 10773 (10 and 25mg Once Daily) and Sitagliptin (100mg Once Daily) Given for Minimum 76 Weeks (Incl. 24 Weeks of Preceding Trial) as Monotherapy or With Different Back-ground Therapies in Patients With Type 2 Diabetes Mellitus Previously Completing Trial 1245.19, 1245.20 or 1245.23	Boehringer Ingelheim Pharmaceuticals	III	Ongoing
00989131	An Open, Randomized, Multicenter Study in Patients With Recurrent Epithelial Cancer, Primary Peritoneal Cancer or Fallopian Tube Cancer to Compare the Efficacy and Safety of Paclitaxel (Micellar) Nanoparticles and Paclitaxel (Cremophor® EL)	Oasmia Pharmaceutical AB	III	Ongoing
00667251	A Randomized, Open-Label, Phase III Study of Taxane Based Chemotherapy With Lapatinib or Trastuzumab as First-Line Therapy for Women With HER2/Neu Positive Metastatic Breast Cancer	NCIC Clinical Trials Group/ GlaxoSmith-Kline	III	Ongoing
01285557	An Open-Label, Multicenter, Randomized, Phase 3 Study of S-1 and Cisplatin Compared With 5-FU and Cisplatin in Patients With Metastatic Diffuse Gastric Cancer Previously Untreated With Chemotherapy	Taiho Pharma, USA	III	Ongoing
01076764	Randomized, Double-blind, Triple-dummy Trial to Compare the Efficacy of Otamixaban With Unfractionated Heparin + Eptifibatide, in Patients With Unstable Angina/Non ST Segment Elevation Myocardial Infarction Scheduled to Undergo an Early Invasive Strategy	Sanofi-Aventis	III	Ongoing
00986154	Evaluation of heparin/edoxaban tosylate (DU176b) versus heparin/warfarin in preventing recurrence of blood clots in patients with acute symptomatic deep-vein blood clots in the legs and/or blood clots in the lungs.	Daiichi Sankyo Inc	III	Ongoing
01313689	An Open Label, Multicenter Study Investigating the Safety and Efficacy of Ofatumumab Therapy Versus Physicians' Choice in Patients With Bulky Fludarabine-Refractory Chronic Lymphocytic Leukaemia (CLL)	GlaxoSmith-Kline	III	Ongoing
01307800	A Phase 3, Multicenter, Double-Blind, Placebo-Controlled Study of 3 Doses of LY2140023 Monohydrate in the Acute Treatment of Patients With DSM-IV-TR Schizophrenia	Eli Lilly and Company	III	Ongoing
00966914	Randomized, Multicenter, Double-blind, Phase 3 Trial of Tavocept Versus Placebo in Patients With Newly Diagnosed or Relapsed Advanced Primary Adenocarcinoma of the Lung Treated With Docetaxel or Paclitaxel Plus Cisplatin	Bionumerik Pharmaceuticals, Inc.	III	Ongoing
00148798	Open, Randomized, Controlled, Multicenter Phase III Study Comparing Cisplatin/Vinorelbine Plus Cetuximab Versus Cisplatin/Vinorelbine as First-line Treatment for Patients With Epidermal Growth Factor Receptor Expressing (EGFR-expressing) Advanced NSCLC.	Merck KGaAIII	III	Ongoing
00321464	A Randomized, Double-Blind, Multicenter Study of Denosumab	Amgen/Daiichi	III	Ongoing

NCT¹²⁵ No.	Title	Sponsor	Phase	Status
	Compared With Zoledronic Acid (Zometa®) in the Treatment of Bone Metastases in Subjects With Advanced Breast Cancer	Sankyo Inc.		
01376700	A Phase 3b Clinical Study to Assess Whether Regular Administration of ADVATE in the Absence of Immunological Danger Signals Reduces the Incidence Rate of Inhibitors in Previously Untreated Patients With Hemophilia A	Baxter Healthcare Corporation/ Baxter Innovations GmbH	III	Ongoing
01001072	An Open- Label Rollover Study for Subjects With Schizophrenia Completing ABILIFY®(Aripiprazole) Clinical Study 31-03-241	Otsuka Pharmaceutical Dev and Comm, Inc.	III	Ongoing
00858364	A Randomized, Double-blind, Placebo-controlled Study to Evaluate the Long-term Safety and Efficacy of Darbepoetin Alfa Administered at 500 µg Once-Every-3-Weeks in Anemic Subjects With Advanced Stage Non-small Cell Lung Cancer Receiving Multi-cycle Chemotherapy	Amgen	III	Ongoing
00679627	A Randomized, Double-Blind, Placebo-controlled Trial of Long-term (2-year) Treatment of Galantamine in Mild to Moderately-Severe Alzheimer's Disease	Janssen Research & Development, LLC	III	Ongoing
01131676	BI 10773 add-on to Usual Care Compared With Usual Care Alone in Patients With Type 2 Diabetes Mellitus at High Cardiovascular Risk	Boehringer Ingelheim Pharmaceuticals /Eli Lilly and Company	III	Ongoing
00338286	A Randomized, Open-label, Multicenter, Phase 3 Study of Epoetin Alfa Plus Standard Supportive Care Versus Standard Supportive Care in Anemic Patients With Metastatic Breast Cancer Receiving Standard Chemotherapy	Janssen Research & Development, LLC	III	Ongoing
01323244	A Phase III, Open-Label, Single Arm, Rollover Trial of TMC435 in Combination With Peginterferon Alpha-2A and Ribavirin for HCV Genotype-1 Infected Subjects Who Participated in the Placebo Group of a Phase II/III TMC435 Study, or Who Received DAA Treatment in a Tibotec-Sponsored Phase I Study.	Janssen R&D Ireland	III	Ongoing
01069900	A Randomized, Double-blind, Multicenter Trial to Evaluate the Safety and Efficacy of Sequential (Intravenous, Oral) Moxifloxacin Versus Comparator in Pediatric Subjects With Complicated Intra-abdominal Infection	Bayer	III	Ongoing
01004029	A Phase 3B, Multi-Center, Randomized, Double-Blind Study of Hydroxyprogesterone Caproate Injection, 250 mg/mL, Versus Vehicle for the Prevention of Preterm Birth in Women With a Previous Singleton Spontaneous Preterm Delivery	KV Pharmaceutical company/ ResearchPoint Global	III	Ongoing
00667823	Long-term Single-arm Open-label Extension Study of the SERAPHIN Study, to Assess the Safety and Tolerability of ACT 064992 in Patients With Symptomatic Pulmonary Arterial Hypertension	Actelion	III	Ongoing
01338415	A Prospective, Multicenter, Open-label Extension of FUTURE 3 to Assess the Safety, Tolerability and Efficacy of the Pediatric Formulation of Bosentan Two Versus Three Times a Day in Children With Pulmonary Arterial Hypertension	Actelion	III	Ongoing
00643201	A Safety and Efficacy Trial Evaluating the Use of Apixaban in the Treatment of Symptomatic Deep Vein Thrombosis and Pulmonary Embolism	Bristol-Myers Squibb/Pfizer	III	Ongoing
01064401	Multicenter, Double-blind, Randomized, Parallel-group, Monotherapy, Active-control Study to Determine the Efficacy and Safety of Daclizumab High Yield Process (DAC HYP)	Biogen Idec/Abbott Biotherapeutics	III	Ongoing

Annex E. List of Phase III/IV Clinical Trials Ongoing in Ukraine That Have Safety As An Outcome of Interest

NCT¹²⁵ No.	Title	Sponsor	Phase	Status
	Versus Avonex® (Interferon β 1a) in Patients With Relapsing-Remitting Multiple Sclerosis	Corp.		
01122927	Otsuka Pharmaceutical Development & Commercialization, Inc	Otsuka Pharmaceutical Development & Commercialization, Inc	III	Ongoing
10326629	A Randomized, Multicenter, Double-Blind, Parallel, Placebo-Controlled Study of the Effects of JNJ 28431754 on Cardiovascular Outcomes in Adult Subjects With Type 2 Diabetes Mellitus	George Institute, Sydney, Australia	III	Ongoing
00844649	A Randomized Phase III Study of Weekly ABI-007 Plus Gemcitabine Versus Gemcitabine Alone in Patients With Metastatic Adenocarcinoma of the Pancreas	Celgene Corporation	III	Ongoing
00835770	A Dose-Blind, Multicenter, Extension Study to Determine the Long-Term Safety and Efficacy of Two Doses of BG00012 Monotherapy in Subjects With Relapsing-Remitting Multiple Sclerosis	Biogen Idec	III	Ongoing
00633893	A Safety and Efficacy Trial Evaluating the Use of Apixaban for the Extended Treatment of Deep Vein Thrombosis and Pulmonary Embolism	Bristol-Myers Squibb	III	Ongoing
01106014	A Multicenter, Double-blind, Placebo-controlled Phase 3 Study to Demonstrate the Efficacy and Safety of ACT-293987 in Patients With Pulmonary Arterial Hypertension	Acetelion	III	Ongoing
00725985	A Phase III, Randomized, Double-blind, Placebo-controlled, Multi-center Clinical Trial of Oral Cladribine in Subjects With a First Clinical Event at High Risk of Converting to MS	EMD Serono	III	Ongoing
01163253	A Phase 3, Multi-Site, Open-Label Study Of The Long Term Safety And Tolerability Of 2 Oral Doses Of CP-690,550 In Subjects With Moderate To Severe Chronic Plaque Psoriasis	Pfizer	III	Ongoing
01500694	A Phase 3, Open-label, Multicentre Study to Provide Access to Guanfacine Hydrochloride Extended-release for European Subjects With Attention-deficit/Hyperactivity Disorder (ADHD) Who Participated in Study SPD503-315 or SPD503-316	Shire Development LLC	III	Ongoing
01215942	A Phase 3b, Multicenter, Open-Label Study to Evaluate the Long-Term Safety and Efficacy of LY2127399 in Patients With Rheumatoid Arthritis (RA)	Eli Lilly and Company	III	Ongoing
01039688	Phase 3 Randomized, Double-Blind Study Of The Efficacy And Safety Of 2 Doses Of CP-690,550 Compared To Methotrexate In Methotrexate-Naive Patients With Rheumatoid Arthritis	Pfizer	III	Ongoing
01259297	A Randomized Controlled Trial of Aliskiren in the Prevention of Major Cardiovascular Events in Elderly People	Novartis/Population health research Institute	III	Ongoing
00146620	An Open-label, Non-randomized, Multicenter, Interventional Study to Investigate the Safety and Efficacy of Canephron® N in the Management of Uncomplicated Urinary Tract Infections (uUTI)	Bionorica SE	III	Ongoing
01076010	An Extension Treatment Protocol for Subjects Who Have Participated in a Phase 3 Study of Tivozanib vs. Sorafenib in Renal Cell Carcinoma (Protocol AV-951-09-301)	AVEO Pharmaceuticals, Inc	III	Ongoing
01242514	(OSKIRA-X): A Long-term Extension Study to Assess the Safety and Efficacy of Fostamatinib Disodium in the Treatment of Rheumatoid Arthritis	AstraZeneca	III	Ongoing
01284517	A Randomized, 6-week Double-blind, Placebo-controlled, Flexible-dose, Parallel-group Study of Lurasidone Adjunctive to Lithium or Dovalproex for the Treatment of Bipolar I Depression	Sunovion	III	Ongoing

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NCT¹²⁵ No.	Title	Sponsor	Phase	Status
	in Subjects Demonstrating Non-response to Treatment With Lithium or Divalproex Alone.			
00488319	A 6-Month, Open-Label, Single-Arm Safety Study of Flexibly Dosed Paliperidone Extended Release (1.5 - 12 mg/Day) in the Treatment of Adolescents (12 to 17 Years of Age) With Schizophrenia	Janssen Research & Development, LLC	III	Ongoing Not recruiting
00147319	A Multinational, Multicenter, Open-label, Single-assignment Extension of the MS-LAQ-302 (BRAVO) Study, to Evaluate the Long-term Safety, Tolerability and Effect on Disease Course of Daily Oral Laquinimod 0.6 mg in Subjects With Relapsing Multiple Sclerosis	Teva Pharmaceuticals	III	Ongoing
01332019	A Dose-Frequency Blinded, Multicenter, Extension Study to Determine the Long-Term Safety and Efficacy of PEGylated Interferon Beta-1a (BIIB017) in Subjects With Relapsing Multiple Sclerosis	Biogen Idec	III	Ongoing
01309828	A Randomized, Open-Label, Phase 3 Study to Compare Long-Term Safety and Tolerability of the TAK-491 and Chlorthalidone Fixed-Dose Combination Versus Olmesartan Medoxomil and Hydrochlorothiazide Fixed-Dose Combination in Hypertensive Subjects With Moderate Renal Impairment	Takeda Global Research & Development Center, Inc	III	Ongoing
00488631	A Phase 3 Multicenter, Randomized, Placebo-controlled, Double-blind Study to Evaluate the Safety and Efficacy of Golimumab Maintenance Therapy, Administered Subcutaneously, in Subjects With Moderately to Severely Active Ulcerative Colitis	Centocor, Inc/Schering Plough	III	Ongoing
01121536	A 6-Month, Open-Label, Flexible-Dosage (150 to 200 mg/Day) Extension Study of the Safety and Efficacy of Armodafinil Treatment as Adjunctive Therapy in Adults With Major Depression Associated With Bipolar I Disorder	Teva Pharmaceutical Industries (Cephalon)	III	Ongoing
00552344	<u>A Phase IIIb, Open-label, follow-on Trial to C87085 Designed to Assess the Long-term Safety of Certolizumab Pegol, in Subjects With Moderately to Severely Active Crohn's Disease Who Have Participated in Study C87085</u>	UCB, Inc.	III	Ongoing
00988052	A Multinational, Multicenter, Open-label, Single-assignment Extension of the MS-LAQ-301 Study, to Evaluate the Long-term Safety, Tolerability and Effect on Disease Course of Daily Oral Laquinimod 0.6 mg in Subjects With Relapsing Multiple Sclerosis	<u>Teva Pharmaceutical Industries</u>	III	Ongoing
01104792	Evaluation of the Long-Term Safety, Tolerability, and Pharmacokinetics of Cariprazine in Patients With Schizophrenia	Forest Laboratories/ Gedeon Richter Ltd.	III	Ongoing
01240694	An Open-Label Long-Term Study of the Safety and Tolerability of Repeated Administration of CEP-33457 in Patients With Systemic Lupus Erythematosus	Teva Pharmaceutical Industries (Cephalon)	III	Ongoing
01485640	A Long-term, Multicenter, Open-Label, Flexible Dose Continuation Study in Subjects Who Have Completed a Prior Lurasidone Study	Sunovion	III	Ongoing
01289782	A Phase III, Randomized, Double-blind, Placebo-controlled Study to Investigate the Efficacy, Safety, and Tolerability of TMC435 vs. Placebo as Part of a Treatment Regimen Including Peginterferon Alfa-2a and Ribavirin in Treatment-naive, Genotype 1 Hepatitis C-infected Subjects	Janssen R&D Ireland	III	Ongoing
01112306	Long-term Single-arm Open-label Study, to Assess the Safety and Tolerability of ACT-293987 in Patients With Pulmonary Arterial Hypertension	Janssen R&D Ireland	III	Ongoing
01376700	A Phase 3b Clinical Study to Assess Whether Regular	Baxter	III	Ongoing

Annex E. List of Phase III/IV Clinical Trials Ongoing in Ukraine That Have Safety As An Outcome of Interest

NCT¹²⁵ No.	Title	Sponsor	Phase	Status
	Administration of ADVATE in the Absence of Immunological Danger Signals Reduces the Incidence Rate of Inhibitors in Previously Untreated Patients With Hemophilia A	Healthcare Corporation/ Baxter Innovations GmbH		
00351468	EXTEND (Eltrombopag Extended Dosing Study): An Extension Study of Eltrombopag Olamine (SB-497115-GR) in Adults, With Idiopathic Thrombocytopenic Purpura (ITP), Previously Enrolled in an Eltrombopag Study	GlaxoSmith-Kline	III	Ongoing
00803049	Long-term Extension of the Multinational, Double-blind, Placebo Controlled Study EFC6049 (HMR1726D/3001) to Document the Safety of Two Doses of Teriflunomide (7 and 14 mg) in Patients With Multiple Sclerosis With Relapses	Sanofi-Aventis	III	Ongoing
01286779	BAX 326 (Recombinant Factor IX): Evaluation of Safety, Immunogenicity, and Hemostatic Efficacy in Previously Treated Patients With Severe (FIX Level < 1%) or Moderately Severe (FIX Level <= 2%) Hemophilia B - A Continuation Study	Baxter Healthcare Corporation/ Baxter Innovations GmbH	III	Ongoing
01488994	BAX 326 (Recombinant Factor IX): A Phase 2/3 Prospective, Uncontrolled, Multicenter Study Evaluating Pharmacokinetics, Efficacy, Safety, and Immunogenicity in Previously Treated Pediatric Patients With Severe (FIX Level < 1%) or Moderately Severe (FIX Level <= 2%) Hemophilia B	Baxter Healthcare Corporation/ Baxter Innovations GmbH	III	Ongoing
00405756	A Phase III, Multicentre, Randomised, Double-Blind, Placebo-Controlled, 3 Arm Parallel-Group Study to Determine the Efficacy and Safety of Lenalidomide (Revlimid) in Combination With Melphalan and Prednisone Versus Placebo Plus Melphalan and Prednisone in Subjects With Newly Diagnosed Multiple Myeloma Who Are 65 Years of Age or Older	Celgene Corporation	III	Ongoing
01307800	A Phase 3, Multicenter, Double-Blind, Placebo-Controlled Study of 3 Doses of LY2140023 Monohydrate in the Acute Treatment of Patients With DSM-IV-TR Schizophrenia	Eli Lilly and Company	III	Ongoing
01173601	Randomized, Placebo-Controlled, Double-Blind Study of LY2216684 Fixed-Dose 12 mg and 18 mg Once Daily as Adjunctive Treatment for Patients With Major Depressive Disorder Who Are Partial Responders to Selective Serotonin Reuptake Inhibitor Treatment	Eli Lilly and Company	III	Ongoing
01198002	<u>A Phase 3, Multicenter, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of LY2127399 in Patients With Moderate to Severe Rheumatoid Arthritis (RA) Who Had an Inadequate Response to Methotrexate Therapy (FLEX M)</u>	Eli Lilly and Company	III	Ongoing
00310388	A Multicenter, Open-Label, Long-Term, Safety, Tolerability and Efficacy Study of Retigabine in Adult Epilepsy Patients With Partial-Onset Seizures (Extension of Study VRX-RET-E22-302)	GlaxoSmith-Kline	III	Ongoing
01200589	Phase III Randomized, Open Label Study of Single Agent Ofatumumab Vs. Single Agent Rituximab in Follicular Lymphoma Relapsed After Rituximab-Containing Therapy	GlaxoSmith-Kline	III	Ongoing
00884000	A Randomised, Open-label, Parallel-group, Multi-centre Trial to Compare the Efficacy and Safety for 12 Months of Zomacton to Genotropin in Children With Idiopathic Growth Hormone Deficiency	Ferring Pharmaceuticals	III	Ongoing
00321620	A Randomized, Double-Blind, Multicenter Study of Denosumab Compared With Zoledronic Acid (Zometa®) in the Treatment of Bone Metastases in Men With Hormone-Refractory Prostate Cancer	Amgen	III	Ongoing

NCT¹²⁵ No.	Title	Sponsor	Phase	Status
01202760	A Phase 3, Multicenter, Randomized, Double-blind, Placebo-controlled Study to Evaluate the Safety and Efficacy of LY2127399 in Patients With Rheumatoid Arthritis (RA) With or Without Background Disease-Modifying Anti-rheumatic Drug (DMARD) Therapy (FLEX O)	Eli Lilly and Company	III	Ongoing
00824265	A Phase III, Open Label, Randomized Trial of Ofatumumab Added to Fludarabine-Cyclophosphamide vs. Fludarabine-Cyclophosphamide Combination in Subjects With Relapsed Chronic Lymphocytic Leukemia	GlaxoSmith-Kline	III	Ongoing
01030783	A Phase 3, Randomized, Controlled, Multi-Center, Open-Label Study to Compare Tivozanib (AV-951) to Sorafenib in Subjects With Advanced Renal Cell Carcinoma (TIVO-1)	Aveo Pharmaceuticals	III	Ongoing
01291511	A Multicenter, Randomized, Double-blind Placebo-controlled, Parallel-group Study to Evaluate Prevention of Relapse in Patients With Schizophrenia Receiving Either Flexible Double Iloperidone (Fanapt) or Placebo in Long-term Use (up to 26 Weeks) Followed by up to 52 Weeks of Open-label Extension	Novartis Pharmaceuticals	III	Ongoing
1270828	A Phase 3 Double-Blind, Randomized, Placebo-Controlled, Safety And Efficacy Study Of Once Daily Controlled Release Pregabalin In The Treatment Of Patients With Postherpetic Neuralgia (Protocol A0081224)	Pfizer	III	Ongoing
01309737	<u>A Phase 3, Multi-Site, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study Of The Efficacy And Safety Of 2 Oral Doses Of Cp-690,550 In Subjects With Moderate To Severe Chronic Plaque Psoriasis</u>	Pfizer	III	Ongoing
00796445	GSK 2132231A Antigen-Specific Cancer Immunotherapeutic as Adjuvant Therapy in Patients With Resected Melanoma	GlaxoSmith-Kline	III	Ongoing
01276639	<u>Phase 3 Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study Of The Efficacy And Safety Of 2 Oral Doses Of Cp-690,550 In Subjects With Moderate To Severe Chronic Plaque Psoriasis</u>	Pfizer	III	Ongoing
01213446	A Phase III Open-label, Multi-centre Study to Assess the Pharmacokinetics, Efficacy, and Safety of Biostate® in Paediatric Subjects With Von Willebrand Disease	CSL Behring/Parexel	III	Ongoing
00680901	Phase III Study for ErbB2 Positive Advanced or Metastatic Gastric, Esophageal, or Gastroesophageal Junction Adenocarcinoma Treated With Capecitabine Plus Oxaliplatin With or Without Lapatinib	GlaxoSmith-Kline	III	Ongoing
01478607	A Randomized, Controlled, Long-term Safety Study Evaluating the Effect of Repeated Applications of QUTENZATM Plus Standard of Care Versus Standard of Care Alone in Subjects With Painful Diabetic Peripheral Neuropathy	Astellas Pharma Inc	III	Ongoing
01474122	Prospective, Randomized, Placebo-controlled, Double-blind, Multicenter, Parallel Group Study to Assess the Efficacy, Safety and Tolerability of Macitentan in Patients With Schemic Digital Ulcers Associated With Systemic Sclerosis	Actelion	III	Ongoing
01435928	A Double-Blind, Placebo-Controlled, Randomized Withdrawal Study Of Lurasidone For The Maintenance Treatment Of Subjects With Schizophrenia	Sunovion	III	Ongoing
00668850	A 26-Week, Open-Label, Randomized, Active Comparator Study of Generex Oral-lyn™ Spray and Injected Human Insulin In Subjects With Type-1 Diabetes Mellitus	Generex Biotechnology Corp./OSMOS Clinical Research, Inc/PSI Pharma Support Intl, inc, eResearch Technology,	III	Ongoing

Annex E. List of Phase III/IV Clinical Trials Ongoing in Ukraine That Have Safety As An Outcome of Interest

NCT¹²⁵ No.	Title	Sponsor	Phase	Status
		Inc., Hoffman, La Roche, ACM Pivotal Global Central Laboratory		
-01445951	A Phase 3, Multicenter, Open-label, Randomized, Forced-titration Clinical Trial Evaluating the Efficacy and Safety of Technosphere® Insulin Inhalation Powder in Combination With a Basal Insulin Versus Insulin Aspart in Combination With a Basal Insulin in Subjects With Type 1 Diabetes Mellitus Over a 24-week Treatment Period	Mannkind Corporation	III	Ongoing
01345955	A Multicenter, Double-Blind, Randomized, Phase 3 Study to Compare the Safety and Efficacy of Intravenous CXA-201 and Intravenous Levofloxacin in Complicated Urinary Tract Infection, Including Pyelonephritis	Cubist Pharmaceuticals	III	Ongoing
00911170	A Ph 3, Randomized, Double-blind, Placebo-controlled Study of Pegfilgrastim Admin'd to Subjects With Newly Dx, Locally-advanced or Metastatic Colorectal Cancer Treated With Bevacizumab & Either 5- Fluorouracil, Oxaliplatin, Leucovorin (FOLFOX) or 5-fluorouracil, Irinotecan, Leucovorin (FOLFIRI)	Amgen	III	Ongoing
01039376	<u>A Phase III, Open Label, Randomized, Multicenter Trial of Ofatumumab Maintenance Treatment Versus no Further Treatment in Subjects With Relapsed Chronic Lymphocytic Leukemia (CLL) Who Have Responded to Induction Therapy</u>	GlaxoSmith-Kline	III	Ongoing
01313689	An Open Label, Multicenter Study Investigating the Safety and Efficacy of Ofatumumab Therapy Versus Physicians' Choice in Patients With Bulky Fludarabine-Refractory Chronic Lymphocytic Leukaemia (CLL)	GlaxoSmith-Kline	III	Ongoing
01499290	A Phase III, Randomized, Multicenter, Double Blind, Double-Dummy, Parallel-Group, Comparative Study to Determine the Efficacy, Safety, and Tolerability of Ceftazidime Avibactam Plus Metronidazole Versus Meropenem in the Treatment of Complicated Intra-Abdominal Infections In Hospitalized Adults	AstraZeneca/ Cerexa, Inc	III	Ongoing
00781391	A Phase 3, Randomized, Double-Blind, Double-Dummy, Parallel Group, Multi-Center, Multi-National Study for Evaluation of Efficacy and Safety of DU-176b Versus Warfarin In Subjects With Atrial Fibrillation - Effective Anticoagulation With Factor Xa Next Generation in Atrial Fibrillation (ENGAGE - AF TIMI - 48)	Daiichi Sankyo Inc/The TIMI Study Group	III	Ongoing
912093	A Phase III Randomized, Double-Blind, Placebo-Controlled, Multicenter Study of Icatibant for Subcutaneous Injection in Patients With Acute Attacks of Hereditary Angioedema (HAE)	Shire Human Genetic Therapies, Inc	III	Ongoing
1474109	Prospective, Randomized, Placebo-controlled, Double-blind, Multicenter, Parallel Group Study to Assess the Efficacy, Safety and Tolerability of Macitentan in Patients With Ischemic Digital Ulcers Associated With Systemic Sclerosis	Actelion	III	Ongoing
988156	Efficacy and Safety Study of Eslicarbazepine Acetate (BIA 2 093) as Adjunctive Therapy for Refractory Partial Seizures in Children	Bial - Portela C S.A.	III	Ongoing
1091168	Trial of Vinflunine Versus Alkylating Agent in Metastatic Breast Cancer	Pierre Fabre Medicament	III	Ongoing
1229007	A Phase III, Open-Label, Multicentre Study to Evaluate Efficacy, Pharmacokinetics, and Safety of Biostate® in Paediatric Subjects With Haemophilia A	CSL Behring/Parexel	III	Ongoing
1224808	<u>An Open-Label, Multi-Centre Extension Study to Assess the Efficacy and Safety of Biostate® in Paediatric, Adolescent, and Adult Subjects With Von Willebrand Disease Who Completed Clinical Studies CSLCT-BIO-08-52 or CSLCTBIO-08-54</u>	CSL Behring	III	Ongoing

NCT¹²⁵ No.	Title	Sponsor	Phase	Status
1408108	Prospective Randomized Phase III Study of Laparoscopic Lightweight Mesh Repair of Large Hiatal Hernias	Odessa National Medical University	III	Pending/ not started recruiting
1475032	A Phase III, 12-week, Multicentre, Multinational, Randomised, Double-blind, Double-dummy, 3 Arm-parallel Group Study to Test the Efficacy of CHF 1535 (Fixed Combination of Beclomethasone Dipropionate (BDP) Plus Formoterol Fumarate (FF)) Versus a Free Combination of Beclomethasone Dipropionate Plus Formoterol Fumarate and Versus a Monotherapy of Beclomethasone Dipropionate in Partly Controlled Asthmatic Children	Chiesi Farmaceutici S.p.A	III	Ongoing
1106651	A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Multicenter Study to Evaluate the Efficacy, Safety, and Tolerability of Canagliflozin Compared With Placebo in the Treatment of Older Subjects With Type 2 Diabetes Mellitus Inadequately Controlled on Glucose Lowering Therapy	Janssen Research & Development, LLC	III	Ongoing
1507896	BAX 326 (Recombinant Factor IX): A Phase 3 Prospective, Multicenter Study Evaluating Efficacy and Safety in Previously Treated Patients With Severe (FIX Level < 1%) or Moderately Severe (FIX Level <= 2%) Hemophilia B Undergoing Surgical or Other Invasive Procedures	Baxter Healthcare Corporation/ Baxter Innovations GmbH	III	Ongoing
00566657	A Randomized Double-Blind Placebo-Controlled Parallel Group Study of the Efficacy and Safety of XRP0038/NV1FGF on Amputation or Any Death in Critical Limb Ischemia Patients With Skin Lesions	Sanofi-Aventis	III	Ongoing
00346216	A Randomized, Double Blind, Parallel-Group Study Of Cardiovascular Safety In Osteoarthritis Or Rheumatoid Arthritis Patients With Or At High Risk For Cardiovascular Disease Comparing Celecoxib With Naproxen And Ibuprofen	Pfizer/The Cleveland Clinic	IV	Ongoing
00807846	A Phase 4, 6-Week, Randomized Double-Blind, Multicenter, Active-Controlled Trial To Evaluate The Effects Of Celecoxib (Celebrex®) Or Naproxen On Blood Pressure In Pediatric Subjects With Juvenile Idiopathic Arthritis	Pfizer	IV	Ongoing
00997347	The Extended Gestational Age Medical Abortion Study: The Effectiveness of Medical Abortion With Mifepristone and Misoprostol at 57-63 Days Versus 64-70 Days Gestation	Gynuity Health Projects	IV	Ongoing
00144430	A 26 Week, Randomized, Double-blind, Parallel-group, Active Controlled, Multicenter, Multinational Safety Study Evaluating the Risk of Serious Asthma-related Events During Treatment With Symbicort®, a Fixed Combination of Inhaled Corticosteroid (ICS) (Budesonide) and a Long Acting β ₂ -agonist (LABA) (Formoterol) as Compared to Treatment With ICS (Budesonide) Alone in Adult and Adolescent (≥12 Years of Age) Patients With Asthma	AstraZeneca	IV	Ongoing
01422330	An Open-Label Study to Evaluate the Safety, Tolerability and Pharmacokinetics of Etravirine (ETR) in Combination With Other Antiretrovirals (ARVs) in Antiretroviral Treatment-Experienced HIV-1 Infected Subjects	Janssen R&D Ireland	IV	Ongoing
00508547	A Multicenter, Open Registry of Patients With Plaque Psoriasis Who Are Candidates for Systemic Therapy Including Biologics	Centocor Ortho Biotech Services, L.L.C	IV	Ongoing