

Technical Assistance for the Development of Instructor's Guides for Implementing Pre-service and In-service Curricula on Pharmacovigilance in Vietnam

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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.

ABSTRACT

The Ministry of Health (MOH), Hanoi University of Pharmacy (HUP), Vietnam Administration for AIDS Control (VAAC) and other stakeholders are making notable efforts toward strengthening the pharmacovigilance (PV) system in Vietnam. A major step was taken when the National Drug Information and Adverse Drug Reaction (DI&ADR) Center was established at HUP in 2009. With USAID/PEPFAR funding, Management Sciences for Health's Strengthening Pharmaceutical Systems (SPS) Program has collaborated with the national stakeholders to support this process, particularly focusing on activities that strengthen broader pharmacovigilance systems. One of the system-strengthening initiatives SPS supported was the development of pharmacovigilance curricula. SPS worked with the DI & ADR Center to help develop a detailed curriculum for in-service training and with HUP's Clinical Pharmacy Department to develop a similarly detailed curriculum for pre-service training at the post-graduate pharmacy level. In early 2012, detailed instructor guides were created which matched each curriculum. This technical report briefly describes the PV instructor guides, how they were created and the plans for their use. The report also includes, as annexes, both the pre- and in-service versions of the PV instructor guide.

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ACRONYMS

ADE	Adverse drug event
ADR	Adverse drug reaction
ART	Antiretroviral therapy
DAV	Drug Administration of Vietnam
DI & ADR Center	National Drug Information and Adverse Drug Reaction Monitoring Center
DIU	Drug Information Unit
DTC	Drug and Therapeutics Committee
EU	European Union
FDA	Food and Drug Administration
HCPs	Health care professionals
HIV/AIDS	Human Immunodeficiency Virus / Acquired Immunodeficiency Syndrome
HUP	Hanoi University of Pharmacy
MOH	Ministry of Health
MSA	Medical Services Administration
NMCP	National Malaria Control Program
NTP	National TB Control Program
OSPE	Objective Structured Practical Examination
PHP	Public health program
PMS	Post-marketing surveillance
PV	Pharmacovigilance
SAQs	Short-answer questions
SE	Side effect
SPS	Strengthening Pharmaceutical Systems Program [MSH]
TB	Tuberculosis
WHO	World Health Organization

CONTENTS

Acronyms	iv
Contents	v
Background.....	1
SPS Technical Assistance for the Creation of PV Instructor Guides	2
Overview of the Instructor Guides.....	2
The In-Service PV Instructor Guide	3
The Pre-Service PV Instructor Guide	3
Next Steps	4
Annexes.....	5

Background

Pharmacovigilance (PV) is defined as the science and activities related to the detection, assessment, understanding and prevention of medicines related problems. According to the World Health Organization (WHO), adverse drug reactions (ADR) are a common, yet often preventable, cause of illness, disability and death. In some countries, ADR ranks among the top 10 leading causes of mortality. In recent years, the scope of pharmacovigilance has slowly broadened from its traditional approach of focusing mainly on adverse drug reactions to one that includes additional critical issues such as medication errors, product quality, and treatment failure.

The Ministry of Health (MOH) and other key stakeholders in Vietnam are strengthening the PV system in their country. A major step was taken when the National Drug Information and Adverse Drug Reaction (DI & ADR) Center was established at the Hanoi University of Pharmacy (HUP) in 2009. With USAID/PEPFAR funding, Management Sciences for Health's Strengthening Pharmaceutical Systems (SPS) Program has collaborated with the national stakeholders to support this process, particularly focusing on activities that strengthen broader pharmacovigilance systems. SPS has provided technical support to HUP, DI&ADR Center, and the Vietnam Administration of AIDS Control (VAAC) in carrying out the following activities —

- Training DI&ADR center staff on drug information and pharmacovigilance, including development of standard operating procedures, question-answer forms for drug information service, and revision of the spontaneous reporting form.
- Developing a framework and protocol for sentinel site-based pilot active surveillance pharmacovigilance within the antiretroviral therapy program.
- Including a pharmacovigilance component in the Global Fund Round 10 application. The World Health Organization (WHO) and SPS provided technical assistance to the national counterparts in conceptualizing and developing this component.
- A Training and Workshop on Strengthening the Network for Safety of Medicines and Pharmacovigilance in Vietnam. SPS collaborated with WHO and the University of Bordeaux (Bordeaux, France) to provide technical support to MOH/HUP/DI&ADR Center to conduct this event.

SPS also collaborated with HUP and the DI & ADR Center on curricular reform activities to identify and include locally-appropriate pharmacovigilance topics. SPS worked with the DI & ADR Center to develop a detailed curriculum for in-service training of health care professionals in Vietnam and with HUP's Clinical Pharmacy Department to develop a similarly detailed curriculum for pre-service training at the post-graduate pharmacy level. Both these draft curricula were reviewed by a wide group of stakeholders during a curriculum review meeting held at HUP in August 2011 and revised.¹

¹ Joshi M. 2011. *Technical Assistance for the Development of Pre-service and In-service Pharmacovigilance Curriculum at the Hanoi University of Pharmacy in Vietnam*. Submitted to the U.S. Agency for International Development by the Strengthening Pharmaceutical Systems (SPS) Program. Arlington, VA: Management Sciences for Health.

SPS Technical Assistance for the Creation of PV Instructor Guides

In order to support the implementation of these PV curricula, SPS collaborated further with the HUP stakeholders and helped develop two versions of a detailed instructor's guide—one for pre-service and the other for in-service training. Each version of the instructor guide matches the respective pre- or in-service version of the curriculum created in August 2011. There are obvious similarities in the topics addressed in each version and it might have seemed efficient to create a single PV instructor guide. However, there is a considerable difference in the target audience for the PV training that will be delivered by the Clinical Pharmacy Department of HUP and the National DI&ADR Center. The two stakeholder groups are also subject to different time constraints and venues of delivery of the PV training. As a result, two different versions of the instructor guides were drafted, each tailored to the needs of the specific instructors and learners.

In March 2012, Dr. Mohan Joshi of SPS and Ms. Marcy Garb of the Training Help Desk, LLC, participated in a week of in-country working meetings during which they reviewed the draft instructor guides with faculty members at HUP's Clinical Pharmacy Department and staff members at the National DI & ADR Center.

Prior to the start of the working meetings, an overview of the guides was presented at an introductory meeting chaired by Professor Nguyen Dang Hoa who serves both as Vice-Rector of HUP and Director of the National DI&ADR Center. During working meetings that followed, faculty members at HUP's Clinical Pharmacy Department and staff members at the National DI & ADR Center suggested revisions and enhancements to, respectively, the pre-service and in-service versions of the guides. Those revisions and enhancements were incorporated into the draft guides and the finalized guides were delivered to each stakeholder group in April 2012. (The guides are shown in ANNEXES 1 and 2.)

Overview of the Instructor Guides

Each version of the guide contains summarized PV course content pertaining to each topic in the curriculum, easy access to in-depth associated resources, and step-by-step guidance on how to conduct each class session. The text guides the instructor to use as many interactive and learner-centered instructional methods as possible to enhance the level of interactivity and enable the students to have a greater role in their learning experience. Each guide also contains many hyperlinks to a very rich assortment of resources and references. The in-service instructor guide contains hyperlinks to 77 reference and resource documents and hyperlinks to 22 different websites. The pre-service instructor guide contains hyperlinks to 64 reference and resource documents and hyperlinks to 53 different websites.

One of the resources common to both guides is an interactive PDF version of Vietnam's approved spontaneous ADR reporting form that will enable the instructor to project the reporting form onto a screen so that participants/students attending the session can observe the instructor filling out the form for demonstration purposes.

The In-Service PV Instructor Guide

The DI&ADR Center staff plan to use their guide in the delivery of PV in-service workshops delivered to health care professionals (HCPs), mainly doctors, pharmacists and nurses, working in hospitals and public health programs throughout the country. Because of the different work situations of those HCPs (hospital staff or those from one of the three public health programs on AIDS, TB or malaria), the in-service PV curriculum and the associated instructor guide consist of four separate tracks with a total of 19 sessions. All workshop participants are expected to attend the same initial four sessions on general PV concepts. But the additional sessions will contain content appropriate for the following four different target audiences:

- HCPs working in hospitals
- HCPs working in the Antiretroviral Therapy Program
- HCPs working in the National Tuberculosis Program
- HCPs working in the National Malaria Control Program

In that way, all participants will receive PV information that is most relevant to their actual working situations. The in-service workshops for all four tracks will include extensive practice in filling out the ADR Reporting Form.

The DI&ADR Center's implementation plan for delivery of PV training to HCPs is based on a cascading training model in which a core cadre of local trainers will be trained to deliver the PV in-service workshops and they will lead the process of implementing further PV trainings in their respective local settings.

The Pre-Service PV Instructor Guide

The Clinical Pharmacy Department of HUP plans to use this instructor guide soon to offer a PV course for masters level pharmacy students.

Beyond containing 10 sessions covering the PV topics in the HUP curriculum, the pre-service guide also includes detailed instructions for conducting three 200-minute seminars. Those seminars will provide the opportunity for the students to revisit three key topics (spontaneous reporting, causality assessment, and risk management) to immerse themselves more deeply in those topics.

In addition to guidance on the conduct of classes in PV, during the working meetings, the faculty of HUP's Clinical Pharmacy Department indicated that they were particularly interested in student assessment and in how to incorporate as much objectivity on the part of the instructor during that important process. As a result, the pre-service guide contains not only a 25-question test set, but also provides a section with guidance to the faculty about how to enhance objectivity in student assessment.

Although the guide provides specific steps the instructor can follow when teaching each PV session, during preparation for teaching the class the instructor can decide when to exercise flexibility in the use of the guide to better meet the level and needs of the students.

Next Steps

Each stakeholder group plans to have the guides translated into Vietnamese. Members of both the groups anticipate that as they use the guides when they deliver the PV training sessions, they are likely to incorporate yet more changes (particularly in the times allotted to cover each topic) based on actual classroom or pilot program experience.

Providing PV training for health care providers and pharmacy students will make a major contribution to the strengthening of Vietnam's pharmacovigilance systems.

Annexes

Annex 1: Training of Health Care Professionals in Vietnam: Instructor's Guide for Implementing the In-service Curriculum on Pharmacovigilance

Annex 2: Instructor Guide to Pharmacovigilance Curriculum for Post-graduate Pharmacy Students at Hanoi University of Pharmacy

ANNEX 1



Training of Health Care Professionals in Vietnam: Instructor's Guide for Implementing the In-service Curriculum on Pharmacovigilance

4 April 2012



Table of Contents

The Purpose and Organization of this Instructor Guide	1
Session 1.1: General Overview of Pharmacovigilance (PV) and Medication safety	4
Session 1.2: PV Program in Vietnam.....	13
Session 2.1: Adverse Drug Reaction as a Factor for Adverse Drug Events	20
Session 3.1: Risk Evaluation and Reporting	28
Session 4.1: Risk Communication, Risk Management, and Risk Minimization.....	33
Sessions 5.1 through 5.5 are designed specifically for healthcare providers working in Vietnam's hospitals.	40
Session 5.1: Setting up PV programs in hospitals	40
Session 5.2: ADR reporting	43
Session 5.3: Adverse Drug Events: Assessment of Severity and Causality, and Prevention in Day-to-Day Practice	47
Session 5.4: Medication Error as a Factor for Adverse Drug Events.....	54
Session 5.5: Other Factors for Adverse Drug Events	61
Sessions 6.1 through 6.3 are designed specifically for healthcare providers working in Vietnam's Antiretroviral Therapy Program.	66
Session 6.1: Importance of PV in Public Health Programs (PHPs) and Burden of ADEs in PHPs	66
Session 6.2: PV in the Antiretroviral Therapy Program	71
Session 6.3: ADR Reporting.....	74
Sessions 7.1 through 7.3 are designed specifically for healthcare providers working in Vietnam's National Tuberculosis Program.....	77
Session 7.1: Importance of PV in Public Health Programs (PHPs) and Burden of ADEs in PHPs	77
Session 7.2: PV in the National Tuberculosis Program	82
Session 7.3: ADR Reporting.....	85
Sessions 8.1 through 8.3 are designed specifically for healthcare providers working in Vietnam's National Malaria Control Program.	89
Session 8.1: Importance of PV in Public Health Programs (PHPs) and Burden of ADEs in PHPs	89
Session 8.2: PV in the National Malaria Control Program	94
Session 8.3: ADR Reporting.....	97

The Purpose and Organization of this Instructor Guide

PURPOSE OF THIS GUIDE

To provide staff members at Vietnam’s National DI&ADR Center guidance for delivering pharmacovigilance (PV) training sessions to healthcare providers at hospitals and clinics. The guide includes summarized pharmacovigilance course content, easy access to in-depth associated resources and step-by-step guidance on how to conduct each session using interactive, learner centered instructional techniques. The goal is to use as many learner-centered instructional methods as possible to enhance the level of interactivity and enable the participants to have a greater role in their learning experience. Interaction and cross-pollination of thought among the participants is also encouraged by having the participants spend at least some of the time working in small groups. But, interactive instructional methods sometimes take more time than straight presentations. As a result, the instructor should avoid the temptation to try to cover more material in a given time segment than can comfortably be covered.

The pharmacovigilance training is organized into two major sections which are further subdivided into modules and sessions. After attending all five of the sessions in Section 1 which cover general concepts, different tracks are provided for the healthcare providers based on their jobs and their patient populations. After completing the training, each participant will have attended either 9 or 10 sessions.

Section 1: General Concepts

Module 1: Overview of PV and Medication Safety

Session 1.1: General Overview of PV and Medication Safety

Session 1.2: PV programs in Vietnam

Module 2: Adverse Drug Reaction as a Factor for Adverse Drug Event

Session 2: Adverse Drug Reaction as a Factor for Adverse Drug Event

Module 3: Risk Evaluation and Reporting

Session 3: Risk Evaluation and Reporting

Module 4: Risk Communication, Risk Management, and Risk Minimization

Session 4: Risk Communication, Risk Management, and Risk Minimization

Section 2: PV Practice in Specific Curriculum

Module 5: PV in Hospitals

Session 5.1: Setting up PV Programs in Hospitals

Session 5.2: ADR Reporting

Session 5.3: Adverse Drug Events: Assessment of Severity and Causality, and Prevention in Day-to-Day Practice

Session 5.4: Medication Error as a Factor for Adverse Drug Events

Session 5.5: Other Factors for Adverse Drug Events

Module 6: PV in the Antiretroviral Therapy Program

Session 6.1: Importance of PV in Public Health Programs (PHPs) and Burden of ADEs in PHPs

Session 6.2: PV in the Antiretroviral Therapy Program

Session 6.3: ADR Reporting

Module 7: PV in the National Tuberculosis Program

Session 7.1: Importance of PV in Public Health Programs (PHPs) and Burden of ADEs in PHPs

Session 7.2: PV in the National Tuberculosis Program

Session 7.3: ADR Reporting

Module 8: PV in the National Malaria Control Program

Session 8.1: Importance of PV in Public Health Programs (PHPs) and Burden of ADEs in PHPs

Session 8.2: PV in the National Malaria Control Program

Session 8.3: ADR Reporting

Guidance for the instructor about each of the sessions is provided with the following components:

Topics to cover in the session: provides a brief summary statement describing each topic.

Objectives: states what the participants are expected to be able to do by the end of the session.

Content Summary and Process Overview / Instructional Methodology: provides a brief summary of the technical content of each topic in the session with references to more detailed content resources and case stories, where appropriate, and guidance for the instructor about activities to use during the process of managing the session, instructional techniques and durations for each topic in the session and the total time to conduct the entire session.

References for additional reading: listing locations of additional information relevant to the session topics.

In addition to the references pertaining to specific sessions, WHO-UMC's list of abbreviations and acronyms associated with pharmacovigilance and WHO-UMC's glossary of terms used in pharmacovigilance are valuable resources that pertain to the entire PV curriculum. Citations for these resources are below.

Uppsala Monitoring Centre. *Glossary of terms used in Pharmacovigilance*. Web. 2011.

Uppsala Monitoring Centre. *A list of abbreviations and acronyms found in the field of, or connected with, pharmacovigilance*. Web. Jan. 2012.

TARGET AUDIENCE FOR THIS GUIDE

DI&ADR Center staff members responsible for delivery of pharmacovigilance training sessions to healthcare providers at hospitals and clinics

COURSE DURATION

Participants following the PV in Hospitals track will spend 735 minutes during the PV training sessions.

Participants following the Antiretroviral Therapy, Tuberculosis or Malaria tracks will spend 645 minutes during the PV training sessions.

Session 1.1: General Overview of Pharmacovigilance (PV) and Medication safety

Topics to cover in this session:

- A. Definition of PV
- B. History of PV
- C. Goals of PV (rational medicine use, communication of risk and benefit of medicines, health worker and patient education)
- D. Widening scopes of PV—adverse drug reaction (ADR), medication error, product quality, therapeutic ineffectiveness
- E. Need and importance of PV (burden of ADRs; morbidity and mortality, cost burden of ADRs, benefits of PV)
- F. Various phases of clinical trials of medicines and post-marketing surveillance, and how PV fits in all these steps (life-cycle approach)
- G. PV information influencing medicines policy and regulation: recall, labeling changes, reschedule withdrawal, policy change

Objectives: At the end of this session, participants will be able to:

- define PV and emphasize that its scope includes not only ADRs but also medication errors, product quality issues, and therapeutic ineffectiveness
- explain the burden and impact of adverse drug events (ADE) and use this context to articulate the need to support PV activities
- link PV as a key ingredient to achieving the broader goals of rational medicine use and pharmaceutical care
- emphasize that monitoring the safety of a medicine is an ongoing process, and needs to happen both during pre-marketing and post-marketing periods
- tell how PV information provides evidence for and influences regulatory decision, giving one example of such a decision taken by drug regulatory authority

Content Summary and Process Overview / Instructional Methodology (Total Duration: 90 Minutes)**A. Definition of PV (source: Ref. 009)**

Pharmacovigilance is the science and activities related to the detection, assessment, understanding and prevention of adverse effects or any other possible drug-related problems. Those drug-related problems include drug interactions, poor quality and counterfeit products, medication use errors and lack of efficacy.

Activity	Time (minutes)
Show the quote on slide 2 of Ref. 072 to provide the participants with underlying reason for this series of sessions about PV. Present PowerPoint slides 2 and 3 in Ref. 121 to provide a definition, in context, for PV.	5

B. History of PV (Sources: Ref. 010 page 5, Ref. 012)

The practice and science of pharmacovigilance emerged following the disaster caused by thalidomide in 1961. At that time many thousands of congenitally deformed infants were born as the result of exposure in utero to an unsafe medicine promoted for use by pregnant mothers. In 1963, the Sixteenth World Health Assembly adopted a resolution that reaffirmed the need for early action in regard to rapid dissemination of information on adverse drug reactions which led to creation of the WHO Pilot Research Project for International Drug Monitoring in 1968. Since 1978 the Program has been carried out by the Uppsala Monitoring Centre (UMC) in Sweden.

The creation of the International Society of Pharmacoepidemiology (ISPE) in 1984 and of the European Society of Pharmacovigilance (ESOP – later ISoP – the International Society) in 1992 marked the introduction of pharmacovigilance formally into the research and academic world. Pharmacovigilance activities have also evolved as a regulatory activity. Recommendations of the Council for International Organizations of Medical Sciences (CIOMS) accepted by the International Conference on Harmonization (ICH) in the 1990s have had a notable impact on international drug regulation.

Activity	Time (minutes)
Present PowerPoint slides 4– 14 in Ref. 121 to provide a foundation about the history of PV.	20

C. Goals of PV (rational medicine use, communication of risk and benefit of medicines, health worker and patient education) (Source: Ref. 009)

The goal of Pharmacovigilance is to safeguard public health and enhance rational medicine use through efficient and timely collection, assessment and communication of risks and benefits to support decision-making at various levels of the health care system. The impact of those Pharmacovigilance activities is reduced mortality and morbidity due to medicines-related problems

Activity	Time (minutes)
Ask participants to cluster in groups of 3 to estimate the percentage of ADRs that are preventable. Ask each group to share its estimate with the rest of the participants. Then show slide 15 in Ref. 121 so they can compare their estimates.	5
<p>Show the participants the following 7 phrases:</p> <ul style="list-style-type: none"> • reduced mortality due to medicines-related problems • safeguard public health • collection of data about risks and benefits • communication of risks and benefits • reduced morbidity due to medicines-related problems • enhance rational medicine use • assessment of risks and benefits <p>Ask the participants to identify each phrase as either a goal of PV, an activity performed during PV or an impact of PV</p> <p>Then, show them section C of the content summary so they can determine if they classified the phrases correctly.</p>	5

D. Widening scopes of PV—adverse drug reaction (ADR), medication error, product quality, therapeutic ineffectiveness (Sources: Ref. 005, Ref. 008)

Medication safety concerns on which pharmacovigilance focuses now go beyond adverse drug reactions and side effects to include drug interactions, poor quality and counterfeit products, medication use errors and lack of efficacy. One factor influencing this expansion in scope is the growing problem of poor quality or counterfeit medicines.

<i>Activity</i>	<i>Time (minutes)</i>
<p>Present slide 26 in Ref. 121 to highlight the expansion of PV beyond adverse drug reactions and side effects to include drug interactions, poor quality and counterfeit products, medication use errors and lack of efficacy.</p> <p>Facilitate a brief brainstorming session to have the participants identify recent issues that might be driving that expansion of PV’s focus. Hopefully, they will identify the growing problem of poor quality or counterfeit medicines. If they do not, then identify that issue for them.</p> <p>Present slides 32– 34 in Ref. 121 to provide more detail about poor quality and counterfeit products, medication use errors and lack of efficacy.</p>	20

E. Need and importance of PV (burden of ADRs; morbidity and mortality, cost burden of ADRs, benefits of PV)(Sources Ref. 009 page 7, Ref. 001, Ref. 003, Ref. 011, Ref. 006 page 2)

The information collected during the pre-marketing studies of new medications is incomplete with regard to possible adverse reactions. Pre-marketing studies involve a limited number of patients, conditions of use which differ from those in clinical practice and limited duration of trials. As a result, pharmacovigilance via post-marketing surveillance is needed to provide a more complete picture of adverse drug reactions resulting from medication use. Post marketing surveillance can identify rare adverse effects which could not have been identified during shorter clinical trials. Pharmacovigilance can also reveal information about potential toxicity from long term use, can highlight potential drug and disease interactions and may result in re-appraisal of indications for that medication. It is only through knowing as much as possible about potential ADRs associated with each medication, through pharmacovigilance, that the impact of ADRs can be diminished.

One example of the huge financial burden of ADRs comes from a 2002 study that estimated the annual cost of drug-related morbidity and mortality resulting from drug-related problems in ambulatory care settings in the United States at \$177.4 billion. And, U.S. Institute of Medicine estimated that up to 98,000 people die each year from medication errors in U.S. hospitals at a cost of up to 29 billion US\$ / year. Other studies estimate the costs at 588 million US\$ / year in Germany (1997) and 847 million US\$ / year in the UK (2006).

From a public health perspective, the burden of ADRs is also striking. ADRs are the 4th-6th leading cause of death in the USA. Up to 19 % of hospitalized patients will have an ADR. From 2004 through 2006, medical errors resulted in 238,337 potentially preventable deaths and cost the U.S. Medicare program US\$8.8 billion. It is estimated that 70% of ADRs are avoidable.

Information gained through pharmacovigilance has the potential to greatly improve patient care while providing huge savings in healthcare costs.

Activity	Time (minutes)
Share some examples of the estimated financial and public health costs mentioned in the first part of page 2 in Ref. 006. Summarize by stressing that these burdens could be greatly reduced through effective PV systems.	5
Present slides 27– 31 in Ref. 121 to introduce active and passive ADR surveillance as the methods that enable PV to provide its benefits.	5

F. Various phases of clinical trials of medicines and post-marketing surveillance, and how PV fits in all these steps (life-cycle approach) (Source Ref. 005 slides 13- 20)

- Phase I - Initial studies in a small number (typically 20-80) of human subjects to determine the metabolism and pharmacologic actions, side effects associated with increasing doses, and to gain early evidence of effectiveness; may include healthy participants and/or patients
- Phase II - Controlled clinical studies conducted to evaluate the effectiveness of the drug for a particular indication or indications in patients with the disease or condition under study and to determine the common short-term side effects and risks. There are usually no more than several hundred patients in Phase II studies.
- Phase III - Controlled clinical studies conducted to evaluate the therapeutic efficacy of the drug for a particular indication or indications in patients with the disease or condition under study and to determine the common short-term side effects and risks. There are typically several hundred to several thousand patients enrolled in Phase III studies.
- Phase IV - Post-marketing studies to delineate additional information including the drug's risks, benefits, and optimal use. Typically large population of users of the medicine enrolled in real-life situations. Provides Improved understanding of the safety profile and information about populations not studied under premarket trials

Pharmacovigilance is an integral part of a medicine’s life cycle and safety data is collected at every Phase of clinical trials.

<i>Activity</i>	<i>Time (minutes)</i>
<p><i>Present slides 16– 25 in Ref. 121 to introduce how ADR monitoring during clinical trials leads up to PV.</i></p> <p>Then, summarize by stressing that pharmacovigilance is an integral part of a medicine’s life cycle because safety data is collected at every phase of clinical trials.</p> <p>If time permits, use Ref. 020 to demonstrate the clinicaltrials.gov website by showing the adverse experiences listed.</p>	<p>10</p>

G. PV information influencing medicines policy and regulation: recall, labeling changes, reschedule, withdrawal, policy change (Sources Ref. 004 pages 43-45, Ref. 013, Ref. 014, Ref. 018, Ref. 019)

Medicines regulation is governed by issues of safety, quality and efficacy. Results of information learned from PV data can lead to regulatory actions including recall, labeling change, reschedule, withdrawal or policy change. Some examples are:

Recall: In 2008, Kenya recalled batches of Duo-cotecxin® (antimalarial) due to presence of counterfeit packs.

Labeling change: On November 18, 2011, the US FDA announced that Avastin (bevacizumab) was no longer approved for the treatment of breast cancer. The drug retains its indications for colon, lung, kidney, and brain cancer. Clozapine (previously withdrawn) reapproved after submission of new data, with a restricted indication for schizophrenia refractory to other therapy; in addition, mandatory white blood- cell monitoring of patients is required wherever the drug is marketed.

Reschedule: In 2011 the antihistamine Fexofenadine hydrochloride was switched by the US FDA to OTC because it was found to be safe enough based on use in larger populations.

Withdrawal: 2004 Vioxx (rofecoxib, which is a COX-II inhibitor) was withdrawn voluntarily due to increased risk of cardiovascular events. Chlorproguanil + Dapson (LapDap®) was withdrawn voluntarily in 2008 due to concerns of anaemia in G-6-PD deficient patients. Clozapine was withdrawn from some markets after reports of agranulocytosis in Finland. In 2010 Propoxyphene (opioid pain medication) was withdrawn from the US market based on new data showing significant changes to the electrical activity of the heart.

Policy change: Indinavir (an antiretroviral medicine) now not used except as salvage therapy due to renal stones.

<i>Activity</i>	<i>Time (minutes)</i>
Present slides 35– 40 in Ref. 121 to provide a foundation about the impact of PV on medicine regulation	5
Show examples of rosiglitazone removal circular from DAV and any related newspaper clipping and circular related to removal of the brand product, “Duxil” This is an opportunity for the instructor to point out some current Vietnam examples of medication recalls.	5
If time permits, present the Case Study from Ref. 015 on Indinavir-Associated Nephrotoxicity (The website provides question to ask the participants and the discussion.)	
Summarize the General Overview of PV and Medication Safety with slide 41 of Ref. 121.	5

Sources used in this session:

- Ref. 001 Farcas, A. & Bojita, M. Adverse Drug Reactions in Clinical Practice: a Causality Assessment of a Case of Drug-Induced Pancreatitis. *J Gastrointest Liver Dis*, 18.3 (2009): 353-358.
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- Ref. 010 World Health Organization. *The Importance of Pharmacovigilance: Safety Monitoring of medicinal products*. 2002.
- Ref. 011 Bernstein, L. R. The Cost of Drug-Related Problems Revisited. Message posted to medscape.com. 4 Mar. 2002.
- Ref. 012 About The Uppsala Monitoring Centre. Website.
- Ref. 013 National Center for Infectious Diseases, Centers for Disease Control and Prevention. *CDC Study Shows Sharp Decline in Reye's Syndrome among U.S. Children*. Web. Last modified 2 Aug. 2006.
- Ref. 014 CIOMS Working Group IV Benefit-Risk Balance for Marketed Drugs: Evaluating Safety Signals. Web. 1998.
- Ref. 015 Spach, D. H. Case 3: Indinavir-Associated Nephrotoxicity. *Antiretroviral Rx: Adverse Effects*. Web. 24 Jan. 2011.
- Ref. 018 Walker, E. FDA Revokes Avastin Approval for Breast Cancer. *MedPage Today*. Web. 18 Nov. 2011.
- Ref. 019 Fultz-Morris, Y. Withdrawal of Products that Contain Propoxyphene. *FDA Drug Safety Podcast*. Web. 21 Nov. 2010.
- Ref. 020 Pfizer, Inc. Clinical Trial: Study Evaluating the Safety of Etanercept in Rheumatoid Arthritis, Ankylosing Spondylitis and Psoriatic Arthritis. Web. Last Updated on 8 Sep. 2011.

- Ref. 072 Joshi, M. P. *A System-oriented Approach to Implementing Pharmacovigilance* [PowerPoint slides]. 29 Sep. 2009.
- Ref. 121 The National DI & ADR Centre (2012). *General Overview of Pharmacovigilance and Medication Safety* [PowerPoint slides]. 2012.

Additional Reading and Resources:

- Ref. 021 US National Institutes of Health. *Understanding Clinical Trials*. Web. Last Updated: 20 Sep. 2007.
- Ref. 022 U.S. Food and Drug Administration. *Drugs Removed from or Restricted in the U.S. Market Because of Drug Interactions*. Web. Last Updated: 03 Feb. 2010.

Session 1.2: PV Program in Vietnam

Topics to cover in this session:

- A. Brief overview of the problems of drug overuse and misuse in Vietnam; safety issues with traditional and herbal medicines in Vietnam; weaknesses of the health care system regarding medicine safety activities
- B. Overview of the legal basis for PV system and framework of the PV system in Vietnam
- C. PV roles and activities the Ministry of Health (MOH), especially the National DI&ADR Center, Drug Administration of Vietnam (DAV), and Medical Services Administration (MSA) of Vietnam
- D. Other PV stakeholders in Vietnam, including hospitals (and their DTCs and DIUs)
- E. Importance of stakeholder coordination and collaboration for conducting PV activities effectively

Objectives: At the end of this session, participants will be able to:

- Describe the legal basis of PV activities in Vietnam
- List the key national stakeholders with regard to PV in Vietnam
- Analyze and explain how these stakeholders are interlinked for an effective and coordinated PV “system” in Vietnam
- Describe the key problems and clinically significant toxicities associated with the use of herbal and traditional medicines in Vietnam

Content Summary and Process Overview / Instructional Methodology (Total Duration: 90 Minutes)

- A. Brief overview of the problems of drug overuse and misuse in Vietnam; safety issues with traditional and herbal medicines in Vietnam; weaknesses of the health care system regarding medicine safety activities (Sources: Ref. 025, Ref. 010 pages 22 and 23, Ref. 034, Ref. 035)

Safety issues with traditional and herbal medicines in Vietnam

In Vietnam as in many other countries, the use of herbal and traditional medicines raises concerns in relation to their safety. There is wide misconception that 'natural' means 'safe'. There is the common belief that long use of a medicine, based on tradition, assures both its efficacy and safety. There are examples of traditional and herbal medicines being adulterated or contaminated with allopathic medicines, chemicals such as corticosteroids, non-steroidal anti-inflammatory agents and heavy metals. Self-medication further aggravates the risk to patients. When traditional and herbal medicines are used in conjunction with other medicines there is the potential of serious adverse drug interactions. As with other products intended for human use (medicines, dietary supplements and foods), herbal medicines should be incorporated within a regulatory framework. Difficulties in achieving this arise from the growth of an ambiguous zone between foods and medicines, into which an increasing number of herbal products fall.

In 2001, WHO conducted a Global Survey about national policies on traditional medicines, and regulation of herbal medicines. The report of survey results revealed that In the Socialist Republic of Vietnam, a national policy on TM/CAM was at that time currently being developed. Laws and regulations were issued in 1989 and a national programme was issued in 1986. The Department of Traditional Medicine is administered by the Ministry of Health, and was established in 1957. There is currently no expert committee. In 1957, the Vietnamese Institute of Traditional Medicine was established, and in 1976 the Ho Chi Minh Institute of Traditional Medicine and Pharmacy was founded. National laws and regulations on herbal medicines were issued in 1989, separately from the laws governing conventional pharmaceuticals. Herbal medicines are regulated as prescription and over the counter medicines. By law, medical, health and nutrient content claims may be made. The Vietnam pharmacopoeia is legally binding, as are the national herbal monographs Regulatory requirements for manufacturing include adherence to information in pharmacopoeias and monographs and the same GMP rules used for conventional pharmaceuticals. Implementation of these requirements is ensured by inspection and visits to manufacturing establishments. Safety requirements for herbal medicines include traditional use without demonstrated harmful effects and reference to documented scientific research on similar products. Classical or traditional remedies are used and promoted without the need to demonstrate the safety of the product. New remedies, indications or uses for herbal medicines must be accompanied by records of clinical trials. Implementation of these requirements is ensured by the registration system.

At the time of the survey, there were 1,573 registered herbal medicines in Vietnam; 267 herbal medicines included on the national essential medicines list of 1996. The post marketing surveillance system included monitoring of adverse effects for herbal medicines. In Vietnam, herbal medicines are sold in pharmacies as prescription and over the counter medicines, in special outlets and by licensed practitioners.

Weaknesses of the healthcare system regarding medical safety activities

The structure of Vietnam's drug information system is not consistent or fully developed from the central to the local level. The drug information projects are small and there is less than sufficient collaboration between different activities. In treatment sites, activities often lack collaboration and instructions from the Drug and Therapy committee. Drug manufacturers and distributors focus mainly on marketing and place little importance on drug information and adverse reaction monitoring. There is some drug information monitoring in some hospitals but the activity is not well-strategized and well-coordinated.

<i>Activity</i>	<i>Time (minutes)</i>
<p>Ask participants how many of them, their family members or their patients have used herbal medicines. Tell them about the WHO survey described in Ref. 034 and about the specific responses provided to that survey by Vietnam as listed in the content summary. (10 minutes)</p> <p>Share case study from Ref. 038 (10 minutes)</p> <p>The warning from the Bach Mai Hospital's Detoxification Centre director Pham Due following the admission of up to eight patients a month with complications from traditional herbal treatment.</p> <p>Show picture from Ref. 144 of Vietnamese patient who experienced ADRs such as mouth ulcers, erythematous rash, and red bruises all over body, after using a herbal medicine product to treat her arthritis.</p> <p>Present Slide 6 of Ref. 122 to highlight weaknesses of Vietnam's healthcare system regarding medicine safety activities.(5 minutes)</p> <p>IF TIME PERMITS: Familiarize the participants with pharmacovigilance of herbal medicines by presenting the 42 slides in Ref. 037</p>	30

B. Overview of the legal basis for PV system and framework of the PV system in Vietnam (Source Ref. 025)

Several laws, decrees and decisions (starting with the Pharmacy Law issued on June 14, 2005) served as the legal basis for establishing The DI & ADR Center as the national and central center for drug information and ADR monitoring in Vietnam. Those included:

- The Pharmacy Law issued on 14/6/2005
- The Decree No 79/2006/NĐ-CP dated 9/8/2006 issued by the Government instructing the implementation of Pharmacy Law
- The Decision No. 154/ 2006/ QĐ-TTg dated 30/6/2006 from Prime Minister about approving the proposal "State management on pharmacy, food and cosmetic safety for the period 2006-2015"

- Decision No. 2557/2002/QĐ-BYT dated 4/7/2002 from Minister of Health about issuing Regulation of Drug and Cosmetic Advertisement Information
- Announcement No. 127/TB- VPCP dated 26/05/2008 from Deputy Prime Minister Nguyen Thien Nhan about implementing state management on Pharmacy and development of Pharmaceutical Industry.
- Regulation of organization and operation of Hanoi University of Pharmacy approved by Minister of health on 25/2/2009

The framework of the PV system is provided in section C.

<i>Activity</i>	<i>Time (minutes)</i>
Present the legal basis for Vietnam's new PV system by using slides 4 – 5 of Ref. 122 Show the participants the actual Vietnamese legal documents and decrees relating to PV	10

- C. PV roles and activities the Ministry of Health (MOH), especially the National DI&ADR Center, Drug Administration of Vietnam (DAV), and Medical Services Administration (MSA) of Vietnam (Sources: Ref. 097, Ref. 098, Ref. 026)

Organizations that play a role in Vietnam's PV and medicine safety systems include:

- **Ministry of Health (MOH)** – is responsible for the governance and guidance of the health, healthcare and health industry of Vietnam. In conjunction with other ministries and the prime minister's office, the Ministry of Health is responsible for creating and promulgating long-term health policy programs.
- **National DI&ADR Center –National Drug Information and Adverse Drug Reaction Center** - Serves as the hub for receiving pharmacovigilance data collected by the regional centers and is responsible for Vietnam's database of PV and drug information. It also supports governmental authorities in assessing and understanding the advantages and disadvantages of drugs available in the market and provides drug information and advice on ADRs for clinical sites, pharmacy staff and the community. The National DI&ADR Center also establishes connections with international drug and ADR centers
- **DAV- Drug Administration of Vietnam** – Plays a role in legislation, regulation, development of policy documents and strategic planning for pharmacovigilance. Makes decisions and takes measures to deal with issues related to pharmacovigilance. Collaborates with the drug regulatory authorities of other countries and international agencies on pharmacovigilance, including reporting ADRs to WHO/Uppsala Monitoring Centre. The DAV monitors product quality, including conducting GMP inspections and post-marketing sampling and testing.
- **MSA – Medical Services Administration** - Provides guidance on the safe and appropriate use of medicines at health facilities. Supervises and trains health care workers on the rational and safe use of medicines in health facilities. In collaboration with Public Health Programs, takes measures to deal with issues related to pharmacovigilance in these programs. Provides advice to hospitals, clinic and providers on case management of medication-related adverse events.

Activity	Time (minutes)
<p>Present the slides 3-18 of the PowerPoint presentation in Ref. 098 to familiarize the participants with Vietnam’s national stakeholders and their roles in medicine safety activities. Stop at slide 6 to ask the participants to articulate what they already know about the roles of the stakeholders listed. Then, proceed with the presentation.</p> <p>Put extra emphasis on slide 13 to ensure that the participants understand the relationship between the Ministry of Health and the National DI&ADR Center, the DAV- Drug Administration of Vietnam and the MSA – Medical Services Administration.</p> <p>If time permits Show the participants examples of Vietnam’s Ministry of Health circulars relating to the roles of key MoH bodies. (Sources: Ref. 103, Ref. 104, Ref. 105, Ref. 106, Ref. 107 or from MoH website, if available) (15 min)</p>	30

D. Other PV stakeholders in Vietnam, including hospitals (and their DTCs and DIUs) (Sources: Ref. 097, Ref. 026)

Additional organizations that play a role in Vietnam’s PV and medicine safety systems include:

- Public/Private hospitals and clinics
- DTCs- Drug and Therapeutic Committees
- DIUs- Drug Information Units
- Public Health Programs
- WHO
- Donors / Development partners
- Academia & Research
- Media
- Manufacturers & Wholesalers
- Patients and Community
- Health Care Workers

Activity	Time (minutes)
<p>Return to slide 3 of Ref. 098 and point out how these stakeholders (including hospitals and their DTCs and DIUs) fit into the picture of PV stakeholders in Vietnam. Explain that:</p> <p>Hospital DTCs- Drug and Therapeutic Committees were established to ensure the quality drug provision and rational use of drugs in hospitals. There are currently DTCs functioning in all public hospitals in Vietnam.</p> <p>Hospital DIUs- Drug Information Units- are the regional, hospital based components of the DI-ADR system in Vietnam. Their functions include providing drug information; collecting, monitoring and processing ADR reports and monitoring drug quality problems in hospitals.</p> <p>Use pages 16-19 of Ref. 026 to highlight some of the opportunities and challenges faced by the hospital based DIUs.</p> <p>If time permits, then facilitate a brainstorming session for the participants to identify some possible solutions for improvement of DIU activities. Ask the participants to prioritize their recommended solutions based on their ease of implementation and the amount of improvement they might provide to the DIU activities. Compare their responses with the suggestions on pages 19 and 20 of Ref. 026.</p>	10

E. Importance of stakeholder coordination and collaboration for conducting PV activities effectively
(Source: Ref. 098)

Sustained collaboration and commitment are essential for optimal performance of pharmacovigilance activities. That collaboration can only be achieved when all those involved have clearly defined roles and expectations and are working through a designated focal point to coordinate all efforts.

Activity	Time (minutes)
<p>Present the slides 20-23 of the PowerPoint presentation in Ref. 098 to familiarize the participants with the coordination and collaboration associated with conducting PV activities in Vietnam</p>	10

Sources used in this session:

- Ref. 010 World Health Organization. *The Importance of Pharmacovigilance: Safety Monitoring of medicinal products*. 2002.
- Ref. 025 Nguyen, D. H. The strategy for the National DI/ADR Center and PV System in Vietnam. Hanoi University of Pharmacy. 2009.
- Ref. 026 The National DI & ADR Centre, Hanoi University of Pharmacy & Ministry of Health *National Capacity Assessment for Drug Information and Pharmacovigilance*. Submitted to World Health Organization (WHO). Dec. 2009.
- Ref. 034 World Health Organization. National Policy on Traditional Medicine and Regulation of Herbal Medicines - Report of a WHO Global Survey. Web. May. 2005.
- Ref. 035 The Museum of Vietnamese Traditional Medicine. Web.
- Ref. 037 Boyd, I. *Pharmacovigilance of Herbal Medicines*. International Society of Pharmacovigilance (ISoP). [PowerPoint slides]. 2009.
- Ref. 038 Herbal Medicines Threaten Health, Pocket. Web. 2009.
- Ref. 097 Nguyen T. P. C. *Role of the Drug and Therapeutic Committee in Safe and Rational Use of Drugs in Vietnam*. Medical Service Department, Ministry of Health. [PowerPoint slides]. 2009.
- Ref. 098 Hanoi University of Pharmacy. *National Stakeholders and their Roles in Medicine Safety Activities*. [PowerPoint slides]. 26 Mar 2009
- Ref. 103 Vietnam Ministry of Health. *Circular No: 09 /2011/TT-BYT: Guidance on criteria and technical scope of ART treatment sites*. Hanoi, 26 Jan. 2011
- Ref. 104 Vietnam Ministry of Health. *Circular No: 22/2011/TT-BYT: Stipulating the Organisation and Operation of Hospital Pharmacies*. Hanoi, 10 Jun. 2011
- Ref. 105 Vietnam Ministry of Health. *Circular No: 23/2011/TT-BYT: Promulgating Instructions on Drug Use in Health Care Establishments with Patient Beds*. Hanoi, 10 Jun. 2011
- Ref. 106 Vietnam Ministry of Health. *Circular No: 47/2010/TT-BYT: Guidelines for the Export and Import of Drugs and Primary Packaging*. Hanoi, 26 Jan. 2011
- Ref. 107 Vietnam Ministry of Health, Vietnam Drug Administration. *Circular No: 2313/QLD-CL: Concerning the Issuance of the List of Good Pharmacy Practices" (GPP), "Good Distribution Practices" (GDP) and a Number of Procedures*. Hanoi, 11 May 2007.
- Ref. 122 National DI&ADR Centre of Vietnam. *Session 1.2 Pharmacovigilance Program in Vietnam Pharmacovigilance In-service Workshop*. [PowerPoint slides]. 2012.
- Ref. 144 Image of Vietnamese patient with ADRs after using herbal medicine. *Nutrition*. Website.

Additional Reading and Resources:

- Ref. 024 Pal, S., Dodoo, A., Mantel, A., & Olsson, S. The World Medicines Situation 2011 Pharmacovigilance and Safety of Medicines. World health Organization. 2011.

Session 2.1: Adverse Drug Reaction as a Factor for Adverse Drug Events

Topics to cover in this session:

- A. Definition: Adverse drug reactions (ADR), adverse drug events (ADE), side effects (SE), post marketing surveillance (PMS), and other PV-related terminologies
- B. Classification of ADRs (e.g., Type A and B and others; immediate, delayed etc.)
- C. Predisposing factors of adverse drug reactions: age, gender, pregnancy, previous history of allergy or reaction, multiple drug therapy, ethnic and genetic factors and concomitant disease processes
- D. Brief overview and listing of organ-system-based ADRs of *major clinical significance* (e.g., dermatological, gastrointestinal, hematological, hepatic, renal, and ocular)
- E. Brief overview of strategies that minimize the occurrence or promote early detection of ADRs

Objectives: At the end of this session, participants will be able to:

- Define the various terms related to PV
- Differentiate the various types of ADRs
- Enumerate three ADRs of high clinical significance for each organ system
- List predisposing factor for ADRs, giving at least one example for each factor (age, gender, previous history of allergy, multiple drug therapy, ethnic/genetic factors, and co-morbidities)
- List at least 5 drugs known to cause major teratogenic effects; list pregnancy risk categories of drugs, giving at least one drug example for each category
- Discuss ongoing or potential strategies feasible in his/her hospital setting that could help minimize or prevent the risk of ADRs
- Narrate self-perception of his/her role in minimizing or preventing ADRs in his or her own hospital practice setting

Content Summary and Process Overview / Instructional Methodology (Total Duration: 45 Minutes)

- A. Definition: Adverse drug reactions (ADR), adverse drug events (ADE), side effects (SE), post marketing surveillance (PMS), and other PV-related terminologies
(Sources: Ref. 050, Ref. 052)

Adverse Event (AE): Any untoward medical occurrence that may present during treatment with a pharmaceutical product but which does not necessarily have a causal relationship with this treatment.

Adverse (Drug) Reaction (ADR): A response which is noxious and unintended, and which occurs at doses normally used in humans for the prophylaxis, diagnosis, or therapy of disease, or for the modification of physiological function (WHO, 1972).

An adverse drug reaction, contrary to an adverse event, is characterized by the suspicion of a causal relationship between the drug and the occurrence, i.e. judged as being at least possibly related to treatment by the reporting or a reviewing health professional.

In the *EU Directive 2010/84*, which will become applicable in July 2012, an adverse reaction is defined as "A response to a medicinal product which is noxious and unintended."

Medication Error: Any preventable event that may cause or lead to inappropriate medication use or patient harm, while the medication is in the control of the health care professional, patient, or consumer. Such events may be related to professional practice, health care products, procedures, and systems including: prescribing; order communication; product labeling, packaging and nomenclature; compounding; dispensing; distribution; administration; education; monitoring; and use."

Side effect: Any unintended effect of a pharmaceutical product occurring at normal dosage which is related to the pharmacological properties of the drug.

Post-marketing: The stage when a drug is generally available on the market.

Pre-marketing: The stage before a drug is available for prescription or sale to the public.

<i>Activity</i>	<i>Time (minutes)</i>
Use slides 4-10 in Ref. 123 to provide definitions of PV related terminologies. Hand out the list of PV terminologies and their definitions as shown in content summary.	10

B. Classification of ADRs (e.g., Type A and B and others; immediate, delayed etc.)
(Source: Ref. 047)

ADR are classified according to:

Frequency

Frequent ADR: if the frequency of occurrence is **> 5%**

Occasional ADR: if the frequency of occurrence is including between **0.1% and 5%**

Unusual ADR: if frequency of occurrence **< 0.1%**

Mechanism of occurrence

Type A reactions: Adverse reactions which are a result of an exaggerated but otherwise usual pharmacological effect. These tend to be common, dose-related, predictable and less serious. They can usually be treated by reducing the dose of the drug.

Type B reactions: Adverse reactions which are aberrant, and may be due to hypersensitivity or immunologic reactions. These tend to be uncommon, not related to dose, unpredictable and potentially more serious. They usually require cessation of the drug.

Predictability

Predictable

- ADR with pharmacological mechanism
- Medicines Interactions

Unpredictable

- Immuno-allergic reaction
- Idiosyncratic

Degree of severity (will be covered in more detail in session 5.3)

Grade 1: Mild

Grade 2: Moderate

Grade 3: Severe

Grade 4: Fatal

Avoidability

Definitely avoidable: treatment procedure inconsistent with present day knowledge of good medical practice (such as concomitant use of medications with known adverse interactions)

Possibly avoidable: cursory review of patient's medical history

Not avoidable: allergic or idiosyncratic reactions

Unevaluable

<i>Activity</i>	<i>Time (minutes)</i>
Use slides 18-31 in Ref. 123 to familiarize the participants with the classifications of ADRs	25

- C. Predisposing factors of adverse drug reactions: age, gender, pregnancy, previous history of allergy or reaction, multiple drug therapy, ethnic and genetic factors and concomitant disease processes
(Sources: Ref. 044; Ref. 051, Ref. 054)

Certain factors predispose patients to ADRs. Listed below are such factors with a brief statement or an example for each:

Age: ADRs more likely in patients of 60 years and over

Gender: Women more likely to experience ADRs than men

Pregnancy: Some medications (teratogens) cause fetal malformation. Examples include: methotrexate (methyaminopterin), tetracyclines, thalidomide, coumarin anticoagulants, isotretinoin (Accutane®)

Previous history of allergy or reaction: even a small amount of drug can trigger an allergic reaction

Ethnic and genetic factors: may account for alterations in the handling of drugs and their effects

Multiple-drug therapy: chance of the drugs interacting with each other increases as the number of drugs given concomitantly increases

Concomitant disease processes: underlying renal or hepatic disease increased the risk of adverse drug reactions due to drugs eliminated by these organs

Activity	Time (minutes)
Use slides 19 – 51 in Ref. 123 to describe the predisposing factors for ADRs. If time permits: Demonstrate the on-line tool that shows pregnancy risk categories from FDA and provides capacity to search the category of any drug using Ref. 048 . Allow the participants to suggest drugs for you to use in the search.	60

- D. Brief overview and listing of organ-system-based ADRs of major clinical significance (e.g., dermatological, gastrointestinal, hematological, hepatic, renal, and ocular) (Source Ref. 145, Ref. 146)

Dermatological

- Fixed drug eruption
- Erythema multiforme, Stevens-Johnson syndrome,
- Toxic epidermal necrolysis

Co-trimoxazole and ampicillin are examples of medications known to cause dermatological ADRs

Gastrointestinal

- Gastrointestinal haemorrhage
- Pancreatitis
- Peptic ulcer

NSAIDs are examples of medications known to cause gastrointestinal ADRs

Hematological

- Anaemia
- Bone marrow suppression / Bone marrow depression
- Thrombosis venous deep

Carbamazepine and NSAIDs are examples of medications known to cause hematological ADRs

Hepatic

- Cholestatic liver injury
- Hepatocellular liver injury
- Liver function tests abnormal

Oral contraceptives are examples of medications known to cause hepatic ADRs

Renal

- Glomerulonephritis (acute or chronic)
- Nephritis, interstitial
- Renal failure

Gentamicin is an example of a drug known to cause renal ADRs

Ocular

- Cataract
- Keratitis
- Retinal disorder

Chloroquine and hydroxychloroquine are examples of medications known to cause ocular ADRs

<i>Activity</i>	<i>Time (minutes)</i>
<p>Use slides 52-70 in Ref. 123 to provide a brief overview of organ-system based ADRs of major clinical significance</p> <p>Ask the participants to share their experiences regarding organ system related ADRs.</p> <p>Handout of a list of organ system-based ADRs of “major clinical significance - provided in content summary.</p>	40

E. Brief overview of strategies that minimize the occurrence or promote early detection of ADRs
(Source: Ref. 006)

Monitoring Product Quality to identify products that are defective or counterfeit, deteriorated, or adulterated because of poor manufacturing practices inadequate distribution and storage, or tampering.

Educating Healthcare providers to reduce medication errors from illegible handwriting, use of dangerous abbreviations, overlooked interactions with other medicines, oral miscommunications, and sound-alike or look-alike products

Participating in post-marketing surveillance and regularly reviewing recent international PSURs (Periodic Safety Update Reports)

Instituting active surveillance methods using registries, sentinel sites, and follow-up of defined patient cohorts

Establishing mechanisms to communicate medicine safety information to health care professionals and the public

Activity	Time (minutes)
<p>Use slides 71-77 in Ref. 123 to ensure that the participants are aware of the strategies that minimize the occurrence or promote the early detection of ADRs</p> <p><i>If time permits:</i> Ask participants to cluster in groups of three to spend 5 minutes discussing and recording how they personally plan to minimize or prevent ADRs in their own hospital setting. Call upon several participants to share one of their plans with the entire group making sure that there is at least one plan related to each of the 5 strategies listed in the summary above. Then, summarize by stressing the importance their future roles will play in reducing ADRs. (5 minutes)</p>	15

Sources used in this session:

- Ref. 006 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. Sep. 2009.
- Ref. 044 Federal Ministry of Health, Nigeria. *Definitions and Classification of Adverse Events*. [PowerPoint slides]. 6 Jan 2011.
- Ref. 047 Stergachi, A. *Pharmacovigilance Training of Trainers: Definitions and Types of Adverse Events* [PowerPoint slides]. Rwanda. Sep. 2009.
- Ref. 048 FDA Categorization of Drug Risks to the Fetus. Web. Last update: 5 Oct. 2006. Web.
- Ref. 050 The Uppsala Monitoring Centre. *Glossary of terms used in Pharmacovigilance*. Web. Aug. 2011.
- Ref. 051 Natalie Hurwitz, N. Predisposing Factors in Adverse Reactions to Drugs [Abstract]. *Br Med J*. 1.5643 (1 March 1969): 536–539. Web.
- Ref. 052 National Coordinating Council for Medication Error Reporting and Prevention. *What is a Medication Error?* Web.
- Ref. 054 University of Washington Medicine Department of Pharmacy Services' Drug Information Center. Teratogens List. Web.
- Ref. 123 National DI&ADR Centre of Vietnam. *Session 2 Adverse Drug Reactions Pharmacovigilance In-service Workshop*. [PowerPoint slides]. 2012.
- Ref. 145 Bankowski, Z., Bruppacher, R., Crusius, I., Gallagher, J., Kremer, G. & Venulet, J. *Reporting Adverse Drug Reactions, Definitions of Terms and Criteria for their Use*. The Council for International Organizations of Medical Sciences (CIOMS). Web. 1999.
- Ref. 146 Pasadhika¹, S. & Fishman, G.A. Effects of chronic exposure to hydroxychloroquine or chloroquine on inner retinal structures. *Eye (2010) 24, 340–346; doi:10.1038/eye.2009.65; 17 April 2009*.

Additional Reading and Resources:

- Ref. 046 Aronson, J. K. & Ferner, R. E. Clarification of Terminology in *Drug Safety*. *Drug Safety*: 28.10 (2005): 851-870.

Session 3.1: Risk Evaluation and Reporting

Topics to cover in this session:

- A. Sources of ADE data: premarket safety data, spontaneous reports, Phase IV studies, scientific literature, product inquiries and complaints, unpublished manuscripts, internet
- B. *Detailed coverage* on passive surveillance methods— roles of spontaneous reporting; strengths and limitations of spontaneous reporting; key data fields in Vietnam spontaneous reporting form: patient details, description of the adverse event or product quality problem, suspected drug(s) or vaccine(s), reporter details
- C. *Brief introduction to* active surveillance methods: case control study, cohort study, prescription events monitoring, registries, sentinel surveillance

Objectives: At the end of this session, participants will be able to:

- Explain strengths and limitations of spontaneous reporting
- Demonstrate knowledge and confidence in filling the various fields of the spontaneous reporting form currently used in Vietnam

Content Summary and Process Overview / Instructional Methodology (Total Duration: 30 Minutes)

- A. Sources of ADE data: premarket safety data, spontaneous reports, Phase IV studies, scientific literature, product inquiries and complaints, unpublished manuscripts, internet (Sources: Ref. 087, Ref. 072)

ADR information can be obtained from clinical trials safety data -both pre-marketing and post-marketing (Phase IV) studies, medical publications, WHO/UMC publications, newspapers, the internet and colleagues. The least reliable information is anecdotal while the most reliable is gained from clinical trials. There are mainly two methods of ADR reporting; passive spontaneous surveillance and active surveillance. Passive, spontaneous surveillance and active surveillance are complementary methods. Data collected by both methods are needed to best meet the PV goals of safeguarding public health and improving rational medicine use.

According to WHO, the following is required for ADR reporting: Identifiable source of information or reporter (who must be literate), Identifiable patient, Name (s) of suspected product (s) and Description of the suspected reaction(s)/event.

<i>Activity</i>	<i>Time (minutes)</i>
Use slides 3-9 of Ref. 124 to introduce the participants to the sources of ADE data.	10

- B. Detailed coverage on passive surveillance methods— roles of spontaneous reporting; strengths and limitations of spontaneous reporting; key data fields in Vietnam spontaneous reporting form: patient details, description of the adverse event or product quality problem, suspected drug(s) or vaccine(s), reporter details (Sources: Ref. 087, Ref. 072, Ref. 090)

In passive spontaneous reporting, health care workers voluntarily submit suspected ADR reports to regulatory authorities followed by re-evaluation of risk and the benefits of the drugs. The advantages of passive spontaneous reporting are that it is simple, low cost and able to detect rare events if continuously done. The main problem with this method is underreporting. In passive surveillance, health professionals and others are encouraged to report adverse events, but no other active measures used. So, spontaneous reporting is dependent on the initiative and motivation of potential reporters. In spite of these limitations, spontaneous reporting is a key method of adverse events surveillance.

According to WHO, the following is required for ADR reporting: Identifiable source of information or reporter (who must be literate), Identifiable patient, Name (s) of suspected product (s) and Description of the suspected reaction(s)/event. The ADR reporting form in use in Vietnam since July 2011 contains all of those key data fields.

Activity	Time (minutes)
Use slides 10-30 of Ref. 124 to provide detailed coverage on passive surveillance methods highlighting the key data fields in the Vietnam spontaneous reporting form.	40

C. Brief introduction to active surveillance methods: case control study, cohort study, prescription events monitoring, registries, sentinel surveillance (Sources: Ref. 087, Ref. 045, Ref. 088)

Active surveillance (in contrast to passive surveillance) seeks to determine the ratio/number of ADRs through formal and continuous monitoring and collection of health outcomes.

Active surveillance methods include case control, cohort studies, prescription event monitoring, registries and sentinel surveillance. Active surveillance methods are more reliable but more expensive than passive surveillance methods.

Case control studies are epidemiologic studies in which the frequency of exposure to a drug in a group of patients who already have had a particular adverse event is compared to the frequency of exposure to that medication in a group of patients who did not experience that adverse event. So, patients are recruited after occurrence of the adverse event and are compared with control patients who did not experience the same adverse event.

Cohort studies are epidemiologic studies in which the frequency of an ADR's occurring in a group that has been exposed to a medication of interest is compared to the frequency of that same ADR's occurring in a group that was not exposed to that same medication. The cohorts of patients must be followed, waiting for the ADR to appear.

Prescription events monitoring is a non-interventional cohort technique in which patients are identified from dispensed prescriptions. Questionnaires are posted to the prescribing doctor requesting detailed info including suspected ADRs since the first prescription for the study drug. This technique is most applicable for new drugs intended for long-term, widespread use. But, its limitations include poor physician- and patient-response rates and the unfocused nature of data collection which can obscure important signals.

Registries are classified according to how the populations are defined. Product registries include patients who have been exposed to medicinal products or medical devices. Health services registries consist of patients who have had a common procedure, clinical encounter, or hospitalization. Disease or condition registries are defined by patients having the same diagnosis. An example is a pregnancy exposure registry which identifies pregnant women and actively collects information on drug exposures during pregnancy and associated pregnancy outcomes.

Sentinel surveillance takes place through reviewing medical records or interviewing patients in a sample of sentinel sites. This surveillance method provides complete and accurate data and information on sub-groups may be obtained. It is most efficient for drugs used mainly in institutional settings e.g., hospitals, nursing homes. But, it has the disadvantages of selection bias, small number of patients, and increased cost.

<i>Activity</i>	<i>Time (minutes)</i>
Use slides 31-49 of Ref. 124 to provide a brief introduction to active surveillance methods	40

Sources used in this session:

- Ref. 045 Federal Ministry of Health, Nigeria. *Active Surveillance* [PowerPoint slides]. 6 Jan 2011.
- Ref. 072 Joshi, M. P. *A System-oriented Approach to Implementing Pharmacovigilance* [PowerPoint slides]. 29 Sep. 2009.
- Ref. 087 "Pharmacovigilance: Quality, Safety and Efficacy of Medicines For Better Health Care: Curriculum and Implementation Guide." Ministry of Public Health and Sanitation & Ministry of Medical Services. Kenya. [PowerPoint slides]. Feb. 2009.
- Ref. 088 Hanoi University of Pharmacy. *Introduction To Pharmacovigilance: Active Surveillance and Formal Pharmacoepidemiology Methods*. [PowerPoint slides]. 26 Mar 2009
- Ref. 090 Ministry of Health; The National DI & ADR Centre. *Vietnam ADR Reporting Form*
- Ref. 124 National DI&ADR Centre of Vietnam. *Session 3 Risk Evaluation and Reporting*. Pharmacovigilance In-service Workshop. [PowerPoint slides]. 2012.

Additional Reading and Resources:

- Ref. 089 Hanoi University of Pharmacy. *Introduction To Pharmacovigilance: Signal Evaluation: Signal Generation and Strengthening*. [PowerPoint slides]. 26 Mar 2009
- Ref. 091 Cobert, B. L. & Biron, P. *Pharmacovigilance from A to Z: Adverse Drug Event Surveillance*. Malden: Blackwell Science, 2002. Print.

Session 4.1: Risk Communication, Risk Management, and Risk Minimization

Topics to cover in this session:

- A. The Erice Declaration on effective communication in PV
- B. Role of the National DI&ADR Center, DAV, hospital DTCs and DIUs and other stakeholders in communicating medicine safety information; relevant circulars from MOH relating to such roles for key MOH bodies
- C. Communicating messages about medicine safety (e.g., “Dear Doctor” letters, medicine alerts, media statements, patient information leaflets, newsletters, and personal feedback to reporters)
- D. Strategies and tools for risk management and minimization

Objectives: At the end of this session, participants will be able to:

- Through a personal narrative, demonstrate commitment to communicating drug safety information ethically and effectively
- Cite actual examples of strategies, approaches or tools used by stakeholders in Vietnam to promote and support risk communication, management and minimization
- Cite examples of risk management and minimization initiative such as FDA’s “risk management framework”, “risk minimization action plans” and “risk evaluation and mitigation strategies”
- Through a personal narrative, demonstrate commitment to promoting safety and preventing risks, taking a “proactive” rather than a “reactive” approach for the safe use of medicines, planning and implementing “risk management” and “risk minimization” strategies in his/her work setting

Content Summary and Process Overview / Instructional Methodology (Total Duration: 120 Minutes)**A. The Erice Declaration on effective communication in PV (Source: Ref. 093)**

The Erice declaration was drawn up at the International Conference on Developing Effective Communications in Pharmacovigilance in Erice, Sicily, 24-27 September 1997.

The conference was attended by health professionals, researchers, academics, media writers, representatives of the pharmaceutical industry, drug regulators, patients, lawyers, consumers and international health organisations. Major points in the declaration include:

- Drug safety information must serve the health of the public
- Information should be ethically and effectively communicated in terms of content and method
- Facts, hypotheses and conclusions should be distinguished
- Uncertainty should be acknowledged
- Information should be provided in ways that meet both general and individual needs
- Education in the appropriate use of medicines is essential for the public, patients and health care providers
- Education requires special commitment and resources
- Information on medicines directed to the public should be balanced with respect to risks and benefits
- All evidence needed to assess and understand risks and benefits must be openly available
- Constraints which hinder communications should be recognised and overcome

Activity	Time (minutes)
<p>Present slide 6 of Ref. 093 to establish the general principals of communication</p> <p>Then, ask the participants to gather in groups of 3 to identify the points they feel should be included when communicating drug safety information to patients. (5 minutes)</p> <p>Present slides 9-11 of Ref. 093 about the points included in the ERICE Declaration. Also distribute a copy of the Erice Declaration Ref. 147 (5 minutes)</p> <p>Ask the participants to compare the points included in the ERIC Declaration with the points they identified. Ask the participants to share the points missing on their lists with the rest of the group.</p> <p>(5 minutes)</p>	15

- B. Role of the National DI&ADR Center, DAV, hospital DTCs and DIUs and other stakeholders in communicating medicine safety information; relevant circulars from MOH relating to such roles for key MOH bodies (Sources: Ref. 097, Ref. 098, Ref. 026)

The role of stakeholders in Vietnam's PV and medicine safety system in communicating medicine safety information includes:

National DI&ADR Center –National Drug Information and Adverse Drug Reaction Center- As the hub for receiving pharmacovigilance data collected by the regional centers, the National DI&ADR Center provides drug information and advice on ADRs for clinical sites, pharmacy staff and the community and also establishes connections with international drug and ADR centers.

DAV- Drug Administration of Vietnam –Collaborates with the drug regulatory authorities of other countries and international agencies on pharmacovigilance, including reporting ADRs to WHO/Uppsala Monitoring Centre

MSA – Medical Services Administration - Provides guidance on the safe and appropriate use of medicines at health facilities training health care workers on the rational and safe use of medicines in health facilities

Hospital DTCs - Drug and Therapeutic Committees –Produce documentation and guidelines for drug use. Provide training to trainers on drug use and provide training (including in minority languages) for the public about rational drug use in collaboration with The Voice of Vietnam.

DIUs- Drug Information Units - Their functions include providing drug information and publishing leaflets and handbooks.

<i>Activity</i>	<i>Time (minutes)</i>
<p>Show page 3 in the in Ref. 098 to remind the participants about Vietnam's PV national stakeholders which were previously discussed in session 1.2. Highlight the roles some of those stakeholders play in in communicating medicine safety information, as shown in section B of the content summary in this session. (5 min)</p> <p>Use slides 29 to 39 of Ref. 125 to present more detail about the role of the National DI&ADR Center in communicating medicine safety information (20 min)</p> <p>Show page 13 in Ref. 097 to show the challenges faced by DTCs in Vietnam. Ask the participants to consider what steps they might take after they join the pharmacy workforce to help reduce those challenges. Invite a few participants to share their thought on this issue. (15 min)</p> <p>Show the participants examples of Vietnam's Ministry of Health circulars relating to the roles of key MoH bodies. (Sources: Ref. 103, Ref. 104, Ref. 105, Ref. 106, Ref. 107 or from MoH website, if available) (10 min)</p>	50

- C. Communicating messages about medicine safety (e.g., “Dear Doctor” letters, medicine alerts, media statements, patient information leaflets, newsletters, and personal feedback to reporters)

Public communication on safety concerns over medicines and advice on how to prevent medicine-induced patient harm is a challenge for the overall success of those responsible for pharmacovigilance. A wide variety of communication mechanisms such as “Dear Doctor” letters, medicine alerts, media statements, patient information leaflets, medicine safety bulletins and newsletters are used to provide healthcare professionals and patients with appropriate and prompt information.

<i>Activity</i>	<i>Time (minutes)</i>
Use Ref. 095 slides 3 – 11 to introduce the topic of communication about medicine safety. Show examples of communications from other countries from pages 12-17 of Ref. 094 and Ref. 101 – the FDA Drug Safety Communications website. Show examples of real messages used to communicate medicine safety information in Vietnam from the DI&ADR website.	25

- D. Strategies and tools for risk management and minimization (Sources: Ref. 099, Ref. 092, Ref. 096)

Risk management for medicinal products is the set of pharmacovigilance activities and interventions designed to identify, characterize, prevent or minimize risks relating to medicinal products, including the assessment of the effectiveness of those interventions. Risk management is an iterative process during which adjustments are made to the risk minimization tools to further improve the benefit-risk balance.

In most countries, the marketing authorization holder submits a “risk management plan” to the health authority as part of the application to market a new medicinal product. The risk management plan must include the risk profile of the drug (at that time point) and the pharmacovigilance activities that are planned.

Activity	Time (minutes)
<p>Present slides 2-22 from Ref. 125 to familiarize the participants with strategies for risk management and risk minimization.</p> <p>If time permits, share page 24 of Ref. 108 which contains ANNEX B: METHODS FOR RISK MINIMISATION of European Medicines Agency’s Guideline on Risk Management Systems for Medicinal Products for Human Use.</p> <p>If time permits present the case study starting on page 30 of Ref. 096 about Rofecoxib’s Risk Management and ask the participants to consider the questions on page 39.</p> <p>Summarize this topic by stressing that the tools for risk minimization can be divided into those where a reduction in risk is achieved primarily through the <u>provision of information</u> and education and those which seek to <u>control the use of the medicine</u>.</p> <p>Ask the participants to cluster in pairs to discuss how they plan on taking a “proactive” rather than a “reactive” approach for the safe use of medicines, planning and implementing “risk management” and “risk minimization” strategies in their work setting. Invite the participants to share the results of those discussions with the entire group.</p>	30

Sources used in this session:

- Ref. 026 The National DI & ADR Centre, Hanoi University of Pharmacy & Ministry of Health *National Capacity Assessment for Drug Information and Pharmacovigilance*. Submitted to World Health Organization (WHO). Dec. 2009.
- Ref. 092 Federal Ministry of Health, Nigeria. *Risk Management Strategies*. [PowerPoint slides]. 6 Jan. 2011.
- Ref. 093 Federal Ministry of Health, Nigeria. *Medicine Information and Risk Communication*. [PowerPoint slides]. 6 Jan. 2011.
- Ref. 094 Joshi M. *Medicine Information and Medicine Safety Bulletins*. U.S. Agency for International Development. 2010.
- Ref. 095 Hanoi University of Pharmacy. *Effective Communication in Pharmacovigilance Programs*. [PowerPoint slides]. 26 Mar 2009
- Ref. 096 Hanoi University of Pharmacy. *Use of Pharmacovigilance for Risk Management*. [PowerPoint slides]. 26 Mar 2009
- Ref. 097 Nguyen T. P. C. *Role of the Drug and Therapeutic Committee in Safe and Rational Use of Drugs in Vietnam*. Medical Service Department, Ministry of Health. [PowerPoint slides]. 2009.
- Ref. 098 Hanoi University of Pharmacy. *National Stakeholders and their Roles in Medicine Safety Activities*. [PowerPoint slides]. 26 Mar 2009
- Ref. 099 Ann Van Ermen, A. V. *Pharmacovigilance and Risk Management*. Belgian Centre for Pharmacotherapeutic Information and Belgian Centre for Pharmacovigilance. [PowerPoint slides]. 26 Aug. 2007.
- Ref. 101 U.S. Food and Drug Administration. 2011 Drug Safety Communications. Web. Last Updated: 10 Jan. 2012.
- Ref. 103 Vietnam Ministry of Health. *Circular No: 09 /2011/TT-BYT: Guidance on criteria and technical scope of ART treatment sites*. Hanoi, 26 Jan. 2011
- Ref. 104 Vietnam Ministry of Health. *Circular No: 22/2011/TT-BYT: Stipulating the Organisation and Operation of Hospital Pharmacies*. Hanoi, 10 Jun. 2011
- Ref. 105 Vietnam Ministry of Health. *Circular No: 23/2011/TT-BYT: Promulgating Instructions on Drug Use in Health Care Establishments with Patient Beds*. Hanoi, 10 Jun. 2011
- Ref. 106 Vietnam Ministry of Health. *Circular No: 47/2010/TT-BYT: Guidelines for the Export and Import of Drugs and Primary Packaging*. Hanoi, 26 Jan. 2011
- Ref. 107 Vietnam Ministry of Health, Vietnam Drug Administration. *Circular No: 2313/QLD-CL: Concerning the Issuance of the List of Good Pharmacy Practices" (GPP), "Good Distribution Practices" (GDP) and a Number of Procedures*. Hanoi, 11 May 2007.
- Ref. 108 European Medicines Agency, Committee for Medicinal Products for Human Use (CHMP). *Guideline on Risk Management Systems for Medicinal Products for Human Use*. Web. 6 Sep. 2005.
- Ref. 125 National DI&ADR Centre of Vietnam. *Session 4 Risk management-minimization and Communication*. Pharmacovigilance In-service Workshop. [PowerPoint slides]. 2012.

- Ref. 147 International Conference on Developing Effective Communications in Pharmacovigilance. *The Erice Declaration on Communicating Drug Safety Information*. Web. 1997.

Additional Reading and Resources:

- Ref. 014 CIOMS Working Group IV Benefit-Risk Balance for Marketed Drugs: Evaluating Safety Signals. Web. 1998.
- Ref. 077 Berdai, D. *Risk and crisis Management in Pharmacovigilance*. Hanoi. [PowerPoint slides]. 2009.
- Ref. 102 Bahri, P., Mol, P. G. M., Theophile, H., et al. Communication in Drug Safety: A report from an interactive debate held at the 10th Annual Meeting of the International Society of Pharmacovigilance (ISoP), 2010. Web. *Drug Safety*, 34.10, (Oct. 2011): 881-882.
- Ref. 109 Institute for Safe Medication Practices. List of Error-Prone Abbreviations, Symbols, and Dose Designations. Web. 2011.
- Ref. 115 Wysowski, D. *Review of Tysabri Risk Minimization Action Plan (RiskMAP)*. FDA Division of Drug Risk Evaluation, Office of Drug Safety. Peripheral and Central Nervous System Drugs Advisory Committee Meeting. [PowerPoint slides]. March 7-8, 2006
- Ref. 116 National Center for Biotechnology Information, U.S. National Library of Medicine. *Natalizumab Injection*. Web. 2011.
- Ref. 302 U.S. Food and Drug Administration. *Guidance for Industry: Development and Use of Risk Minimization Action Plans*. Web. 2005.

Sessions 5.1 through 5.5 are designed specifically for healthcare providers working in Vietnam's hospitals.

Session 5.1: Setting up PV programs in hospitals

Topics to cover in this session:

- A. Role of hospitals, including Drug & Therapeutics Committees (DTCs) and Drug Information Unit (DIU), in promoting PV and medicine safety in Vietnam
- B. Minimum requirements for setting up PV programs in hospitals in Vietnam

Objectives: At the end of this session, participants will be able to:

- Articulate how and in what roles his/her hospital (including its DTC and DIU) fits as a stakeholder in the overall PV system in Vietnam
- Describe the “basic minimum requirements” for setting up a PV program in his/her hospital

Content Summary and Process Overview / Instructional Methodology (Total Duration: 45 Minutes)**A. Role of hospitals, including Drug & Therapeutics Committees (DTCs) and Drug Information Unit (DIU), in promoting PV and medicine safety in Vietnam (Sources: Ref. 076, Ref. 097)**

Patients with serious adverse drug reactions are likely to be admitted to hospital. And, adverse drug reactions and interactions are common in the hospital environment. As a result, the proper study, documentation and reporting of such cases are a natural part of the hospital setting. The establishment of pharmacovigilance centers in hospitals also improves the care of patients with drug-induced diseases and increases, qualitatively and quantitatively, adverse reaction reporting. Hospital PV activities are accompanied by their DTCs and DIUs drug information and communication activities in promoting PV and medicine safety in Vietnam. At the present time, hospitals are the main source of ADR reports in Vietnam.

Activity	Time (minutes)
Show slides 4-11 of Ref. 126 to reinforce the participant's awareness about The role of hospitals in promoting PV and medicine safety in Vietnam. If time permits: Display real examples of PV-related activities or initiatives carried out by hospitals or their DTCs in Vietnam (if available).	15

B. Minimum requirements for setting up PV programs in hospitals in Vietnam (Sources: Ref. 126, Ref. 072)

Beyond the underlying political support that is required in order to set up PV programs in hospitals, additional requirements include: designated, trained staff, facilities and technology and established procedures for the entire reporting process. Those procedures need to identify the reporters, method of reporting and events which should be reported.

Activity	Time (minutes)
Facilitate a brainstorming session for the participants to identify what they feel are the minimum requirements for setting up PV programs in hospitals. (10 minutes) Then, show slides 12-21 of Ref. 126 to provide the details associated with the minimum requirements for setting up PV programs in hospitals and to enable the participants to compare the results of their brainstorming with the requirements shown in the presentation. (20 minutes)	30

Sources used in this session:

- Ref. 072 Joshi, M. P. *A System-oriented Approach to Implementing Pharmacovigilance* [PowerPoint slides]. 29 Sep. 2009.
- Ref. 076 Meyboom, R. H. B., Egberts, A. C. G., Gribnau, F. W. J., & Hekster, Y. A. Pharmacovigilance in Perspective. *Drug Safety*, 21.6 (Dec. 1999): 429-447.
- Ref. 097 Nguyen T. P. C. *Role of the Drug and Therapeutic Committee in Safe and Rational Use of Drugs in Vietnam*. Medical Service Department, Ministry of Health. [PowerPoint slides]. 2009.
- Ref. 126 National DI&ADR Centre of Vietnam. *Session 5.1 Setting up PV Programs in Hospitals*. Pharmacovigilance In-service Workshop. [PowerPoint slides]. 2012.

Session 5.2: ADR reporting

Topics to cover in this session:

- A. Strategies to improve ADR reporting and analysis (e.g., ADR form widely available, reporting as routine and normal part of administering healthcare, distribution network, feedback to reporters)

Objectives: At the end of this session, participants will be able to:

- Through a personal narrative, demonstrate enthusiasm and conscientiousness (in his/her role as a health care worker) toward filling and sending spontaneous reporting form when an ADR is suspected in his/her work setting
- Demonstrate correct understanding by telling that spontaneous reporting and active surveillance approaches are complementary methods
- Describe practically feasible strategies for improving ADR reporting in his/her practice setting

Content Summary and Process Overview / Instructional Methodology (Total Duration: 120 Minutes)**A. Strategies to improve ADR reporting and analysis (e.g., ADR form widely available, reporting as routine and normal part of administering healthcare, distribution network, feedback to reporters)**

(Sources: Ref. 072, Ref. 089)

Strategies for improving ADE analysis cannot take place in the absence of ADE reports, so it is essential to increase the reporting rate. Some approaches to increasing the rate of reporting include:

- Ensure that the ADR forms are widely available by making them available to each health facility nationwide. Define priorities for reporting and provide quick access to the PV system.
- Incorporate reporting as routine and normal part of administering healthcare by including it in health facility SOPs and by incorporating PV into the education of all healthcare workers.
- Establish and use regional networks and facilitate communication among them to increase ADR awareness among healthcare professionals and the public.
- Provide feedback to reporters to encourage them to continue to report ADRs.

Optimize opportunities to improve ADE analysis by exploiting opportunities for integrating PV functions into existing tools and software.

Activity	Time (minutes)
<p>Open the topic by stressing that strategies for improving ADE analysis cannot take place in the absence of ADE reports, so it is essential to increase the reporting rate. Discuss the approaches to increasing the rate of reporting listed in the content summary.</p> <p>Ask the participants to consider why providing feedback to reporters might increase the rate of reporting. (5 min)</p> <p>Discuss potential opportunities to improve ADE analysis by exploiting existing tools and software. (5 min)</p> <p>If time permits, discuss statistical screening of data bases and data mining.</p> <p>Ask the participants to identify which of the strategies are most practically feasible for improving ADR reporting in his/her practice setting. (10 min)</p>	20
<p>Use all 37 slides in Ref. 127 to provide detailed guidance on the ADR reporting process and guidelines for reporting. Stop at slide13 (causality classification) and tell the participants that this topic will be covered in more detail in session 5.3.</p>	60

<p>Demonstrate filling out an ADR form. Use Ref. 090 (interactive PDF that allows you to type into it) or Ref: 148 – the DI&ADR on-line reporting system, if internet access is available. (10 minutes)</p> <p>Alert to the instructor: Do NOT use the official, live DI&ADR on-line reporting system during the training sessions to avoid accidentally submitting practice ADRs into the system.</p> <p>Provide the participants the opportunity to practice filling out blank forms in small groups based on real case scenarios, including those they have personally observed in their patients. (20 minutes)</p> <p>Then ask the participants to share their experiences in filling out the spontaneous reporting forms. (10 minutes)</p>	40
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Sources used in this session:

- Ref. 072 Joshi, M. P. *A System-oriented Approach to Implementing Pharmacovigilance* [PowerPoint slides]. 29 Sep. 2009.
- Ref. 089 Hanoi University of Pharmacy. *Introduction To Pharmacovigilance: Signal Evaluation: Signal Generation and Strengthening*. [PowerPoint slides]. 26 Mar 2009
- Ref. 090 The National DI & ADR Centre, Hanoi. *Suspected Adverse Drug Reaction Report*. Interactive form. Web. 29 Nov. 2010.
- Ref. 127 National DI&ADR Centre of Vietnam. *Session 5.2 ADR Reporting*. Pharmacovigilance In-service Workshop. [PowerPoint slides]. 2012.
- Ref: 148 The National DI & ADR Centre, Hanoi. Vietnam On-line ADR Reporting System. Interactive form. Web.

Additional Reading and Resources:

- Ref. 027 U.S. Food and Drug Administration. Reporting Serious Problems to FDA. Web. Last Updated: 23 Jun. 2011.

Session 5.3: Adverse Drug Events: Assessment of Severity and Causality, and Prevention in Day-to-Day Practice

Topics to cover in this session:

- A. Assessing severity of ADRs (mild, moderate, severe, fatal)
- B. Method of assessing causality of ADRs: WHO-UMC scales
- C. Prevention of ADRs in Hospitals

Objectives: At the end of this session, participants will be able to:

- Based on presentations and findings in a patient, demonstrate ability to evaluate and classify the severity of ADR
- Demonstrate competence to practically apply the WHO-UMC causality scale and assess causality of a reported ADR

Content Summary and Process Overview / Instructional Methodology (Total Duration: 120 Minutes)

A. Assessing severity of ADRs (mild, moderate, severe, severe life-threatening)
(Source: Ref. 128)

Based on their impact on the patient, ADRs are classified into the following four categories.

Mild

- The ADR requires no change in treatment with the suspected drug
- The ADR requires that the suspected drug be withheld, discontinued or otherwise changed. No antidote or other treatment is required.
- No increase in length of stay.

Moderate

- The ADR requires that the suspected drug be withheld, discontinued or otherwise changed, and/or an antidote or other treatment is required.
- Increases length of stay by at least one day
- The ADR is the reason for admission

Severe

- The ADR requires that the suspected drug be withheld, discontinued or otherwise changed, and/or an antidote or other treatment is required.
- The ADR requires intensive medical care
- The ADR causes permanent harm to the patient

Fatal

- The ADR either directly or indirectly leads to the death of the patient

<i>Activity</i>	<i>Time (minutes)</i>
<p>Open the class by briefly describing these three specific ADRs but do not share assessments of their severity.</p> <p>Mild - Hyperpigmentation in HIV-Infected Patients Receiving Emtricitabine Ref. 085</p> <p>Mild - Symptomatic hyperlactatemia in an HIV-positive patient Ref. 080</p> <p>Severe -Fluconazole induced toxic epidermal necrolysis: a case report Ref. 086</p>	15
<p>Use slides 1-9 in Ref. 128 to present the categories used in assessing severity of ADRs (mild, moderate, severe, severe life-threatening) and the characteristics of ADRs which fall into each of the categories.</p>	15
<p>Ask the participants to assess the three ADRs in terms of severity and then to share the results of their assessments with the person next to them. Was every pair of participants in agreement on all three assessments? If not, allow a few who disagreed to share the justifications for their assessments. Then show the answers to the class.</p>	15

B. Method of assessing causality of ADRs: WHO-UMC scales

Causality of ADRs refers to an assessment of relatedness between exposure to a medicine and an adverse event.

Factors determining causality (Source: Ref. 072, slide 37; Ref. 059, page 10)

Strength of the association: if the odds are known and are very high for an observed event, such as GI upset with aspirin, then the case is strengthened for causation.

Consistency of the observed evidence: When there is an association between a drug and an adverse reaction that has been demonstrated consistently over years of clinical practice, causality becomes more likely.

Temporality of the relationship: The closer the relationship of the administration of the drug and the occurrence of the ADR, the more likely that the drug may be the actual cause of the reaction. This is not always true as some adverse events may occur several days or weeks after the administration of the offending drug.

Dose-response relationship: Reaction more severe when the dose was increased or less severe when the dose was decreased. (Not always true as very low doses of some drugs, e.g., penicillin, can elicit serious anaphylactic responses.)

Confounding factors: Alternative causes (other than the drug) that could on their own have caused the reaction. Confounding factors such as the administration of other medicines, food, and beverages can account for observed events. The existence of concurrent diseases and infections can also cause certain observed effects, so distinguishing them from the suspected medicine is difficult. Environmental factors, such as air pollutants, weather conditions, and exposure to allergens, may also play a role.

WHO-UMC Causality Categories for causality assessment of the relationship between the intake of a medicine and an adverse reaction. Various causality terms and methods are in use but the ones in this method are most widely used. (Sources: Ref. 083; Ref. 077, slide 17)

Certain

- Event or laboratory test abnormality, with plausible time relationship to drug intake
- Cannot be explained by disease or other drugs
- Response to withdrawal plausible (pharmacologically, pathologically)
- Event definitive pharmacologically or phenomenologically (i.e. an objective and specific medical disorder or a recognized pharmacological phenomenon)
- Rechallenge satisfactory, if necessary

Probable/Likely

- Event or laboratory test abnormality, with reasonable time relationship to drug intake
- Unlikely to be attributed to disease or other drugs
- Response to withdrawal clinically reasonable

- Rechallenge not required

Possible

- Event or laboratory test abnormality, with reasonable time relationship to drug intake
- Could also be explained by disease or other drugs
- Information on drug withdrawal may be lacking or unclear

Unlikely

- Event or laboratory test abnormality, with a time to drug intake that makes a relationship improbable (but not impossible)
- Disease or other drugs provide plausible explanations

Conditional/Unclassified

- Event or laboratory test abnormality
- More data for proper assessment needed
- Additional data under examination

Unassessable/Unclassifiable

- Report suggesting an adverse reaction
- Cannot be judged because information is insufficient or contradictory
- Data cannot be supplemented or verified

Naranjo Algorithm (Source: Ref. 082)

Uses scoring based on answers to ten questions to assess the adverse drug reaction causality.

Question	Yes	No	Do not know or not done	Score
1. Are there previous conclusive reports on this reaction?	+1	0	0	
2. Did the adverse event appear after the suspected drug was administered?	+2	-1	0	
3. Did the adverse reaction improve when the drug was discontinued or a specific antagonist was administered?	+1	0	0	
4. Did the adverse reaction reappear when the drug was readministered?	+2	-1	0	
5. Are there alternative causes (other than the drug) that could on their own have caused the reaction?	-1	+2	0	
6. Did the reaction reappear when a placebo was given?	-1	+1	0	
7. Was the drug detected in the blood (or other fluids) in concentrations known to be toxic?	+1	0	0	
8. Was the reaction more severe when the dose was increased or less severe when the dose was decreased?	+1	0	0	
9. Did the patient have a similar reaction to the same or similar drugs in any previous exposure? +1 0 0	+1	0	0	
10. Was the adverse event confirmed by any objective evidence?	+1	0	0	

Naranjo scores of 9 or 10 indicate that an event was "definitely" an ADR; scores of 5-8 rate the likelihood as "probable"; scores of 1-4 are "possible"; and scores of less than 1 are "doubtful."

Activity	Time (minutes)
Introduce the topic by admitting that there are a variety of assessment scales and that none of the scales are perfect. Use slides 10 -41 of Ref. 128 to present the criteria, factors and methods of causality assessment.	35
Ask the participants to review slides 34 and 38 of Ref. 128 for examples of real ADRs. If time permits, provide the opportunity for participants to practice on other cases in small groups.	25
Summarize by pointing out that the participants activity highlighted the fact that successful causality assessment depends not only on the scale used, but also on the completeness of the information provided about the ADR.	5

C. Prevention of ADRs in Hospitals (Source: Ref. 128)

Careful review of the patient's medical history to identify potential drug allergies and to prevent co-administration of drugs that are known to interact can prevent ADRs in hospitalized patients. ADRs in hospitalized patients can be further reduced by proactively monitoring patients, in particular, for patients with high-risk of experiencing ADRs or when high-risk medications are used by patients. That proactive monitoring can result in early detection of ADRs to allow for prompt drug and dosage changes, if needed.

Activity	Time (minutes)
Present slides 42 to 45 of Ref. 128 to familiarize participants with methods of preventing ADRs in hospitals.	10

Sources used in this session:

- Ref. 059 Rational Pharmaceutical Management Plus, Center for Pharmaceutical Management, & Management Sciences for Health. *Drug and Therapeutics Committee Training Course, Session 4, Assessing and Managing Medicine Safety: Participants' Guide*. 2007.
- Ref. 072 Joshi, M. P. *A System-oriented Approach to Implementing Pharmacovigilance* [PowerPoint slides]. 29 Sep. 2009.
- Ref. 077 Berdai, D. *Risk and crisis Management in Pharmacovigilance*. Hanoi. [PowerPoint slides]. 2009.
- Ref. 080 Antoniou, T., Weisdorf, T., & Gough, K. Symptomatic Hyperlactatemia in an HIV-Positive Patient: A Case Report and Discussion. *CMAJ*, 168.2 (21Jan. 2003).
- Ref. 082 How Can I Recognize an Adverse Drug Event? Medscape Education. Web. 2008.
- Ref. 081 Hanoi University of Pharmacy. *Introduction To Pharmacovigilance: Signal Evaluation: Assessing Causality and Characterizing Risk*. [PowerPoint slides]. 26 Mar 2009.
- Ref. 083 The Uppsala Monitoring Centre. The use of the WHO-UMC system for standardised case causality assessment. Web. 2011.
- Ref. 085 Rashbaum B. Evaluation of Hyperpigmentation in HIV-Infected Patients Receiving Emtricitabine. Poster Exhibition: The 3rd IAS Conference on HIV Pathogenesis and Treatment: Abstract no. TuPe2.4C15. 2005.
- Ref. 086 Ofoma, U. R. & Chapnick, E. K. Fluconazole Induced Toxic Epidermal Necrolysis: A Case Report. *Cases Journal* 2009, 2:9071 doi:10.1186/1757-1626-2-9071.
- Ref. 128 National DI&ADR Centre of Vietnam. *Session 5.3 ADEs - Assessment of Severity and Causality and Prevention in Day-to-day Practice*. Pharmacovigilance In-service Workshop. [PowerPoint slides]. 2012.

Additional Reading and Resources:

- Ref. 068 U.S. Food and Drug Administration. Preventable Adverse Drug Reactions: A Focus on Drug Interactions. Web. Last Updated: 30 Apr 2009.

Session 5.4: Medication Error as a Factor for Adverse Drug Events

Topics to cover in this session:

- A. Burden of medication error; causes of medication error
- B. Overview of common problem-prone areas with regard to medication errors
- C. Approaches to prevent medication errors

Objectives: At the end of this session, participants will be able to:

- Highlight, with some international data, the burden of medication error in hospitals
- Analyze how system weakness contributes to medication errors in hospitals
- Demonstrate awareness of the problems of medication error as also being PV issue (not just ADRs) and narrate how this issue directly impacts his/her professional practice and ability to provide “safe” care to their patients
- Citing real examples, highlight key strategies, tools or interventions that can be used to prevent medication errors
- Narrate self-perception of his/her role in minimizing or preventing medication errors in his or her own hospital practice setting

Content Summary and Process Overview / Instructional Methodology (Total Duration: 45 Minutes)**A. Burden of medication error; causes of medication error**

(Sources: Ref. 062; Ref. 059, page 18; Ref. 064)

Medication error includes any error occurring in the medication use process.

One US study found that each preventable ADE that took place in a hospital added about \$8,750 (in 2006 dollars) to the cost of the hospital stay. Assuming 400,000 of these events each year, the total annual cost would be \$3.5 billion in this one group. Another study looked at preventable ADEs in US's Medicare system enrollees aged 65 and older and found an annual cost of \$887 million for treating medication errors in this group. These figures do not take into account lost earnings or compensation for pain and suffering.

Most causes of medication errors can be attributed to the following three factors:

- Human factors: Heavy staff workload and fatigue, Inexperience, lack of training, poor handwriting, and oral orders
- Workplace factors: Poor lighting, noise, interruptions, excessive workload
- Pharmaceutical factors: Excessive prescribing; confusing medicine nomenclature; packaging, or labeling; Increased number or quantity of medicines per patient; Frequency and complexity of calculations needed to prescribe, dispense, or administer a medicine; Lack of effective policies and procedures

<i>Activity</i>	<i>Time (minutes)</i>
Present slides 1-9 of Ref. 129 to establish a foundation about medicine errors and the burdens associated with it.	10

B. Overview of common problem-prone areas with regard to medication errors

(Sources: Ref. 060, Ref. 063 slide 9, Ref. 056, slides 14 and 16, Ref. 066, Ref. 065)

One study of where medication errors take place showed the breakdown as follows:

Prescribing and transcribing – 60%

- illegible and/or imprecise prescription
- incomplete, inadequate or incorrect instructions
- wrong indication, dose, duration, dilution, formulation
- identity of the patient unclear
- failure to consider a contra-indication (medical history, pre-existing condition, or interaction with a co-prescribed drug)

Administration – 30%

- wrong patient
- wrong dose, time, route of administration, site

- inadequate preparation before administration
- errors of manipulation : contaminants (air, others) when injected
- incompatible drugs mixed in the same injectable solution

Dispensing – 10%

Dispensing errors usually occur due to wrong drugs being dispensed because of the problem of sound-alike or look-alike medications.

High-risk drugs cause harm in 6% or more of reported medication errors (USP)

Top 10 drugs most frequently reported in Canada as causing harm because of medication error:

- | | |
|---------------|--------------------------|
| Insulin | Morphine |
| Hydromorphone | Heparin (unfractionated) |
| Fentanyl | Warfarin |
| Furosemide | Dalteparin |
| Metoprolol | Ramipril |

These 10 drugs accounted for 199 of 465 harmful medication incidents that were voluntarily reported to ISMP (Institute for Safe Medication Practices) Canada over a 5-year period (2001 to 2005). Ref. 060

<i>Activity</i>	<i>Time (minutes)</i>
Ask participants to list possible factors that contribute to medicine errors. Then, present slides 10-20 of Ref. 129 and allow them see how many of the factors they identified.	15
<p>Case Study</p> <p><i>If time permits, discuss this case study about medication error from page 4 of Ref. 070 which shows a breakdown in communication that occurred when a physician gave a verbal order for insulin. Although the physician ordered 16 units of regular insulin, the nurse heard it as an order for 60 units; therefore, a 60-unit dose was administered.</i></p>	

C. Approaches to prevent medication errors
(Source: Ref. 059 pages 18 and 19, Ref. 065, Ref. 068)

Broad interventions to reduce medication errors are:

Improving physician prescribing

- Institute educational programs that focus on the most common prescribing errors
- Require legible handwriting by ordering physicians.
- Require complete spelling of a medicine's name.
- Use a standardized designation for doses (i.e., milligrams = mg, micrograms = mcg, and grams = g; use the word "units" rather than "U"; and use a leading zero for values less than 1 but not a trailing zero after a decimal, e.g., write 0.2 mg or 2 mg instead of .2 mg or 2.0 mg).
- Write the route of administration on all orders.
- Write out directions completely. Write "daily" instead of "QD" and "every other day" instead of "QOD."
- Limit the use of oral or telephone orders to emergency situations, and require that the order be read back to the prescriber.

Improving dispensing

- Separate the storage of drugs that have similar packages and names
- Change the appearance of look-alike drug names on order entry screens and alter the sequence of the products so that look-alike names are not right next to each other on the screen.
- Apply uppercase lettering to different portions of drug names of drugs with similar names

Improving drug administration

- Check the patient's identity.
- Ensure that dosage calculations are checked independently by another health care professional before the drug is administered.
- Ensure that the prescription, drug, and patient are in the same place in order that they may be checked against one another.
- Ensure the medication is given at the correct time.
- Minimize interruptions during drug rounds.

Correcting systems flaws that predispose to error

- Introduce a system to identify and record information about medication errors.
- Where feasible, institute pharmacy-based admixture of IV fluids. If ward personnel must perform IV admixture, there should be clear written procedures and skills certification of the personnel.
- Develop special procedures for high-risk drugs. These procedures should include written guidelines, checklists, and educational materials.

- When preparing to administer a medication, confirm the identity of the patient by reading the patient’s wristband and talking to the patient or family member.
- To minimize the likelihood that a dose will be missed, standardize administration times and develop a policy to provide doses when a patient is off the floor.
- Analyze medicine names as new products are added to the formulary. For look-alike and sound-alike names, establish a policy requiring that prescribers write both brand and generic name.
- Use pharmacy staff effectively to monitor and manage medicine use and distribution.

Activity	Time (minutes)
Present slides 21-28 of Ref. 129 to show the participants Vietnam’s approaches to preventing medication errors.	10
<p>Ask the participants to vote by show of hands</p> <p>Which is better?</p> <ul style="list-style-type: none"> • 150 microgram of clonidine OR 0.15 mg • 0.25 mg of digoxin OR 250 microgram • 1 mg atropine OR 1.0 mg • .5 mg atropine OR 0.5 mg atropine <p>If time permits, ask participants to identify what error might occur if the better choice is not used.</p> <p>(Source: Ref. 057, slide 45)</p>	5
<p>Ask participants to interpret the following dates:</p> <ul style="list-style-type: none"> • Expiry date 12 09 04 • Expiry date 09 12 04 • Expiry date 25 09 04 <p>Stress the importance of using unambiguous dates. In the example above, it is easy to confuse December 9, 2004 with September 12, 2004.</p>	5
<p>Case Study</p> <p><i>If time permits, discuss case study from page 4 of Ref. 070 involving an insulin order written for “4 U NPH insulin in which, because of poor handwriting, the “U” for “units” was mistaken for a zero, resulting in the patient’s receiving 40 units of neutral protamine Hagedorn insulin.</i></p>	

Case Study

If time permits, discuss case study from Ref. 067 describing using technology to reduce medication error.

The Physician order entry (POE) at Brigham and Women's Hospital. This computerized medication order entry system has the potential to prevent an estimated 84 % of dose, frequency, and route errors. Such a system eliminates illegible orders that lead to medication errors. Also, because the system requires the name of the medication, dosage, route, and frequency of administration to be entered, errors that arise from omission of critical information are eliminated. Programmed within the system are algorithms that check dosage frequency, medication interactions, and patient allergies. Once an order is entered, this computerized system also provides physicians with information about the consequences of therapy, benefits, risks, and contraindications.

Sources used in this session:

- Ref. 056 Moore, N. *Medication Errors*. Training Course in Pharmacovigilance. Hanoi. [PowerPoint slides]. Dec. 2010.
- Ref. 057 Hartigan-Go, K. *Patient Safety & Medication Errors International Society of Pharmacovigilance (ISoP)*. [PowerPoint slides]. 2009.
- Ref. 059 Rational Pharmaceutical Management Plus, Center for Pharmaceutical Management, & Management Sciences for Health. *Drug and Therapeutics Committee Training Course, Session 4, Assessing and Managing Medicine Safety: Participants' Guide*. 2007.
- Ref. 060 Institute for Safe Medication Practices Canada. Top 10 Drugs Reported as Causing Harm through Medication Error. *ISMP Canada Safety Bulletin*, 6.1 (Feb. 2006).
- Ref. 062 Institute of Medicine of the National Academies. Preventing Medication Errors. *Report Brief*. Jul. 2006.
- Ref. 063 Federal Ministry of Health, Nigeria. *Safety of Medicines in Nigeria; National Pharmacovigilance Training Curriculum: Medication Errors and Patient Safety* [PowerPoint slides]. Jan. 2011.
- Ref. 064 Institution for Safe Medication Practices. *Frequently Asked Questions (FAQ)*. Web.
- Ref. 065 Williams, D.J.P. Medication Errors. *J R Coll Physicians Edinb*, 37 (Jul 2007):343–346.
- Ref. 066 Olsson, S. *Current trends in pharmacovigilance – a global perspective*. WHO Collaborating Centre for International Drug Monitoring. [PowerPoint slides]. Web. 2005.
- Ref. 067 Agency for Healthcare Research and Quality. Reducing and Preventing Adverse Drug Events To Decrease Hospital Costs. Web. Mar 2001.
- Ref. 068 U.S. Food and Drug Administration. Preventable Adverse Drug Reactions: A Focus on Drug Interactions. Web. Last Updated: 30 Apr 2009.
- Ref. 069 U.S. Food and Drug Administration. Strategies to Reduce Medication Errors: Working to Improve Medication Safety. Web. Last Updated: 12 Aug. 2011.
- Ref. 070 Grissinger, M. *Avoiding Medication Errors with Insulin Therapy*. May 2010.
- Ref. 129 National DI&ADR Centre of Vietnam. *Session 5.4 Medication Error as a Factor for ADEs*. Pharmacovigilance In-service Workshop. [PowerPoint slides]. 2012.

Additional Reading and Resources:

- Ref. 061 Institute of Medicine of the National Academies. What You Can Do To Avoid Medication Errors. *Fact Sheet*. Jul. 2006.

Session 5.5: Other Factors for Adverse Drug Events

Topics to cover in this session:

- A. Brief overview of the burden of substandard and counterfeit products, and the impact of low quality medicines
- B. Brief overview of therapeutic ineffectiveness and the factors contributing to it, including drug resistance

Objectives: At the end of this session, participants will be able to:

- Demonstrate awareness of the problems of poor product quality and therapeutic ineffectiveness as also being PV issues (not just ADRs and medication errors) and narrate how these issues directly impact their professional practice and their abilities to provide “safe” and “effective” care to their patients
- Differentiate drug “efficacy” (in clinical trial settings) from “effectiveness” (during use in the real world)
- Articulate that appropriate record-keeping of the burden of treatment failure can inform subsequent revision of the national guidelines

Content Summary and Process Overview / Instructional Methodology (Total Duration: 30 Minutes)**A. Brief overview of the burden of substandard and counterfeit products, and the impact of low quality medicines**

(Source: Ref. 074)

Substandard drugs are “genuine drug products which do not meet the quality specifications set for them. **Counterfeits** are “deliberately and fraudulently mislabeled with respect to identity and/or source”. Counterfeiting can apply to branded and generic products. Counterfeits may include products with correct or incorrect ingredients, without active ingredients, with insufficient active ingredient, or with fake packaging”. It is not always clear if poor-quality medicines are counterfeit or substandard, but it is important that they are correctly classified because they have different origins and different solutions.

It is difficult to estimate the extent of substandard and counterfeit products. However, The International Medical Products Anti-Counterfeiting Taskforce (IMPACT) has suggested that many developing countries of Africa, parts of Asia, and parts of Latin America have areas where >30% of the medicines on sale can be counterfeit. Other developing markets, however, have <10%.

Low quality medicines result in:

- Increased mortality and morbidity
- Engendering of drug resistance and loss of medicine efficacy
- Loss of confidence in health systems and health workers
- Economic loss for patients, their families, health systems, and the producers and traders in good-quality medicines
- Adverse effects from incorrect active ingredients
- Waste of enormous human effort and financial outlay in development of medicines, optimizing dosage, carrying out clinical trials, discussing policy change, and manufacturing medicines
- Increased burden for health workers, medicine regulatory authorities, customs officials and police officers

Activity	Time (minutes)
Present slides 1-15 of Ref. 130 to provide a foundation about the burden of substandard and counterfeit products and the impact of low quality medicines. If time permits: Lead a brief discussion on the burden sub-standard and counterfeit products, citing some real local and international examples	20

<p>IF TIME PERMITS: Provide these examples of results of substandard and counterfeit medications being used (Sources: Ref. 071, Ref. 073, Ref. 074) and pose the follow-up questions.</p> <p>Gentamicin eye drops contaminated with gentamicin-resistant <i>Pseudomonas aeruginosa</i> led to severe eye infections.</p> <p>After hundreds of patients with visceral leishmaniasis failed to respond to ‘miltefosine’ in Bangladesh, capsules were found not to contain miltefosine.</p> <p>Placebo tablets containing no active ingredients were stolen and sold as a contraceptive medicine, leading, it was claimed, to unexpected pregnancy.</p> <p>23-year-old man with hyperparasitaemic falciparum malaria treated with oral artesunate. After his death from cerebral malaria, analysis of his medication revealed that the main active ingredient in this drug was acetaminophen. Artesunate was also present in the tablet but only 10 mg per tablet, instead of the 50 mg of artesunate present in the genuine product. Ask participants to estimate the percentage of counterfeit artesunate (containing no or sub-therapeutic active ingredient) bought in South-East Asia. (Estimated to be one-third to one-half.)</p> <p>An antidepressant (fluvoxamine) and a muscle relaxant (cyclobenzaprine hydrochloride) were labeled as anti-retrovirals in the Democratic Republic of Congo. Ask participants to hypothesize about the possible results of this last example.</p>	
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B. Brief overview of therapeutic ineffectiveness and the factors contributing to it, including drug resistance

(Sources: Ref. 006 page 5, Ref. 072 slide 4, Ref. 074)

The scope of Pharmacovigilance is expanding to include therapeutic ineffectiveness which may result from the use of substandard or counterfeit products, non-adherence, drug interactions, and drug resistance. While reporting of therapeutic ineffectiveness can alert to substandard and counterfeit products, awareness of therapeutic ineffectiveness can also highlight non-adherence, drug interactions, and drug resistance. Such information can then be communicated to health care professionals and consumers for risk-benefit decision making. High level of therapeutic ineffectiveness may necessitate review and possible modification or change in the recommended treatment regimen if the underlying reason gets identified as drug resistance. If other factors listed above are in play, efforts should be made to remove or minimize them.

Anti-infectives containing sub-therapeutic amounts of the active ingredient (whether counterfeit or substandard) increase the risk of the selection and spread of drug-resistant pathogens. For diseases treated with combination therapy (e.g. tuberculosis, HIV, falciparum malaria), poor-quality combination medicines risk the spread of resistance due to the poor-quality active ingredient and the ‘unprotected’ co-ingredient.

Activity	Time (minutes)
Present slides 16-18 of Ref. 130 to focus on therapeutic ineffectiveness.	5
<p>Stress that anti-infectives containing sub-therapeutic amounts of the active ingredient (whether counterfeit or substandard) increase the risk of the selection and spread of drug-resistant pathogens.</p> <p>If time permits: Lead a brief discussion on the issues of treatment failure in the public health programs such as HIV/AIDS, TB, and malaria</p>	3
Present slide 19 of Ref. 130 to summarize the topics in this session.	2

Sources used in this session:

- Ref. 006 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. Sep. 2009.
- Ref. 071 Newton, P. N., McGready, R., Fernandez, F., Green, M. D., Sunjio, M., Bruneton, C., White, N. J. Manslaughter by Fake Artesunate in Asia—Will Africa Be Next? *PLoS Medicine*, 3.6 (2006): 752-5.
- Ref. 072 Joshi, M. P. *A System-oriented Approach to Implementing Pharmacovigilance* [PowerPoint slides]. 29 Sep. 2009.
- Ref. 073 World Health Organization. *The Safety of Medicines in Public Health Programmes: Pharmacovigilance an essential tool*. 2006.
- Ref. 074 Newton, P. N., Green, M. D., & Fernandez, F. Impact of Poor-Quality Medicines in the ‘Developing’ World. *Trends Pharmacol Sci*. 2010 March; 31(3-3): 99–101. doi: [10.1016/j.tips.2009.11.005](https://doi.org/10.1016/j.tips.2009.11.005)
- Ref. 130 National DI&ADR Centre of Vietnam. *Session 5.5 Other Factors for ADEs - Poor Product Quality and Therapeutic Ineffectiveness*. Pharmacovigilance In-service Workshop. [PowerPoint slides]. 2012.

Additional Reading and Resources:

- Ref. 075 Meyboom, R. H. B., Lindquist, M., Flygare, A., Biriell, C., & Edwards, I. R. The Value of Reporting Therapeutic Ineffectiveness as an Adverse Drug Reaction. *Drug Safety*, 23.2 (Aug. 2000): 95-99.
- Ref. 076 Meyboom, R. H. B., Egberts, A. C. G., Gribnau, F. W. J., & Hekster, Y. A. Pharmacovigilance in Perspective. *Drug Safety*, 21.6 (Dec. 1999): 429-447.

Sessions 6.1 through 6.3 are designed specifically for healthcare providers working in Vietnam's Antiretroviral Therapy Program.

Session 6.1: Importance of PV in Public Health Programs (PHPs) and Burden of ADEs in PHPs

Topics to cover in this session:

- A. Importance of PV in PHPs: strengths, challenges and mutual benefits
- B. Epidemiology of adverse events and drug-related morbidity and mortality in PHPs; problem of treatment failure in PHPs

Objectives: At the end of this session, participants will be able to:

- Explain why the conduct of PV is critical for a “safe” and rational use of medicines in the major PHPs such as HIV/AIDS, malaria, TB, and immunization
- Show awareness of about the significant problem of ADEs in PHPs by describing the burdens of ADRs and treatment failures

Content Summary and Process Overview / Instructional Methodology (Total Duration: 60 Minutes)**A. Importance of PV in PHPs: strengths, challenges and mutual benefits (Source: Ref. 110, Ref. 003, Ref. 112)**

Public health programs (PHPs) provide prevention, treatment, and control of infectious diseases such as malaria, TB, HIV/AIDS through the administration of medicines and vaccines, typically in mass scale or large populations.

The importance of PV in Public health programs is reflected in the fact that PV programs and public health programs are mutually beneficial. Public health programs provide a valuable opportunity for PV activities by offering cohorts of patients under controlled conditions to be monitors for safety over a period of time. In turn, that enhanced PV enables detection, evaluation and prevention of adverse events in those PHPs. The synergy between PHPs and PV results in a stronger spontaneous reporting system and active surveillance components in public health programs for HIV/AIDS, Malaria, Tuberculosis and Immunization. Some of the strengths of PHPs include:

- They are well established programs using a limited number of drugs or vaccines
- The quality of product being used can be assured
- There are large populations involved
- They usually operate according to standard guidelines
- They are often well-funded with national and international support

Some of the challenges PHPs might encounter include:

- Disease may not be well-diagnosed/presumptive treatment
- Use fast-tracked medicines which may not have been sufficiently studied in some patient groups
- Self-medication
- Inadequate patient information
- Co-morbid conditions, nutrition, special patient groups
- Drug resistance
- Drug interactions, alternative therapies
- Poor medication adherence

Incorporating PV into PHPs can identify preventable/modifiable risk factors for drug-related harm, and identify new, previously unknown adverse drug reactions to medicines used in public health programs. The results can be improved clinical practice guidelines that are more locally relevant and evidence-based and a culture of drug safety awareness among health professionals. The knowledge gained from the PHP-based PV can inform future therapeutics research into safety of medicines used in public health programs.

<i>Activity</i>	<i>Time (minutes)</i>
Present slides 2 and 3 of Ref. 131 to set participant’s expectations about the Antiretroviral Therapy track of the PV sessions. Present all slides in Ref. 132 to provide a foundation about the Importance of PV in PHPs and Burden of ADEs in PHPs	40

B. Epidemiology of adverse events and drug-related morbidity and mortality in PHPs; problem of treatment failure in PHPs (Sources: Ref. 003, Ref. 112)

Most data on burden of ADR are from resource-rich countries such as New Zealand, Australia, US, UK, and France, and very few are from resource-constrained countries. Very few developing countries have optimally functional reporting schemes and are members of the WHO collaborating center on drug monitoring. But, it is not appropriate to extrapolate data from developed countries. The burden of ADRs in resource **limited settings may differ from resource-rich countries because of:**

- High prevalence of HIV/AIDS, TB, Malaria and other comorbid conditions
- Risk-benefit generalization may not apply
- Poor medicine labeling, off-label use
- Traditional medicines and associated adverse events and interactions
- Genetic make-up, nutrition status
- Regular monitoring for early signs of toxicity often not well-established

ADRs are a significant cause of morbidity and mortality in PHPs. They affect treatment adherence which increases the risk of drug resistance and erodes public confidence in PHPs resulting in wasted financial resources and suboptimal outcomes. Therapeutic ineffectiveness or treatment failure is a particularly important issue in public health programs such as HIV/AIDS, malaria, and TB. PHPs should collect data about the percentage of patients undergoing treatment whose regimen was modified because of treatment failure to inform future treatment guideline decisions.

<i>Activity</i>	<i>Time (minutes)</i>
<p>Show slide 21 of Ref. 112 to point out the countries providing the majority of ADR data.</p> <p>Ask the participants to cluster in twos to spend 5 minutes listing some reasons why it is not appropriate to extrapolate ADR data from developed countries to resource limited settings.</p> <p>Invite participants to share the reasons and create a list based on their contributions. Then add any additional reasons that might have been overlooked by the participants.</p>	20
<p>If time permits, discuss this case study in Ref. 114 about drug resistance and treatment failure associated with malaria treatment “ WHO, the Global Fund, and medical malpractice in malaria treatment”. The opinion article written in 2004 states that “Most African countries reluctantly cling to chloroquine, sulfadoxine-pyrimethamine, or the insignificantly better combination of chloroquine and sulfadoxinepyrimethamine, because ACT is ten times more expensive and, therefore, unaffordable to them.” That was taking place even though there were links to drug resistance, treatment failure and deaths from malaria. Ask the participants if they think this situation still taking place. Then, share the results of this study shown in Ref. 150 conducted in 2007.</p>	

Sources used in this session:

- Ref. 003 "Pharmacovigilance: Quality, Safety and Efficacy of Medicines For Better Health Care: Participants' Manual." Ministry of Public Health and Sanitation & Ministry of Medical Services. Kenya. [PowerPoint slides]. Feb. 2009.
- Ref. 110 Karema, C. *Pharmacovigilance Training of Trainers: Integrating Pharmacovigilance into Public Health Program (PHP)*. Rwanda. [PowerPoint slides]. Sep. 2009.
- Ref. 112 The Uppsala Monitoring Centre. *Implementing Pharmacovigilance in Public Health Programs*. [PowerPoint slides]. 2009
- Ref. 114 Attaran, A., Barnes, K. I., Curtis, C., d'Alessandro, U., Fanello, C. I., Galinski, M. R., . . . Watkins, W. M. WHO, the Global Fund, and medical malpractice in malaria treatment. *The Lancet*, 363, (17 Jan. 2004): 237–40.
- Ref. 131 National DI&ADR Centre of Vietnam. *Module 6 Introduction and Summary: PV in the ART program*. Pharmacovigilance In-service Workshop. [PowerPoint slides]. 2012.
- Ref. 132 National DI&ADR Centre of Vietnam. *Session 6.1 Importance of PV in PHPs and Burden of ADEs in PHPs*. Pharmacovigilance In-service Workshop. [PowerPoint slides]. 2012.
- Ref. 150 Frosch, A.E.P, Venkatesan, M. & Laufer, M.K. Patterns of chloroquine use and resistance in sub-Saharan Africa: a systematic review of household survey and molecular data. *Malar J.* 2011; 10: 116. doi: 10.1186/1475-2875-10-116

Additional Reading and Resources:

- Ref. 113 Strengthening Pharmaceutical Systems (SPS) Program. *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. Web. 2009.

Session 6.2: PV in the Antiretroviral Therapy Program

Topics to cover in this session:

- A. ADRs of clinical significance with ARVs and OI drugs included in the national guidelines recommended by the Antiretroviral Therapy (ART) Program in Vietnam; measures to reduce ARV- and OI-related morbidities; improving adverse event reporting within the ART Program (covered in session 6.3)

Objectives: At the end of this session, participants will be able to:

- List clinically significant adverse effects and drug interactions associated with the ARVs and OIs included in the national guideline
- Explain measures that are locally feasible to reduce ARV- and OI-related morbidities
- Explain how an effectively functioning system to collect ADR and treatment failure information can inform an evidence-based revision or change in the guideline

Content Summary and Process Overview / Instructional Methodology (Total Duration: 90 Minutes)

- A. ADRs of clinical significance with ARVs and OI drugs included in the national guidelines recommended by the Antiretroviral Therapy (ART) Program in Vietnam; measures to reduce ARV- and OI-related morbidities; improving adverse event reporting within the ART Program (covered in session 6.3) (Source: Ref. 133)

Examples of ADRs of clinical significance associated with NRTIs include: peripheral neuropathy (PN), pancreatitis, lipodystrophy, hepatotoxicity, and lactic acidosis. Those associated with NNRTIs include: hypersensitivity, hepatotoxicity and neuropsychiatric disorders. And, examples of ADRs of clinical significance associated with PIs include: lipodystrophy and hyperlipidemia.

Activity	Time (minutes)
<p>Use the slides in Ref. 133 to familiarize the participants with ADRs of clinical significance for Vietnam’s ART program. Slides 5-7 of that presentation will serve as reminders of material covered in session 6.1.</p> <p>If available, provide participants with national IEC/BCC (information, education, communication/ behavior change communication) materials relating to ADR and safety of medicines used in their program</p>	60
<p>Facilitate a brief brainstorming session during which the participants identify measures to reduce ARV and OI- related morbidities.</p> <p>If the participants seem to have difficulty coming up with measures, the section about “Improving the safe use of HIV medications – from reporting to risk management” in Ref. 151 may provide some food for thought on this topic.</p>	20
<p>To reinforce the participant’s appreciation about how ADR and treatment failure information can inform an evidence-based revision or change in guidelines (covered in session 1.1) present slides 35– 40 in Ref. 121 about the impact of PV on medicine regulation.</p>	10

Sources used in this session:

- Ref. 121 The National DI & ADR Centre (2012). *General Overview of Pharmacovigilance and Medication Safety* [PowerPoint slides]. 2012.
- Ref. 133 National DI&ADR Centre of Vietnam. *Session 6.2 PV in the ARV program*. Pharmacovigilance In-service Workshop. [PowerPoint slides]. 2012.
- Ref. 151 Bisson, G., Gross, R., Miller, M., Weller, I. & Walker, A. Monitoring of Long-Term Toxicities of Hiv Treatments: An International Perspective. *AIDS 2003, 17:2407–2417*

Additional Reading and Resources:

- Ref. 111 World Health Organization. *Pharmacovigilance for Antiretrovirals in Resource-Poor Countries*. 2007.

Session 6.3: ADR Reporting

Topics to cover in this session:

- A. Strategies to improve ADR reporting and analysis (e.g., ADR form widely available, reporting as routine and normal part of administering healthcare, distribution network, feedback to reporters)
- B. Practice filling out ADR Reporting forms.

Objectives: At the end of this session, participants will be able to:

- Through a personal narrative, demonstrate enthusiasm and conscientiousness (in his/her role as a health care worker) toward filling and sending spontaneous reporting form when an ADR is suspected in his/her work setting
- Demonstrate correct understanding by telling that spontaneous reporting and active surveillance approaches are complementary methods
- Describe practically feasible strategies for improving ADR reporting in his/her practice setting

Content Summary and Process Overview / Instructional Methodology (Total Duration: 90 Minutes)

- A. Strategies to improve ADR reporting and analysis (e.g., ADR form widely available, reporting as routine and normal part of administering healthcare, distribution network, feedback to reporters)
(Sources: Ref. 072, Ref. 089)

Strategies for improving ADE analysis cannot take place in the absence of ADE reports, so it is essential to increase the reporting rate. Some approaches to increasing the rate of reporting include:

- Ensure that the ADR form widely is widely available by making ADR reporting forms available to each health facility nationwide. Define priorities for reporting and provide quick access to the PV system.
- Incorporate reporting as routine and normal part of administering healthcare by including it in health facility SOPs and by incorporating PV into the education of all healthcare workers.
- Establish and use a distribution network to foster communication and to increase ADR awareness among healthcare professionals and the public.
- Provide feedback to reporters to encourage them to continue to report ADRs.

Optimize opportunities to improve ADE analysis by exploiting opportunities for integrating PV functions into existing tools and software.

<i>Activity</i>	<i>Time (minutes)</i>
<p>Open the topic by stressing that strategies for improving ADE analysis cannot take place in the absence of ADE reports, so it is essential to increase the reporting rate. Discuss some of the approaches to increasing the rate of reporting listed in the content summary. Ask the participants to consider why providing feedback to reporters might increase the rate of reporting. (10 min)</p> <p>Ask participants to cluster in groups of 3 to discuss practically feasible strategies for improving ADR reporting in their practice setting. Ask each group to share the results of their discussions. (10 min)</p> <p>Present the slides in Ref. 134 to provide detailed guidance on the ADR reporting process and guidelines for reporting. (30 min)</p> <p>Demonstrate filling out an ADR form. Use Ref. 090 (interactive PDF that allows you to type into it) or Ref: 148 – the DI&ADR on-line reporting system, if internet access is available. (5 min)</p> <p>Alert to the instructor: Do NOT use the official, live DI&ADR on-line reporting system during the training sessions to avoid accidentally submitting practice ADRs into the system.</p> <p>Conduct exercise to have the participants practice filling out ADR reporting forms (20 min)</p> <p>Facilitate a discussion during which participants will have the opportunity to share their experiences in filling out the ADR reporting forms and also to share their enthusiasm about using a spontaneous reporting form when an ADR is suspected in the work setting (10 min)</p> <p>Remind participants that that as they learned in session 3.1, spontaneous reporting and active surveillance approaches are complementary methods and that data collected by both methods are needed to best meet the PV goals of safeguarding public health and improving rational medicine use.</p> <p>Then, use the final slide in Ref. 131 to summarize the Antiretroviral Therapy track of the PV training program. (5 min)</p>	90

Sources used in this session:

- Ref. 072 Joshi, M. P. *A System-oriented Approach to Implementing Pharmacovigilance* [PowerPoint slides]. 29 Sep. 2009.
- Ref. 089 Hanoi University of Pharmacy. *Introduction To Pharmacovigilance: Signal Evaluation: Signal Generation and Strengthening*. [PowerPoint slides]. 26 Mar 2009
- Ref. 090 The National DI & ADR Centre, Hanoi. *Suspected Adverse Drug Reaction Report*. Interactive form. Web. 29 Nov. 2010.
- Ref. 131 National DI&ADR Centre of Vietnam. *Module 6 Introduction and Summary: PV in the ART program*. Pharmacovigilance In-service Workshop. [PowerPoint slides]. 2012.
- Ref. 134 National DI&ADR Centre of Vietnam. *Session 6.3 ADR Reporting*. Pharmacovigilance In-service Workshop. [PowerPoint slides]. 2012.
- Ref: 148 The National DI & ADR Centre, Hanoi. Vietnam On-line ADR Reporting System. Interactive form. Web.

Additional Reading and Resources:

- Ref. 027 U.S. Food and Drug Administration. Reporting Serious Problems to FDA. Web. Last Updated: 23 Jun. 2011.

Sessions 7.1 through 7.3 are designed specifically for healthcare providers working in Vietnam's National Tuberculosis Program.

Session 7.1: Importance of PV in Public Health Programs (PHPs) and Burden of ADEs in PHPs

Topics to cover in this session:

- A. Importance of PV in PHPs: strengths, challenges and mutual benefits
- B. Epidemiology of adverse events and drug-related morbidity and mortality in PHPs; problem of treatment failure in PHPs

Objectives: At the end of this session, participants will be able to:

- Explain why the conduct of PV is critical for a “safe” and rational use of medicines in the major PHPs such as HIV/AIDS, malaria, TB, and immunization
- Show awareness of about the significant problem of ADEs in PHPs by describing the burdens of ADRs and treatment failures

Content Summary and Process Overview / Instructional Methodology (Total Duration: 60 Minutes)**A. Importance of PV in PHPs: strengths, challenges and mutual benefits (Sources: Ref. 110, Ref. 003, Ref. 112)**

Public health programs (PHPs) provide prevention, treatment, and control of infectious diseases such as malaria, TB, HIV/AIDS through the administration of medicines and vaccines, typically in mass scale or large populations.

The importance of PV in Public health programs is reflected in the fact that PV programs and public health programs are mutually beneficial. Public health programs provide a valuable opportunity for PV activities by offering cohorts of patients under controlled conditions to be monitors for safety over a period of time. In turn, that enhanced PV enables detection, evaluation and prevention of adverse events in those PHPs. The synergy between PHPs and PV results in a stronger spontaneous reporting system and active surveillance components in public health programs for HIV/AIDS, Malaria, Tuberculosis and Immunization. Some of the strengths of PHPs include:

- They are well established programs using a limited number of drugs or vaccines
- The quality of product being used can be assured
- There are large populations involved
- They usually operate according to standard guidelines
- They are often well-funded with national and international support

Some of the challenges PHPs might encounter include:

- Disease may not be well-diagnosed/presumptive treatment
- Use fast-tracked medicines which may not have been sufficiently studied in some patient groups
- Self-medication
- Inadequate patient information
- Co-morbid conditions, nutrition, special patient groups
- Drug resistance
- Drug interactions, alternative therapies
- Poor medication adherence

Incorporating PV into PHPs can identify preventable/modifiable risk factors for drug-related harm, and identify new, previously unknown adverse drug reactions to medicines used in public health programs. The results can be improved clinical practice guidelines that are more locally relevant and evidence-based and a culture of drug safety awareness among health professionals. The knowledge gained from the PHP-based PV can inform future therapeutics research into safety of medicines used in public health programs.

<i>Activity</i>	<i>Time (minutes)</i>
<p>Present slides 2 and 3 of Ref. 131 to set participant’s expectations about the Antiretroviral Therapy track of the PV sessions.</p> <p>Present all slides in Ref. 136 to provide a foundation about the Importance of PV in PHPs and Burden of ADEs in PHPs</p>	40

B. Epidemiology of adverse events and drug-related morbidity and mortality in PHPs; problem of treatment failure in PHPs (Sources: Ref. 003, Ref. 112)

Most data on burden of ADR are from resource-rich countries such as New Zealand, Australia, US, UK, and France, and very few are from resource-constrained countries. Very few developing countries have optimally functional reporting schemes and are members of the WHO collaborating center on drug monitoring. But, it is not appropriate to extrapolate data from developed countries. The burden of ADRs in resource **limited settings may differ from resource-rich countries because of:**

- High prevalence of HIV/AIDS, TB, Malaria and other comorbid conditions
- Risk-benefit generalization may not apply
- Poor medicine labeling, off-label use
- Traditional medicines and associated adverse events and interactions
- Genetic make-up, nutrition status
- Regular monitoring for early signs of toxicity often not well-established

ADRs are a significant cause of morbidity and mortality in PHPs. They affect treatment adherence which increases the risk of drug resistance and erodes public confidence in PHPs resulting in wasted financial resources and suboptimal outcomes. Therapeutic ineffectiveness or treatment failure, is a particularly important issue in public health programs such as HIV/AIDS, malaria, and TB. PHPs should collect data about the percentage of patients undergoing treatment whose regimen was modified because of treatment failure to inform future treatment guideline decisions.

<i>Activity</i>	<i>Time (minutes)</i>
<p>Show slide 21 of Ref. 112 to point out the countries providing the majority of ADR data.</p> <p>Ask the participants to cluster in twos to spend 5 minutes listing some reasons why it is not appropriate to extrapolate ADR data from developed countries to resource limited settings.</p> <p>Invite participants to share the reasons and create a list based on their contributions. Then add any additional reasons that might have been overlooked by the participants.</p>	20

<p>If time permits, discuss this case study in Ref. 114 about drug resistance and treatment failure associated with malaria treatment “WHO, the Global Fund, and medical malpractice in malaria treatment”. The opinion article written in 2004 states that “Most African countries reluctantly cling to chloroquine, sulfadoxine-pyrimethamine, or the insignificantly better combination of chloroquine and sulfadoxinepyrimethamine, because ACT is ten times more expensive and, therefore, unaffordable to them.” That was taking place even though there were links to drug resistance, treatment failure and deaths from malaria. Ask the participants if they think this situation still taking place. Then, share the results of this study shown in Ref. 150 conducted in 2007.</p>	
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Sources used in this session:

- Ref. 003 "Pharmacovigilance: Quality, Safety and Efficacy of Medicines For Better Health Care: Participants' Manual." Ministry of Public Health and Sanitation & Ministry of Medical Services. Kenya. [PowerPoint slides]. Feb. 2009.
- Ref. 110 Karema, C. *Pharmacovigilance Training of Trainers: Integrating Pharmacovigilance into Public Health Program (PHP)*. Rwanda. [PowerPoint slides]. Sep. 2009.
- Ref. 112 The Uppsala Monitoring Centre. *Implementing Pharmacovigilance in Public Health Programs*. [PowerPoint slides]. 2009
- Ref. 114 Attaran, A., Barnes, K. I., Curtis, C., d'Alessandro, U., Fanello, C. I., Galinski, M. R., . . . Watkins, W. M. WHO, the Global Fund, and medical malpractice in malaria treatment. *The Lancet*, 363, (17 Jan. 2004): 237–40.
- Ref. 131 National DI&ADR Centre of Vietnam. *Module 6 Introduction and Summary: PV in the ART program*. Pharmacovigilance In-service Workshop. [PowerPoint slides]. 2012.
- Ref. 136 National DI&ADR Centre of Vietnam. *Session 7-1 Importance of PV in PHPs and Burden of ADEs in PHPs*. Pharmacovigilance In-service Workshop. [PowerPoint slides]. 2012.
- Ref. 150 Frosch, A.E.P, Venkatesan, M. & Laufer, M.K. Patterns of chloroquine use and resistance in sub-Saharan Africa: a systematic review of household survey and molecular data. *Malar J.* 2011; 10: 116. doi: 10.1186/1475-2875-10-116

Additional Reading and Resources:

- Ref. 113 Strengthening Pharmaceutical Systems (SPS) Program. *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. Web. 2009.

Session 7.2: PV in the National Tuberculosis Program

Topics to cover in this session:

- A. ADRs of clinical significance with anti-TB drugs included in the national guidelines recommended by the National TB Program (NTP) in Vietnam; measures to reduce anti-TB agents-related morbidities; improving adverse event reporting within NTP (covered in session 7.3)

Objectives: At the end of this session, participants will be able to:

- List clinically significant adverse effects and drug interactions associated with the anti-TB drugs included in the national guideline
- Explain measures that are locally feasible to reduce anti-TB drugs-related morbidities
- Explain how an effectively functioning system to collect ADR and treatment failure information can inform an evidence-based revision or change in the guideline

Content Summary and Process Overview / Instructional Methodology (Total Duration: 90 Minutes)

- A. ADRs of clinical significance with anti-TB drugs included in the national guidelines recommended by the National TB Program (NTP) in Vietnam; measures to reduce anti-TB agents-related morbidities; improving adverse event reporting within NTP (covered in session 7.3) (Source: Ref. 137)

Example of ADRs of clinical significance associated with isoniazid include: Hepatitis, Peripheral neuropathy, and mental disorders. Examples of those associated with rifampicin include: Increased transaminase, increased alkaline phosphatase, increased serum bilirubin, jaundice, and exfoliate dermatitis (more frequent in HIV-positive TB patients).. ADRs of clinical significance associated with pyrazinamid include: Hepatitis, increased serum uric acid levels resulting gout attacks, and arthralgia. Those associated with streptomycin include: ototoxicity and nephrotoxicity. Those associated with ethambutol include: Optic neuritis, Hepatitis, and peripheral neuritis.

Activity	Time (minutes)
Use the slides in Ref. 137 to familiarize the participants with ADRs of clinical significance for Vietnam's National Tuberculosis program. Slides 6-8 of that presentation will serve as reminders of material covered in session 7.1.	60
Facilitate a brief brainstorming session during which the participants identify measures to reduce anti-TB- agents- related morbidities.	20
To reinforce the participant's appreciation about how ADR and treatment failure information can inform an evidence-based revision or change in guidelines (covered in session 1.1) present slides 35– 40 in Ref. 121 about the impact of PV on medicine regulation.	10

Sources used in this session:

- Ref. 121 National DI&ADR Centre of Vietnam. *Session 1.1 General Overview of Pharmacovigilance and Medication Safety*. Pharmacovigilance In-service Workshop. [PowerPoint slides]. 2012.
- Ref. 137 National DI&ADR Centre of Vietnam. *Session 7.2 PV in the national TB program*. Pharmacovigilance In-service Workshop. [PowerPoint slides]. 2012.

Additional Reading and Resources:

- Ref. 088 Hanoi University of Pharmacy. *Introduction To Pharmacovigilance: Active Surveillance and Formal Pharmacoepidemiology Methods*. [PowerPoint slides]. 26 Mar 2009

Session 7.3: ADR Reporting

Topics to cover in this session:

- A. Strategies to improve ADR reporting and analysis (e.g., ADR form widely available, reporting as routine and normal part of administering healthcare, distribution network, feedback to reporters)
- B. Practice filling out ADR Reporting forms.

Objectives: At the end of this session, participants will be able to:

- Through a personal narrative, demonstrate enthusiasm and conscientiousness (in his/her role as a health care worker) toward filling and sending spontaneous reporting form when an ADR is suspected in his/her work setting
- Demonstrate correct understanding by telling that spontaneous reporting and active surveillance approaches are complementary methods
- Describe practically feasible strategies for improving ADR reporting in his/her practice setting

Content Summary and Process Overview / Instructional Methodology (Total Duration: 120 Minutes)

- A. Strategies to improve ADR reporting and analysis (e.g., ADR form widely available, reporting as routine and normal part of administering healthcare, distribution network, feedback to reporters)
(Sources: Ref. 072, Ref. 089)

Strategies for improving ADE analysis cannot take place in the absence of ADE reports, so it is essential to increase the reporting rate. Some approaches to increasing the rate of reporting include:

- Ensure that the ADR form widely is widely available by making ADR reporting forms available to each health facility nationwide. Define priorities for reporting and provide quick access to the PV system.
- Incorporate reporting as routine and normal part of administering healthcare by including it in health facility SOPs and by incorporating PV into the education of all healthcare workers.
- Establish and use a distribution network to foster communication and to increase ADR awareness among healthcare professionals and the public.
- Provide feedback to reporters to encourage them to continue to report ADRs.

Optimize opportunities to improve ADE analysis by exploiting opportunities for integrating PV functions into existing tools and software. Use statistical screening of data bases – data mining.

<i>Activity</i>	<i>Time (minutes)</i>
<p>Open the topic by stressing that strategies for improving ADE analysis cannot take place in the absence of ADE reports, so it is essential to increase the reporting rate. Discuss some of the approaches to increasing the rate of reporting listed in the content summary. Ask the participants to consider why providing feedback to reporters might increase the rate of reporting. (10 min)</p> <p>Ask participants to cluster in groups of 3 to discuss practically feasible strategies for improving ADR reporting in their practice setting. Ask each group to share the results of their discussions. (10 min)</p> <p>Present the slides in Ref. 138 to provide detailed guidance on the ADR reporting process and guidelines for reporting. (30 min)</p> <p>Demonstrate filling out an ADR form. Use Ref. 090 (interactive PDF that allows you to type into it) or Ref: 148 – the DI&ADR on-line reporting system, if internet access is available. (5 min)</p> <p>Alert to the instructor: Do NOT use the official, live DI&ADR on-line reporting system during the training sessions to avoid accidentally submitting practice ADRs into the system.</p> <p>Conduct exercise to have the participants practice filling out ADR reporting forms (20 min)</p> <p>Facilitate a discussion during which participants will have the opportunity to share their experiences in filling out the ADR reporting forms and also to share their enthusiasm about using a spontaneous reporting form when an ADR is suspected in the work setting (10 min)</p> <p>Remind participants that that as they learned in session 3.1, spontaneous reporting and active surveillance approaches are complementary methods and that data collected by both methods are needed to best meet the PV goals of safeguarding public health and improving rational medicine use.</p> <p>Present the final slide in Ref. 135 to summarize the tuberculosis track of the PV training program. (5 min)</p>	90

Sources used in this session:

- Ref. 072 Joshi, M. P. *A System-oriented Approach to Implementing Pharmacovigilance* [PowerPoint slides]. 29 Sep. 2009.
- Ref. 089 Hanoi University of Pharmacy. *Introduction To Pharmacovigilance: Signal Evaluation: Signal Generation and Strengthening*. [PowerPoint slides]. 26 Mar 2009
- Ref. 090 The National DI & ADR Centre, Hanoi. *Suspected Adverse Drug Reaction Report*. Interactive form. Web. 29 Nov. 2010.
- Ref. 135 National DI&ADR Centre of Vietnam. *Module 7 Introduction and Summary: PV in the National TB Program*. Pharmacovigilance In-service Workshop. [PowerPoint slides]. 2012.
- Ref. 138 National DI&ADR Centre of Vietnam. *Session 7.3 ADR Reporting*. Pharmacovigilance In-service Workshop. [PowerPoint slides]. 2012.
- Ref: 148 The National DI & ADR Centre, Hanoi. Vietnam On-line ADR Reporting System. Interactive form. Web.

Additional Reading and Resources:

- Ref. 027 U.S. Food and Drug Administration. Reporting Serious Problems to FDA. Web. Last Updated: 23 Jun. 2011.

Sessions 8.1 through 8.3 are designed specifically for healthcare providers working in Vietnam's National Malaria Control Program.

Session 8.1: Importance of PV in Public Health Programs (PHPs) and Burden of ADEs in PHPs

Topics to cover in this session:

- A. Importance of PV in PHPs: strengths, challenges and mutual benefits
- B. Epidemiology of adverse events and drug-related morbidity and mortality in PHPs; problem of treatment failure in PHPs

Objectives: At the end of this session, participants will be able to:

- Explain why the conduct of PV is critical for a “safe” and rational use of medicines in the major PHPs such as HIV/AIDS, malaria, TB, and immunization
- Show awareness of about the significant problem of ADEs in PHPs by describing the burdens of ADRs and treatment failures

Content Summary and Process Overview / Instructional Methodology (Total Duration: 60 Minutes)**A. Importance of PV in PHPs: strengths, challenges and mutual benefits (Sources: Ref. 110, Ref. 003, Ref. 112)**

Public health programs (PHPs) provide prevention, treatment, and control of infectious diseases such as malaria, TB, HIV/AIDS through the administration of medicines and vaccines, typically in mass scale or large populations.

The importance of PV in Public health programs is reflected in the fact that PV programs and public health programs are mutually beneficial. Public health programs provide a valuable opportunity for PV activities by offering cohorts of patients under controlled conditions to be monitors for safety over a period of time. In turn, that enhanced PV enables detection, evaluation and prevention of adverse events in those PHPs. The synergy between PHPs and PV results in a stronger spontaneous reporting system and active surveillance components in public health programs for HIV/AIDS, Malaria, Tuberculosis and Immunization. Some of the strengths of PHPs include:

- They are well established programs using a limited number of drugs or vaccines
- The quality of product being used can be assured
- There are large populations involved
- They usually operate according to standard guidelines
- They are often well-funded with national and international support

Some of the challenges PHPs might encounter include:

- Disease may not be well-diagnosed/presumptive treatment
- Use fast-tracked medicines which may not have been sufficiently studied in some patient groups
- Self-medication
- Inadequate patient information
- Co-morbid conditions, nutrition, special patient groups
- Drug resistance
- Drug interactions, alternative therapies
- Poor medication adherence

Incorporating PV into PHPs can identify preventable/modifiable risk factors for drug-related harm, and identify new, previously unknown adverse drug reactions to medicines used in public health programs. The results can be improved clinical practice guidelines that are more locally relevant and evidence-based and a culture of drug safety awareness among health professionals. The knowledge gained from the PHP-based PV can inform future therapeutics research into safety of medicines used in public health programs.

<i>Activity</i>	<i>Time (minutes)</i>
Present slides 2 and 3 of Ref. 131 to set participant’s expectations about the Antiretroviral Therapy track of the PV sessions. Present all slides in Ref. 114 to provide a foundation about the Importance of PV in PHPs and Burden of ADEs in PHPs	40

B. Epidemiology of adverse events and drug-related morbidity and mortality in PHPs; problem of treatment failure in PHPs (Sources: Ref. 003, Ref. 112)

Most data on burden of ADR are from resource-rich countries such as New Zealand, Australia, US, UK, and France, and very few are from resource-constrained countries. Very few developing countries have optimally functional reporting schemes and are members of the WHO collaborating center on drug monitoring. But, it is not appropriate to extrapolate data from developed countries. The burden of ADRs in resource **limited settings may differ from resource-rich countries because of:**

- High prevalence of HIV/AIDS, TB, Malaria and other comorbid conditions
- Risk-benefit generalization may not apply
- Poor medicine labeling, off-label use
- Traditional medicines and associated adverse events and interactions
- Genetic make-up, nutrition status
- Regular monitoring for early signs of toxicity often not well-established

ADRs are a significant cause of morbidity and mortality in PHPs. They affect treatment adherence which increases the risk of drug resistance and erodes public confidence in PHPs resulting in wasted financial resources and suboptimal outcomes. Therapeutic ineffectiveness or treatment failure is a particularly important issue in public health programs such as HIV/AIDS, malaria, and TB. PHPs should collect data about the percentage of patients undergoing treatment whose regimen was modified because of treatment failure to inform future treatment guideline decisions.

Activity	Time (minutes)
<p>Show slide 21 of Ref. 112 to point out the countries providing the majority of ADR data.</p> <p>Ask the participants to cluster in twos to spend 5 minutes listing some reasons why it is not appropriate to extrapolate ADR data from developed countries to resource limited settings.</p> <p>Invite participants to share the reasons and create a list based on their contributions. Then add any additional reasons that might have been overlooked by the participants.</p>	20
<p>If time permits, discuss this case study in Ref. 114 about drug resistance and treatment failure associated with malaria treatment “ WHO, the Global Fund, and medical malpractice in malaria treatment”. The opinion article written in 2004 states that “Most African countries reluctantly cling to chloroquine, sulfadoxine-pyrimethamine, or the insignificantly better combination of chloroquine and sulfadoxinepyrimethamine, because ACT is ten times more expensive and, therefore, unaffordable to them.” That was taking place even though there were links to drug resistance, treatment failure and deaths from malaria. Ask the participants if they think this situation still taking place. Then, share the results of this study shown in Ref. 150 conducted in 2007.</p>	

Sources used in this session:

- Ref. 003 "Pharmacovigilance: Quality, Safety and Efficacy of Medicines For Better Health Care: Participants' Manual." Ministry of Public Health and Sanitation & Ministry of Medical Services. Kenya. [PowerPoint slides]. Feb. 2009.
- Ref. 110 Karema, C. *Pharmacovigilance Training of Trainers: Integrating Pharmacovigilance into Public Health Program (PHP)*. Rwanda. [PowerPoint slides]. Sep. 2009.
- Ref. 112 The Uppsala Monitoring Centre. *Implementing Pharmacovigilance in Public Health Programs*. [PowerPoint slides]. 2009
- Ref. 114 Attaran, A., Barnes, K. I., Curtis, C., d'Alessandro, U., Fanello, C. I., Galinski, M. R., . . . Watkins, W. M. WHO, the Global Fund, and medical malpractice in malaria treatment. *The Lancet*, 363, (17 Jan. 2004): 237–40.
- Ref. 131 National DI&ADR Centre of Vietnam. *Module 6 Introduction and Summary: PV in the ART program*. Pharmacovigilance In-service Workshop. [PowerPoint slides]. 2012.
- Ref. 140 National DI&ADR Centre of Vietnam. *Session 8.1 Importance of PV in PHPs and Burden of ADEs in PHPs*. Pharmacovigilance In-service Workshop. [PowerPoint slides]. 2012.
- Ref. 150 Frosch, A.E.P, Venkatesan, M. & Laufer, M.K. Patterns of chloroquine use and resistance in sub-Saharan Africa: a systematic review of household survey and molecular data. *Malar J.* 2011; 10: 116. doi: 10.1186/1475-2875-10-116

Additional Reading and Resources:

- Ref. 113 Strengthening Pharmaceutical Systems (SPS) Program. *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. Web. 2009.

Session 8.2: PV in the National Malaria Control Program

Topic to cover in this session:

- A. ADRs of clinical significance with antimalarial agents included in the national guidelines recommended by the National Malaria Control Program (NMCP) in Vietnam; measures to reduce antimalarial drugs-related morbidities; improving adverse event reporting within NMCP (covered in session 8.3)

Objectives: At the end of this session, participants will be able to:

- List clinically significant adverse effects and drug interactions associated with the antimalarials included in the national guideline
- Explain measures that are locally feasible to reduce antimalarial agents-related morbidities
- Explain how an effectively functioning system to collect ADR and treatment failure information can inform an evidence-based revision or change in the guideline

Content Summary and Process Overview / Instructional Methodology (Total Duration: 90 Minutes)

- A. ADRs of clinical significance with antimalarial agents included in the national guidelines recommended by the National Malaria Control Program (NMCP) in Vietnam; measures to reduce antimalarial drugs-related morbidities; improving adverse event reporting within NMCP (covered in session 8.3) (Source: Ref. 141)

ADRs associated with Chloroquine include: Headache, rash, itching, diarrhea, nausea, vomiting, psychotic disorders, anxiety, changing behavior, unclear eyes, cornea diseases, visual disturbances, retinopathy, and *rarely* - loss of hearing, deafness, neuromuscular disease, myopathy, hair loss, change of hair color, hypersensitivity, photosensitivity, bone marrow impairment, recoverable agranulocytosis, neutropenia, thrombocytopenia, seizure, tinnitus, cardiac arrest and apnea.

ADRs associated with Dihydroartemisinin + piperaquin include: Nausea and vomiting, headache, dizziness, vertigo and Leucopenia. ADRs associated with Artesunate include: headache, nausea, vomiting, abdominal pain, diarrhea, dizziness, tinnitus, elevated liver enzyme values and neutropenia.

ADRs associated with Quinine include: cinchonism (tinnitus, headache, blurred vision, temporary), blindness, impaired hearing, nausea, diarrhea, rash, confusion, hypoglycemia, renal damage (reduced urine output), blood disorders, cardiovascular, gastrointestinal & CNS effects, hypersensitivity reactions (angioedema). ADRs associated with Primaquine include: nausea, epigastric pain, abdominal cramping, hemolytic anemia, minor anemia, leukocytosis, methemoglobinemia and rarely - hypertension, arrhythmias, leukocytopenia, agranulosis / granulopenia and pruritus.

ADRs associated with Doxycycline include: diarrhea, nausea, vomiting, anorexia, flushing, tinnitus, photosensitivity, hypersensitivity, headache, visual disturbances, oral ulcers, hepatotoxicity, blood

disorders, pancreatitis, antibiotic-related colitis, staining of growing teeth and occasionally abnormal teeth. ADRs associated with Clindamycin include: nausea, vomiting, abdominal discomfort, diarrhea, colitis, rash, itching, Steven-Johnson syndrome; rarely - anaphylaxis; jaundice, altered liver function tests, neutropenia, and thrombocytopenia.

Activity	Time (minutes)
Use the slides in Ref. 141 to familiarize the participants with ADRs of clinical significance for Vietnam's National Malaria Control program. Slides 6-8 of that presentation will serve as reminders of material covered in session 8.1.	60
Facilitate a brief brainstorming session during which the participants identify measures to reduce anti-malarial drugs- related morbidities.	20
To reinforce the participant's appreciation about how ADR and treatment failure information can inform an evidence-based revision or change in guidelines (covered in session 1.1) present slides 35– 40 in Ref. 121 about the impact of PV on medicine regulation.	10

Sources used in this session:

- Ref. 141 National DI&ADR Centre of Vietnam. *Session 8.2 PV in the national Malaria Control Program*. Pharmacovigilance In-service Workshop. [PowerPoint slides]. 2012.
- Ref. 121 The National DI & ADR Centre (2012). *General Overview of Pharmacovigilance and Medication Safety* [PowerPoint slides]. 2012.

Additional Reading and Resources:

- Ref. 118 Frosch, A. E. P., Venkatesan, M. and Laufer, M. K. Patterns of chloroquine use and resistance in sub-Saharan Africa: a systematic review of household survey and molecular data. *Malar J.* 2011; 10: 116. Web. Published online 2011 May 9. doi: 10.1186/1475-2875-10-116.

Session 8.3: ADR Reporting

Topics to cover in this session:

- A. Strategies to improve ADR reporting and analysis (e.g., ADR form widely available, reporting as routine and normal part of administering healthcare, distribution network, feedback to reporters)
- B. Practice filling out ADR Reporting forms.

Objectives: At the end of this session, participants will be able to:

- Through a personal narrative, demonstrate enthusiasm and conscientiousness (in his/her role as a health care worker) toward filling and sending spontaneous reporting form when an ADR is suspected in his/her work setting
- Demonstrate correct understanding by telling that spontaneous reporting and active surveillance approaches are complementary methods
- Describe practically feasible strategies for improving ADR reporting in his/her practice setting

Content Summary and Process Overview / Instructional Methodology (Total Duration: 120 Minutes)

- A. Strategies to improve ADR reporting and analysis (e.g., ADR form widely available, reporting as routine and normal part of administering healthcare, distribution network, feedback to reporters)
(Sources: Ref. 072, Ref. 089)

Strategies for improving ADE analysis cannot take place in the absence of ADE reports, so it is essential to increase the reporting rate. Some approaches to increasing the rate of reporting include:

- Ensure that the ADR form widely is widely available by making ADR reporting forms available to each health facility nationwide. Define priorities for reporting and provide quick access to the PV system.
- Incorporate reporting as routine and normal part of administering healthcare by including it in health facility SOPs and by incorporating PV into the education of all healthcare workers.
- Establish and use a distribution network to foster communication and to increase ADR awareness among healthcare professionals and the public.
- Provide feedback to reporters to encourage them to continue to report ADRs.

Optimize opportunities to improve ADE analysis by exploiting opportunities for integrating PV functions into existing tools and software. Use statistical screening of data bases – data mining.

<i>Activity</i>	<i>Time (minutes)</i>
<p>Open the topic by stressing that strategies for improving ADE analysis cannot take place in the absence of ADE reports, so it is essential to increase the reporting rate. Discuss some of the approaches to increasing the rate of reporting listed in the content summary. Ask the participants to consider why providing feedback to reporters might increase the rate of reporting. (10 min)</p> <p>Ask participants to cluster in groups of 3 to discuss practically feasible strategies for improving ADR reporting in their practice setting. Ask each group to share the results of their discussions. (10 min)</p> <p>Present the slides in Ref. 142 to provide detailed guidance on the ADR reporting process and guidelines for reporting. (30 min)</p> <p>Demonstrate filling out an ADR form. Use Ref. 090 (interactive PDF that allows you to type into it) or Ref: 148 – the DI&ADR on-line reporting system, if internet access is available. (5 min)</p> <p>Alert to the instructor: Do NOT use the official, live DI&ADR on-line reporting system during the training sessions to avoid accidentally submitting practice ADRs into the system.</p> <p>Conduct exercise to have the participants practice filling out ADR reporting forms (20 min)</p> <p>Facilitate a discussion during which participants will have the opportunity to share their experiences in filling out the ADR reporting forms and also to share their enthusiasm about using a spontaneous reporting form when an ADR is suspected in the work setting (10 min)</p> <p>Remind participants that that as they learned in session 3.1, spontaneous reporting and active surveillance approaches are complementary methods and that data collected by both methods are needed to best meet the PV goals of safeguarding public health and improving rational medicine use.</p> <p>Present the final slide of Ref. 139 to summarize the malaria control track of the PV training program.</p>	90

Sources used in this session:

- Ref. 072 Joshi, M. P. *A System-oriented Approach to Implementing Pharmacovigilance* [PowerPoint slides]. 29 Sep. 2009.
- Ref. 089 Hanoi University of Pharmacy. *Introduction To Pharmacovigilance: Signal Evaluation: Signal Generation and Strengthening*. [PowerPoint slides]. 26 Mar 2009
- Ref. 090 The National DI & ADR Centre, Hanoi. *Suspected Adverse Drug Reaction Report*. Interactive form. Web. 29 Nov. 2010.
- Ref. 139 National DI&ADR Centre of Vietnam. *Module 8 Introduction and Summary: PV in the National Malaria Control Program*. Pharmacovigilance In-service Workshop. [PowerPoint slides]. 2012.
- Ref. 142 National DI&ADR Centre of Vietnam. *Session 8.3 ADR Reporting*. Pharmacovigilance In-service Workshop. [PowerPoint slides]. 2012.
- Ref: 148 The National DI & ADR Centre, Hanoi. Vietnam On-line ADR Reporting System. Interactive form. Web.

Additional Reading and Resources:

- Ref. 027 U.S. Food and Drug Administration. Reporting Serious Problems to FDA. Web. Last Updated: 23 Jun. 2011.

ANNEX 2:



Instructor Guide to Pharmacovigilance Curriculum for Post-graduate Pharmacy Students at Hanoi University of Pharmacy

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Table of Contents

The Purpose and Organization of this Instructor Guide	1
Session 1.1: General Overview of Pharmacovigilance (PV) and Medication Safety	3
Session 1.2: PV Program in Vietnam and in the world	11
Session 1.3: PV of herbal medicines in Vietnam and in the world	18
Session 2.1: Adverse Drug Reaction as a Factor for Adverse Drug Events:	22
Session 2.2: Medication Error as a Factor for Adverse Drug Events.....	30
Session 2.3: Other Factors for Adverse Drug Events	38
Session 2.4: Adverse Drug Events: Assessment of Severity and Causality	43
Session 3.1: Passive and Active Methods of Surveillance.....	49
Session 4.1: Strategies to Improve Risk Communications, and Principles of Risk Management and Risk Minimization	57
Session 5.1: Importance of PV in Public Health Programs (PHPs), Burden of ADEs in PHPs, Strategies to Improve Adverse Events Reports in PHPs.....	65
Seminars.....	71
Annex 1: Guidance on Enhancing the Objectivity of Student Assessment.....	77
Annex 2: Test Questions	78
Annex 3: Test Answers	83
Annex 4: How to Facilitate Structured Brainstorming Sessions.....	84

The Purpose and Organization of this Instructor Guide

PURPOSE OF THIS GUIDE

To provide faculty members at HUP with summarized pharmacovigilance (PV) course content, easy access to in-depth associated resources and step-by-step guidance on how to conduct each class session using interactive, learner-centered instructional techniques. The goal is to use as many learner-centered instructional methods as possible to enhance the level of interactivity and enable the students to have a greater role in their learning experience. In classes with many students, breaking into groups for discussions and exercises might be limited to the clustering of two or three students sitting nearest each other. In such situations, interaction and cross-pollination of thought among the students can be optimized by asking them not to sit in the same seats for every class. Finally, interactive instructional methods sometimes take more time than straight presentation. As a result, the faculty member should avoid the temptation to try to cover more material in a given time segment than can comfortably be covered.

This pharmacovigilance curriculum is organized into 5 modules that are further subdivided into sessions for total of 10 sessions as shown below. Prior to starting to present actual pharmacovigilance content, the instructor is advised to share the information about these modules and sessions with the class to help establish the students' expectations.

1. Overview of PV and Medication Safety

- 1.1. General Overview of PV and Medication Safety
- 1.2. PV Program in Vietnam and in the World
- 1.3. PV of herbal medicines in Vietnam and in the world

2. Risk Identification

- 2.1. Adverse Drug Reaction as a Factor for Adverse Drug Events
- 2.2. Medication Error as a Factor for Adverse Drug Events
- 2.3. Other Factors for Adverse Drug Events
- 2.4. Adverse Drug Events: Assessment of Severity and Causality

3. Risk Evaluation and Reporting

- 3.1. Passive and Active Methods of Surveillance

4. Risk Communication, Risk Management, and Risk Minimization

- 4.1. Strategies to Improve Risk Communications, and Principles of Risk Management and Risk Minimization

5. Pharmacovigilance in public health programs

- 5.1. Importance of PV in PHPs, Burden of ADEs in PHPs, Strategies to Improve Adverse Events Reports in PHPs

Guidance for the instructor about each of the 10 sessions is provided with the following components:

Topics to cover in the session: provides a brief summary statement describing each topic

Objectives: states what the students are expected to be able to do by the end of the session

Content Summary and Process Overview / Instructional Methodology: provides a brief summary of the technical content of each topic in the session with references to more detailed content resources and case stories, where appropriate, and guidance for the instructor about the activities to use during the process of managing the session. Instructional techniques and duration for each topic in the session and the total time to conduct the entire session are also included.

The associated content resources provided are often in the form of PowerPoint slides which can be presented exactly as they are or with customizations/abridgments as the instructor sees fit. The instructors should decide how to present the contents depending on the level and needs of their students and their own level of comfort with the material.

References for additional reading: listing locations of additional information relevant to the topics.

In addition to the references pertaining to specific sessions, WHO-UMC's list of abbreviations and acronyms associated with pharmacovigilance and WHO-UMC's glossary of terms used in pharmacovigilance are valuable resources that pertain to the entire PV curriculum. Citations for these resources are below.

TARGET AUDIENCE FOR THIS GUIDE

Faculty members at HUP responsible for teaching the Pharmacovigilance course.

STUDENT ASSESSMENT

In addition to the opportunities for students to display competency on pharmacovigilance during discussion of case studies and during the interactive portions of the sessions and seminars, Appendix 1 provides 25 test questions for use in student assessment. The test is preceded by a section containing guidance for the instructor on how to enhance the objectivity associated with student assessment.

COURSE DURATION

The Pharmacovigilance course on which this guide is based was designed to take a total of 800 minutes of classroom time.

Resources

Uppsala Monitoring Centre. *Glossary of terms used in Pharmacovigilance*. Web. 2011.

Uppsala Monitoring Centre. *A list of abbreviations and acronyms found in the field of, or connected with, pharmacovigilance*. Web. Jan. 2012.

Session 1.1: General Overview of Pharmacovigilance (PV) and Medication Safety

Topics to cover in this session:

- A. Definition of PV
- B. Brief history of PV
- C. Goals of PV (rational medicine use, communication of risk and benefit of medicines, health worker and patient education)
- D. Widening scope of PV—adverse drug reaction (ADR), medication error, product quality, therapeutic ineffectiveness
- E. Brief overview of the need and importance of PV (burden of ADRs; morbidity and mortality, cost burden of ADRs, benefits of PV)
- F. Brief revisit on the various phases of clinical trials of medicines and post-marketing surveillance, and how PV fits in all these steps (life-cycle approach)
- G. Brief introduction on how PV information can influence medicines policy and regulation: recall, labeling changes, reschedule withdrawal, policy change

Objectives: By the end of the session, students will be able to:

- Define PV and emphasize that its scope includes not only ADRs but also medication errors, product quality issues, and therapeutic ineffectiveness
- Explain the burden and impact of adverse drug events (ADE) and use this context to articulate the need to support PV activities
- Link PV as a key ingredient to achieving the broader goals of rational medicine use and pharmaceutical care
- Emphasize that monitoring the safety of a medicine is an ongoing process, and needs to happen both during pre-marketing and post-marketing periods
- Tell how PV information provides evidence for and influences regulatory decision, giving one example of such a decision taken by drug regulatory authority

Content Summary and Process Overview / Instructional Methodology (Total Duration: 100 Minutes)**A. Definition of PV (Source: Ref. 009)**

Pharmacovigilance is the science and activities related to the detection, assessment, understanding and prevention of adverse effects or any other possible drug-related problems. Those drug-related problems include drug interactions, poor quality and counterfeit products, medication use errors and lack of efficacy.

Activity	Time (minutes)
Open the class by showing slide 2 of Ref. 002 to highlight the constantly changing human perspective on medications. Then provide the definition of PV as shown in section A of the content summary.	10

B. Brief history of PV (Sources: Ref. 010 page 5, Ref. 012)

The practice and science of pharmacovigilance emerged following the disaster caused by thalidomide in 1961. At that time many thousands of congenitally deformed infants were born as the result of exposure in utero to an unsafe medicine promoted for use by pregnant mothers. In 1963, the Sixteenth World Health Assembly adopted a resolution that reaffirmed the need for early action in regard to rapid dissemination of information on adverse drug reactions which led to creation of the WHO Pilot Research Project for International Drug Monitoring in 1968. Since 1978 the Program has been carried out by the Uppsala Monitoring Centre (UMC) in Sweden. The creation of the International Society of Pharmacoepidemiology (ISPE) in 1984 and the European Society of Pharmacovigilance (ESOP; later ISoP – the International Society) in 1992 marked the introduction of pharmacovigilance formally into the research and academic world. Pharmacovigilance activities have also evolved as a regulatory activity. Recommendations of the Council for International Organizations of Medical Sciences (CIOMS), accepted by the International Conference on Harmonization (ICH) in the 1990s, has had a notable impact on international drug regulation.

Activity	Time (minutes)
Provide a mini-lecture about the history of PV while showing slides 3-7 of Ref. 005	10

C. Goals of PV (rational medicine use, communication of risk and benefit of medicines, health worker and patient education) (Source: Ref. 009)

The goal of Pharmacovigilance is to safeguard public health and improve rational medicine use through efficient and timely collection, assessment and communication of risks and benefits to support decision-making at various levels of the health care system. The impact of those Pharmacovigilance activities is reduced mortality and morbidity due to medicines-related problems

<i>Activity</i>	<i>Time (minutes)</i>
<p>Show the students the following 7 phrases:</p> <ul style="list-style-type: none"> • reduced mortality due to medicines-related problems • safeguard public health • collection of data about risks and benefits • communication of risks and benefits • reduced morbidity due to medicines-related problems • improve rational medicine use • assessment of risks and benefits <p>Ask the students to identify each phrase as either a goal of PV, an activity performed during PV or an impact of PV.</p> <p>Then, show them section C of the content summary so they can determine if they classified the phrases correctly.</p>	10

D. Widening scopes of PV—adverse drug reaction (ADR), medication error, product quality, therapeutic ineffectiveness (Sources: Ref. 005, Ref. 008)

Medication safety concerns on which pharmacovigilance focuses now go beyond adverse drug reactions and side effects to include drug interactions, poor quality and counterfeit products, medication use errors and lack of efficacy. One factor influencing this expansion in scope is the growing problem of poor quality or counterfeit medicines.

Activity	Time (minutes)
<p>Ask students to consider how information collected regarding lack of efficacy can contribute to the goals of PV that were just discussed. Ask a few students to share their thoughts with the class.</p> <p>Present the areas of expanded focus for PV shown in the content summary.</p> <p>Explain that this topic will be covered in depth in sessions 2.2 and 2.3.</p>	10

- E. Brief overview of the need and importance of PV (burden of ADRs; morbidity and mortality, cost burden of ADRs, benefits of PV. (Sources: Ref. 009 page 7, Ref. 001, Ref. 003, Ref. 011, Ref. 006 page 2)

The information collected during the pre-marketing studies of new medications is incomplete with regard to possible adverse reactions. Pre-marketing studies involve a limited number of patients, conditions of use which differ from those in clinical practice and limited duration of trials. As a result, pharmacovigilance via post-marketing surveillance is needed to provide a more complete picture of adverse drug reactions resulting from medication use. Post marketing surveillance can identify rare adverse effects which could not have been identified during shorter clinical trials. Pharmacovigilance can also reveal information about potential toxicity from long term use and can highlight potential drug and disease interactions and may result in re-appraisal of indications for that medication. It is only through knowing as much as possible about potential ADRs associated with each medication through pharmacovigilance, that the impact of ADRs can be diminished.

One example of the huge financial burden of ADRs comes from a 2002 study that estimated the annual cost of drug-related morbidity and mortality resulting from drug-related problems in ambulatory care settings in the United States at \$177.4 billion. And, U.S. Institute of Medicine estimated that up to 98,000 people die each year from medication errors in U.S. hospitals at a cost of up to 29 billion US\$ / year. Other studies estimate the costs at 588 million US\$ / year in Germany (1997) and 847 million US\$ / year in the UK (2006).

From a public health perspective, the burden of ADRs is also striking. ADRs are the 4th-6th leading cause of death in the USA. Up to 19 % of hospitalized patients will have an ADR. From 2004 through 2006, medical errors resulted in 238,337 potentially preventable deaths and cost the U.S. Medicare program 8.8 billion US\$. It is estimated that 70% of ADRs are avoidable.

Information gained through pharmacovigilance has the potential to greatly improve patient care while providing huge savings in healthcare costs.

Activity	Time (minutes)
Share some examples of the estimated financial and public health costs mentioned on page 2 of Ref. 006. Summarize by stressing that these burdens could be greatly reduced through effective PV systems.	10

F. Brief revisit on the various phases of clinical trials of medicines and post-marketing surveillance, and how PV fits in all these steps (life-cycle approach). (Source: Ref. 005, slides 13- 20)

- Phase I - Initial studies in a small number (typically 20-80) human subjects to determine the metabolism and pharmacologic actions, side effects associated with increasing doses, and to gain early evidence of effectiveness; may include healthy participants and/or patients
- Phase II- Controlled clinical studies conducted to evaluate the effectiveness of the drug for a particular indication or indications in patients with the disease or condition under study and to determine the common short-term side effects and risks. There are usually no more than several hundred patients in Phase II studies.
- Phase III- Controlled clinical studies conducted to evaluate the therapeutic efficacy of the drug for a particular indication or indications in patients with the disease or condition under study and to determine the common short-term side effects and risks. There are typically several hundred to several thousand patients enrolled in Phase III studies.
- Phase IV- Post-marketing studies to delineate additional information including the drug's risks, benefits, and optimal use. Typically large population of users of the medicine enrolled in real-life situations. Provides Improved understanding of the safety profile and information about populations not studied under premarket trials

Pharmacovigilance is an integral part of a medicine's life cycle and safety data is collected at every Phase of clinical trials.

Activity	Time (minutes)
<p>Show one of the clinical research cartoons (Ref. 016 or Ref. 017) as an introduction to brief overview of clinical trials. Use Ref. 005, slides 13- 20 to present a brief overview of the phases of clinical trials. Then, summarize by stressing that pharmacovigilance is an integral part of a medicine's life cycle because safety data is collected at every phase of clinical trials.</p> <p>If time permits, use Ref. 020 to demonstrate the clinicaltrials.gov website by showing the adverse experiences listed.</p>	20

- G. Brief introduction on how PV information can influence medicines policy and regulation: recall, labeling changes, reschedule withdrawal, policy change. (Sources: Ref. 004 pages 43-45, Ref. 013, Ref. 014, Ref. 018, Ref. 019)

Medicines regulation is governed by issues of safety, quality and efficacy. Results of information learned from PV data can lead to regulatory actions including recall, labeling change, reschedule, withdrawal or policy change. Some examples are:

Recall: In 2008, Kenya recalled batches of Duo-cotecxin® (antimalarial) due to presence of counterfeit packs.

Labeling change: On November 18, 2011, the US FDA announced that Avastin (bevacizumab) was no longer approved for the treatment of breast cancer. The drug retains its indications for colon, lung, kidney, and brain cancer. Clozapine (previously withdrawn) reapproved after submission of new data, with a restricted indication for schizophrenia refractory to other therapy; in addition, mandatory white blood- cell monitoring of patients is required wherever the drug is marketed.

Reschedule: In 2011 the antihistamine Fexofenadine hydrochloride was switched by the US FDA to OTC because it was found to be safe enough based on use in larger populations.

Withdrawal: 2004 Vioxx (rofecoxib, which is a COX-II inhibitor) withdrawn voluntarily due to increased risk of cardiovascular events. Chlorproguanil + Dapson (LapDap®) was withdrawn voluntarily in 2008 due to concerns of anaemia in G-6-PD deficient patients. Clozapine was withdrawn from some markets after reports of agranulocytosis in Finland. In 2010 Propoxyphene (opioid pain medication) was withdrawn from the US market based on new data showing significant changes to the electrical activity of the heart.

Policy change: Indinavir (an antiretroviral medicine) now not used except as salvage therapy due to renal stones.

<i>Activity</i>	<i>Time (minutes)</i>
<p>Present the examples (in section G of the content summary) of situations where information learned from PV data led to regulatory actions including recall, labeling change, reschedule, withdrawal and policy change. Then, discuss recent withdrawals in Vietnam using slide 39 of Ref. 023. (10 minutes)</p> <p>Lead discussion on Ref. 015 Case - Indinavir-Associated Nephrotoxicity. (20 minutes) (The website provides question to ask the students and the discussion.)</p>	30

Sources used in this session:

- Ref. 001 Farcas, A. & Bojita, M. Adverse Drug Reactions in Clinical Practice: a Causality Assessment of a Case of Drug-Induced Pancreatitis. *J Gastrointestin Liver Dis*, 18.3 (2009): 353-358.
- Ref. 002 Hartigan-Go, K. *Why is Pharmacovigilance Important?* International Society of Pharmacovigilance (ISoP). [PowerPoint slides]. 2009
- Ref. 003 "Pharmacovigilance: Quality, Safety and Efficacy of Medicines For Better Health Care: Participants' Manual." Ministry of Public Health and Sanitation & Ministry of Medical Services. Kenya. [PowerPoint slides]. Feb. 2009.
- Ref. 004 "Pharmacovigilance: Quality, Safety and Efficacy of Medicines For Better Health Care: Trainers' Manual." Ministry of Public Health and Sanitation & Ministry of Medical Services. Kenya. [PowerPoint slides]. Feb. 2009.
- Ref. 005 No Author. *Pharmacovigilance Training of Trainers: History of Pharmacovigilance and life-cycle of a Medicine*. Rwanda. [PowerPoint slides]. Sep 2009.
- Ref. 006 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. Sep. 2009.
- Ref. 008 Joshi, M. *Report on Technical Assistance for Drug Information and Pharmacovigilance Activities of the DI & ADR Centre in Vietnam*. Submitted to the U.S. Agency for International Development by the Strengthening Pharmaceutical Systems (SPS) Program. Arlington, VA: Management Sciences for Health. 2010.
- Ref. 009 Hanoi University of Pharmacy. *Introduction To Pharmacovigilance: Use of Pharmacovigilance for Risk Management*. [PowerPoint slides]. 26 Mar 2009.
- Ref. 010 World Health Organization. *The Importance of Pharmacovigilance: Safety Monitoring of medicinal products*. 2002.
- Ref. 011 Bernstein, L. R. The Cost of Drug-Related Problems Revisited. Message posted to medscape.com. 4 Mar. 2002.
- Ref. 012 About The Uppsala Monitoring Centre. Website.
- Ref. 013 National Center for Infectious Diseases, Centers for Disease Control and Prevention. *CDC Study Shows Sharp Decline in Reye's Syndrome among U.S. Children*. Web. Last modified 2 Aug. 2006.
- Ref. 014 CIOMS Working Group IV Benefit-Risk Balance for Marketed Drugs: Evaluating Safety Signals. Web. 1998.
- Ref. 015 Spach, D. H. Case 3: Indinavir-Associated Nephrotoxicity. *Antiretroviral Rx: Adverse Effects*. Web. 24 Jan. 2011.
- Ref. 016 Clinical Research Cartoon. Image file.
- Ref. 017 Clinical Research Cartoon. Image file.
- Ref. 018 Walker, E. FDA Revokes Avastin Approval for Breast Cancer. *MedPage Today*. Web. 18 Nov. 2011.

- Ref. 019 Fultz-Morris, Y. Withdrawal of Products that Contain Propoxyphene. *FDA Drug Safety Podcast*. Web. 21 Nov. 2010.
- Ref. 020 Pfizer, Inc. Clinical Trial: Study Evaluating the Safety of Etanercept in Rheumatoid Arthritis, Ankylosing Spondylitis and Psoriatic Arthritis. Web. Last Updated on 8 Sep. 2011.
- Ref. 023 The National DI & ADR Centre (2012). *General Overview of Pharmacovigilance and Medication Safety* [PowerPoint slides]. 2012.

Additional Reading and Resources:

- Ref. 021 US National Institutes of Health. Understanding Clinical Trials. Web. Last Updated: 20 Sep. 2007.
- Ref. 022 U.S. Food and Drug Administration. Drugs Removed from or Restricted in the U.S. Market Because of Drug Interactions. Web. Last Updated: 03 Feb. 2010.

Session 1.2: PV Program in Vietnam and in the world

Topics to cover in this session:

- A. Brief overview of the problems of drug overuse and misuse in Vietnam; safety issues with traditional and herbal medicines in Vietnam; weaknesses of the health care system regarding medicine safety activities
- B. Overview of the legal basis for PV system and framework of the PV system in Vietnam
- C. PV roles and activities in the Ministry of Health (MOH), the National DI&ADR Center, Drug Administration of Vietnam (DAV), and Medical Services Administration (MSA) of Vietnam
- D. Brief overview of PV management model of WHO, FDA, and EU

Objectives: By the end of the session, students will be able to:

- Describe the legal basis of PV activities in Vietnam
- List the key national stakeholders with regard to PV in Vietnam
- Briefly describe PV management model of WHO, FDA and EU

Content Summary and Process Overview / Instructional Methodology (Total Duration: 50 Minutes)

- A. Brief overview of the problems of drug overuse and misuse in Vietnam; safety issues with traditional and herbal medicines in Vietnam; weaknesses of the health care system regarding medicine safety activities. (Sources: Ref. 025, Ref. 010 pages 22 and 23, Ref. 034, Ref. 035)

Safety issues with traditional and herbal medicines in Vietnam (also covered in session 1.3)

In Vietnam as in many other countries, the use of herbal and traditional medicines raises concerns in relation to their safety. There is wide misconception that 'natural' means 'safe'. There is the common belief that long use of a medicine, based on tradition, assures both its efficacy and safety. There are examples of traditional and herbal medicines being adulterated or contaminated with allopathic medicines, chemicals such as corticosteroids, non-steroidal anti-inflammatory agents and heavy metals. Self-medication further aggravates the risk to patients. When traditional and herbal medicines are used in conjunction with other medicines there is the potential of serious adverse drug interactions. As with other products intended for human use (medicines, dietary supplements and foods), herbal medicines should be incorporated within a regulatory framework. Difficulties in achieving this arise from the growth of an ambiguous zone between foods and medicines, into which an increasing number of herbal products fall.

In 2001, WHO conducted a Global Survey about national policies on traditional medicines and regulation of herbal medicines. The report of survey results revealed that In the Socialist Republic of Vietnam, a national policy on TM/CAM was at that time currently being developed. Laws and regulations were issued in 1989 and a national programme was issued in 1986. The Department of Traditional Medicine is administered by the Ministry of Health, and was established in 1957. There is currently no expert committee. In 1957, the Vietnamese Institute of Traditional Medicine was established, and in 1976 the Ho Chi Minh Institute of Traditional Medicine and Pharmacy was founded. National laws and regulations on herbal medicines were issued in 1989, separately from the laws governing conventional pharmaceuticals. Herbal medicines are regulated as prescription and over the counter medicines. By law, medical, health and nutrient content claims may be made.

The Vietnam pharmacopoeia is legally binding, as are the national herbal monographs. Regulatory requirements for manufacturing include adherence to information in pharmacopoeias and monographs and the same GMP rules used for conventional pharmaceuticals. Implementation of these requirements is ensured by inspection and visits to manufacturing establishments. Safety requirements for herbal medicines include traditional use without demonstrated harmful effects and reference to documented scientific research on similar products. Classical or traditional remedies are used and promoted without the need to demonstrate the safety of the product. New remedies, indications or uses for herbal medicines must be accompanied by records of clinical trials. Implementation of these requirements is ensured by the registration system.

At the time of the survey, there were 1573 registered herbal medicines in Vietnam; 267 herbal medicines included on the national essential medicines list of 1996. The post marketing surveillance system included monitoring of adverse effects for herbal medicines. In Vietnam, herbal medicines are sold in pharmacies as prescription and over the counter medicines, in special outlets and by licensed practitioners.

Weaknesses of the healthcare system regarding medical safety activities.

The structure of Vietnam's drug information system is not consistent or fully developed from the central to the local level. Activities rely on donations for funding. The drug information projects are small and there is no collaboration between different activities. In treatment sites, activities are not effective and they lack collaboration and instructions from the Drug and Therapy committee. Drug manufacturers and distributors only focus on marketing and place little importance on drug information and adverse reaction monitoring. There is some drug information monitoring in some hospitals but the activity is not effective, and is without specialized experts and a clear strategy.

<i>Activity</i>	<i>Time (minutes)</i>
Opportunity for the Instructor to update the students on progress or plans to improve Vietnam's medical safety activities.	10

B. Overview of the legal basis for PV system and framework of the PV system in Vietnam. (Source: Ref. 025)

Several laws, decrees and decisions (starting with the Pharmacy Law issued on June 14, 2005) served as the legal basis for establishing The DI & ADR Center as the national center for drug information and ADR monitoring in Vietnam. Those included

- The Pharmacy Law issued on 14/6/2005
- The Decree No 79/2006/NĐ-CP dated 9/8/2006 issued by the Government instructing the implementation of Pharmacy Law
- The Decision No. 154/ 2006/ QĐ-TTg dated 30/6/2006 from Prime Minister about approving the proposal "State management on pharmacy, food and cosmetic safety for the period 2006-2015"
- Decision No. 2557/2002/QĐ-BYT dated 4/7/2002 from Minister of Health about issuing Regulation of Drug and Cosmetic Advertisement Information
- Announcement No. 127/TB- VPCP dated 26/05/2008 from Deputy Prime Minister Nguyen Thien Nhan about implementing state management on Pharmacy and development of Pharmaceutical Industry
- Regulation of organization and operation of Hanoi University of Pharmacy approved by Minister of health on 25/2/2009

The framework of the PV system is provided in section C.

<i>Activity</i>	<i>Time (minutes)</i>
Use the presentation in Ref. 025 to provide the legal basis and framework for Vietnam's PV system, with special focus on slides 12 and 20.	20

- C. PV roles and activities in the Ministry of Health (MOH), especially the National DI&ADR Center, Drug Administration of Vietnam (DAV), and Medical Services Administration (MSA) of Vietnam. (Sources: Ref. 097, Ref. 098, Ref. 026)

Organizations that play a role in Vietnam's PV and medicine safety systems include:

- **Ministry of Health (MOH)** – is responsible for the governance and guidance of the health, healthcare and health industry of Vietnam. In conjunction with other ministries and the prime minister's office, the Ministry of Health is responsible for creating and promulgating long-term health policy programs.
- **National DI&ADR Center –National Drug Information and Adverse Drug Reaction Center** - Serves as the hub for receiving pharmacovigilance data collected by the regional centers and is responsible for Vietnam's database of PV and drug information. It also supports governmental authorities in assessing and understanding the advantages and disadvantages of drugs available in the market and provides drug information and advice on ADRs for clinical sites, pharmacy staff and the community. The National DI&ADR Center also establishes connections with international drug and ADR centers
- **DAV- Drug Administration of Vietnam** – Plays a role in legislation, regulation, development of policy documents and strategic planning for pharmacovigilance. Makes decisions and takes measures to deal with issues related to pharmacovigilance. Collaborates with the drug regulatory authorities of other countries and international agencies on pharmacovigilance, including reporting ADRs to WHO/Uppsala Monitoring Centre. The DAV monitors product quality, including conducting GMP inspections and post-marketing sampling and testing .
- **MSA – Medical Services Administration** - Provides guidance on the safe and appropriate use of medicines at health facilities. Supervises and trains health care workers on the rational and safe use of medicines in health facilities. In collaboration with Public Health Programs, takes measures to deal with issues related to pharmacovigilance in these programs. Provides advice to hospitals, clinic and providers on case management of medication-related adverse events.

<i>Activity</i>	<i>Time (minutes)</i>
Present the 23 slides of the PowerPoint presentation in Ref. 098 to familiarize the students with Vietnam's national stakeholders and their roles in medicine safety activities. Put extra emphasis on slide 13 to ensure that the students understand the relationship between the Ministry of Health and the National DI&ADR Center, the DAV- Drug Administration of Vietnam and the MSA – Medical Services Administration.	10

- D. Brief overview of PV management model of WHO, FDA, and EU. (Sources: Ref. 024 pages 2 and 5, Ref. 029, Ref. 031, Ref. 036)

Under the WHO Programme for International Drug Monitoring, systems have been developed in Member States for the collection of individual case safety reports (ICSRs) and their evaluation. Health professionals report adverse events to a regional or national PV centre. The national PV centre (which is usually a part of or closely linked to the national drug regulatory authority (NDRA) forwards the reports to a central database that is managed and maintained by the WHO Collaborating Centre for International Drug Monitoring, the Uppsala Monitoring Centre (UMC) in Sweden. In December 2010, there were 136 countries participating in the Programme.

In the US, the FDA's Adverse Event Reporting System (AERS) computerized information database supports the FDA's post-marketing safety surveillance program for all approved drug and therapeutic biologic products. The FDA uses AERS to monitor for new adverse events and medication errors that might occur with these marketed products.

Reporting of adverse events from the point of care is voluntary in the United States. FDA receives some adverse event and medication error reports directly from health care professionals (such as physicians, pharmacists, nurses and others) and consumers (such as patients, family members, lawyers and others). Healthcare professionals and consumers may also report these events to the products' manufacturers. If a manufacturer receives an adverse event report, it is required to send the report to FDA as specified by regulations.

The European Medicines Agency uses the EudraVigilance data processing network and management system for reporting and evaluating suspected ADRs during the development of and following the marketing authorization of medicinal products in the European Economic Area (EEA). Each Member State has established a pharmacovigilance system for the collection and evaluation of information relevant to the risk-benefit balance of medicinal products; data they collect are shared between Member States and the Agency via EudraVigilance.

In addition, the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) strengthens the post-authorization monitoring of medicinal products in Europe by facilitating the conduct of multi-centre independent post-authorization safety studies and studies focusing on lack of efficacy.

Activity	Time (minutes)
<p>Share descriptions of the WHO, FDA, and EU PV management models shown in the content summary. Then, ask the students to draw diagrams of each of those models. Summarize by highlighting the differences and similarities among the three models. (Figure 1.1 on page 2 of Ref. 024 is a diagram showing the flow of reports on adverse drug reactions (ADRs) from countries to the UMC, as an example.)</p>	10
<p>CASE STUDY</p> <p>If time permits, present this additional PV management model from Ref. 032</p> <p>Pharmacovigilance in India: The Central Drugs Standard Control Organization (CDSCO), Ministry of Health and Family Welfare, Govt. of India's National Pharmacovigilance Programme (NPP) is based on the WHO recommendations made in the document titled "Safety Monitoring of Medicinal Products: Guidelines for Setting Up and Running a Pharmacovigilance Centre". The whole country is divided into zones and regions for operational efficiency. CDSCO, New Delhi is at the top of the hierarchy followed by two zonal pharmacovigilance centers: Seth GS Medical College, Mumbai, and AIIMS, New Delhi. Graphic shown on page 8 of Ref. 119.</p>	

Sources used in this session:

- Ref. 010 World Health Organization. *The Importance of Pharmacovigilance: Safety Monitoring of medicinal products*. 2002.
- Ref. 024 Pal, S., Doodoo, A., Mantel, A., & Olsson, S. The World Medicines Situation 2011 Pharmacovigilance and Safety of Medicines. World health Organization. 2011.
- Ref. 025 Nguyen, D. H. The strategy for the National DI/ADR Center and PV System in Vietnam. Hanoi University of Pharmacy. 2009.
- Ref. 097 Nguyen T. P. C. *Role of the Drug and Therapeutic Committee in Safe and Rational Use of Drugs in Vietnam*. Medical Service Department, Ministry of Health. [PowerPoint slides]. 2009.
- Ref. 098 Hanoi University of Pharmacy. *National Stakeholders and their Roles in Medicine Safety Activities*. [PowerPoint slides]. 26 Mar 2009
- Ref. 026 The National DI & ADR Centre, Hanoi University of Pharmacy & Ministry of Health *National Capacity Assessment for Drug Information and Pharmacovigilance*. Submitted to World Health Organization (WHO). Dec. 2009.
- Ref. 029 European Medicines Agency. *EudraVigilance*. Web
- Ref. 031 U.S. Food and Drug Administration. Adverse Event Reporting System (AERS). Web. Last Updated: 20 Aug. 2009.
- Ref. 032 Pharmaceutical Drug Manufacturers. What is Pharmacovigilance? Definition and System. Web
- Ref. 034 World Health Organization. National Policy on Traditional Medicine and Regulation of Herbal Medicines - Report of a WHO Global Survey. Web. May. 2005.
- Ref. 035 The Museum of Vietnamese Traditional Medicine. Web.
- Ref. 036 Guidelines on Pharmacovigilance for Medicinal Products for Human Use. *The Rules Governing Medicinal Products in the European Union*, volume 9A. Sep. 2008.
- Ref. 119 Singh, S. *National Drug Authority – Its Structure and Activities*. Seminar on Clinical Trials: The Heart of Medical Science (India). [PowerPoint Slides]. 4 Nov. 2008.

Additional Reading and Resources:

- Ref. 028 FDA Science Board Subcommittee. *Review of the FDA/CDER Pharmacovigilance Program*. Submitted to the FDA Science Board. Web. 20 May 2011.
- Ref. 030 *ENCePP Database of Research Resources*. Version 3.0.48. European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP). Web.
- Ref. 033 Barfield, A. "Pharmacovigilance in the US & EU." Slideshare. 20 Jan. 2009. Web
- Ref. 027 U.S. Food and Drug Administration. Reporting Serious Problems to FDA. Web. Last Updated: 23 Jun. 2011.

Session 1.3: PV of herbal medicines in Vietnam and in the world

Topics to cover in this session:

- A. Brief overview of the issues with PV of herbal medicines in Vietnam
- B. Brief overview of the issues with PV of herbal medicines in other countries of the world

Objectives: By the end of the session, students will be able to:

- Describe the key problems and clinically significant toxicities associated with the use of herbal and traditional medicines in Vietnam

Content Summary and Process Overview / Instructional Methodology (Total Duration: 50 Minutes)

- A. Brief overview of the issues with PV of herbal medicines in Vietnam. (Sources: Ref. 010, pages 22 and 23, Ref. 034, Ref. 035)

In Vietnam as in many other countries, the use of herbal and traditional medicines raises concerns in relation to their safety. There is wide misconception that 'natural' means 'safe'. There is the common belief that long use of a medicine, based on tradition, assures both its efficacy and safety. There are examples of traditional and herbal medicines being adulterated or contaminated with allopathic medicines, chemicals such as corticosteroids, non-steroidal anti-inflammatory agents and heavy metals. Self-medication further aggravates the risk to patients. When traditional and herbal medicines are used in conjunction with other medicines there is the potential of serious adverse drug interactions. As with other products intended for human use (medicines, dietary supplements and foods), herbal medicines should be incorporated within a regulatory framework. These products should be governed by standards of safety, quality and efficacy that are equivalent to those required for other pharmaceutical products. Difficulties in achieving this arise from the growth of an ambiguous zone between foods and medicines, into which an increasing number of herbal products fall. The regulatory status of herbal products differs significantly from country to country. More attention needs to be given to research and to training of healthcare providers and consumers in this area.

In 2001, WHO conducted a Global Survey about national policies on traditional medicines, and regulation of herbal medicines. The report of survey results revealed that In the Socialist Republic of Vietnam, a national policy on traditional medicines / complementary and alternative medicines (TM/CAM) was at that time currently being developed. Laws and regulations were issued in 1989 and a national programme was issued in 1986. The Department of Traditional Medicine is administered by the Ministry of Health, and was established in 1957. There is currently no expert committee. In 1957, the Vietnamese Institute of Traditional Medicine was established, and in 1976 the Ho Chi Minh Institute of Traditional Medicine and Pharmacy was founded.

National laws and regulations on herbal medicines were issued in 1989, separately from the laws governing conventional pharmaceuticals. Herbal medicines are regulated as prescription and over the counter medicines. By law, medical, health and nutrient content claims may be made. The Vietnam pharmacopoeia is legally binding, as are the national herbal monographs found in Vietnam medicinal plants.

Regulatory requirements for manufacturing include adherence to information in pharmacopoeias and monographs and the same GMP rules used for conventional pharmaceuticals. Implementation of these requirements is ensured by inspection and visits to manufacturing establishments. Safety requirements for herbal medicines include traditional use without demonstrated harmful effects and reference to documented scientific research on similar products. Classical or traditional remedies are used and promoted without the need to demonstrate the safety of the product. New remedies, indications or uses for herbal medicines must be accompanied by records of clinical trials. Implementation of these requirements is ensured by the registration system.

At the time of the survey, there were 1,573 registered herbal medicines in Vietnam; 267 herbal medicines included on the national essential medicines list of 1996. The post marketing surveillance system included monitoring of adverse effects for herbal medicines. In Vietnam, herbal medicines

are sold in pharmacies as prescription and over the counter medicines, in special outlets and by licensed practitioners.

B. Brief overview of the issues with PV of herbal medicines in other countries of the world. (Sources: Ref. 034)

The 2001 WHO Global Survey about national policies on traditional medicines, and regulation of herbal medicines received responses from 141 countries (74% of the 191 Member States of WHO at that time). Forty five (32%) of the responding Member States reported having a policy on traditional medicines and complementary and alternative medicines (TM/CAM and 51 (56%) indicated that such policies were currently being developed. Seventy five countries (53% of the responding Member States) reported having a national office in charge of TM/CAM. The survey identified the main difficulties regarding regulatory issues for herbal medicines as lack of research data, lack of appropriate control mechanisms, lack of education and training and lack of expertise.

<i>Activity</i>	<i>Time (minutes)</i>
<p>Ask students to raise their hands to show how many of them or their family members have used herbal medicines.</p> <p>Tell them about the WHO survey described in Ref. 034 and about the specific responses provided to that survey by Vietnam.</p> <p>Familiarize the students with pharmacovigilance of herbal medicines by presenting the 42 slides in Ref. 037.</p>	50
<p>CASE STUDY <i>If time permits, present case study from</i> Ref. 038</p> <p>The warning from the Bach Mai Hospital's Detoxification Centre director Pham Due following the admission of up to eight patients a month with complications from traditional herbal treatment. Or...</p> <p>Case study from Ref. 039 The HCM City market management authorities have seized more than 2.2 tons of dubious herbal medicines stored in two dirty, unhygienic warehouses. (August 8, 2011)</p>	

Sources used in this session:

- Ref. 010 World Health Organization. *The Importance of Pharmacovigilance: Safety Monitoring of medicinal products*. 2002.
- Ref. 034 World Health Organization. National Policy on Traditional Medicine and Regulation of Herbal Medicines - Report of a WHO Global Survey. Web. May. 2005.
- Ref. 035 The Museum of Vietnamese Traditional Medicine. Web.
- Ref. 037 Boyd, I. *Pharmacovigilance of Herbal Medicines*. International Society of Pharmacovigilance (ISoP). [PowerPoint slides]. 2009.
- Ref. 038 Herbal Medicines Threaten Health, Pocket. Web. 2009.
- Ref. 039 Mai Linh, 2.2 tonnes of unhygienic herbal medicines seized. dtinews.vn. Web. 8 Aug. 2011

Additional Reading and Resources:

- Ref. 040 Runckel, C. W. The Future of Vietnamese Traditional Medicine. *business-in-asia.com*. Web. 2010.
- Ref. 041 Second Conference on Traditional Medicine in ASEAN Countries held in Hanoi, Vietnam. Ha Noi Declaration on Traditional Medicine in Asean. Web. Nov. 2010.
- Ref. 042 Tachjian, A., Maria, V, & Jahangir, A. (2010). Use of Herbal Products and Potential Interactions in Patients With Cardiovascular Diseases. *J Am Coll Cardiol*, 2012; 55:515-525, doi:10.1016/j.jacc.2009.07.074

Session 2.1: Adverse Drug Reaction as a Factor for Adverse Drug Events:

Topics to cover in this session:

- A. Definitions of PV-related terminologies: Adverse drug reactions (ADR), adverse drug event (ADE), Side effect (SE), post marketing surveillance (PMS), and other PV-related terminologies
- B. Classification and mechanism of ADRs (e.g., Type A and B and others; immediate, delayed, etc.)
- C. Predisposing factors of adverse drug reactions: age, gender, pregnancy, previous history of allergy or reaction, multiple drug therapy, ethnic and genetic factors and concomitant disease processes
- D. Brief overview of strategies that minimize the occurrence or promote early detection of ADRs

Objectives: By the end this session, the student will be able to:

- Define the various terms related to PV
- Differentiate the various types of ADRs
- List predisposing factor for ADRs, giving at least one example for each factor (age, gender, previous history of allergy, multiple drug therapy, ethnic/genetic factors, and co-morbidities)
- List at least 5 drugs known to cause major teratogenic effects; list pregnancy risk categories of drugs, giving at least one drug example for each category
- Discuss strategies that help minimize or prevent the risk of ADRs
- Narrate self-perception of his/her role in minimizing or preventing ADRs upon joining the pharmacy workforce after graduation

Content Summary and Process Overview / Instructional Methodology (Total Duration: 100 Minutes)

- A. Definitions: Adverse drug reactions (ADR), adverse drug event (ADE), Side effect (SE), post marketing surveillance (PMS), and other PV-related terminologies. (Sources: Ref. 050, Ref. 052, Ref.006)

Adverse Event (AE): Any untoward medical occurrence that may present during treatment with a pharmaceutical product but which does not necessarily have a causal relationship with this treatment.

Adverse (Drug) Reaction (ADR): A response which is noxious and unintended, and which occurs at doses normally used in humans for the prophylaxis, diagnosis, or therapy of disease, or for the modification of physiological function. (WHO, 1972).

An adverse drug reaction, contrary to an adverse event, is characterized by the suspicion of a causal relationship between the drug and the occurrence, i.e. judged as being at least possibly related to treatment by the reporting or a reviewing health professional.

In the *EU Directive 2010/84*, which will become applicable in July 2012, an adverse reaction is defined as "A response to a medicinal product which is noxious and unintended." **Note:** There is a hierarchical relationship between AEs and ADEs. ADEs are a subset of AEs. Not all AEs are caused by medicines; some may result from the patient's illness, genetic or environmental factors, diet, or other causes. But, ADEs are directly related to medicines and may be due to poor product quality, medication error or pharmacological properties.

Medication Error: Any preventable event that may cause or lead to inappropriate medication use or patient harm, while the medication is in the control of the health care professional, patient, or consumer. Such events may be related to professional practice, health care products, procedures, and systems including: prescribing; order communication; product labeling, packaging and nomenclature; compounding; dispensing; distribution; administration; education; monitoring; and use."

Side effect: Any unintended effect of a pharmaceutical product occurring at normal dosage which is related to the pharmacological properties of the drug.

Post-marketing: The stage when a drug is generally available on the market.

Pre-marketing: The stage before a drug is available for prescription or sale to the public.

<i>Activity</i>	<i>Time (minutes)</i>
Show the students the cross matching exercise found in Ref. 055. Ask them to associate the number of each term with the number of its correct definitions. When they are finished, show them the correct associations. Then, reinforce their understanding of the relationship of ADE and ADR by showing Ref. 047 slide 7.	10

B. Classification and mechanism of ADRs (e.g., Type A and B and others; immediate, delayed, etc.).

(Source: Ref.046 , Ref. 047)

ADRs are classified according to:

Frequency

Frequent ADR: if the frequency of occurrence is **> 5%**

Occasional ADR: if the frequency of occurrence is including between **0.1% and 5%**

Unusual ADR: if frequency of occurrence **< 0.1%**

Mechanism of occurrence

Type A reactions: Adverse reactions which are a result of an exaggerated but otherwise usual pharmacological effect. These tend to be common, dose-related, predictable and less serious. They can usually be treated by reducing the dose of the drug.

Type B reactions: Adverse reactions which are aberrant, and may be due to hypersensitivity or immunologic reactions. These tend to be uncommon, not related to dose, unpredictable and potentially more serious. They usually require cessation of the drug.

Type

- **Type A** - Augmented (dose-related) e.g. hypotension with a beta blocker
- **Type B** - Bizarre (non dose-related) e.g. anaphylaxis after penicillin injection
- **Type C** - Continuous (long term) e.g. osteoporosis with oral steroids
- **Type D** - Delayed (lag time) e.g. teratogenic effect with anticonvulsants
- **Type E** - Ending of Use (withdrawal) e.g. withdrawal syndrome with benzodiazepines
- **Type F** - Failure of Efficacy (no response) e.g. resistance to antibiotics

Dose, Time, and Susceptibility (DoTS)

- Dose-related (concentration-related) reactions
- Time-related effects
- Susceptibility factors

Predictability

Predictable

- ADR with pharmacological mechanism
- Medicines Interactions

Unpredictable

- Immuno-allergic reaction
- Idiosyncratic

Degree of severity (will be covered in more detail in session 2.4)

Grade 1: Mild

Grade 2: Moderate

Grade 3: Severe

Grade 4: Life-threatening or disabling

Grade 5: Death

Avoidability

Definitely avoidable: treatment procedure inconsistent with present day knowledge of good medical practice (such as concomitant use of medications with known adverse interactions)

Possibly avoidable: cursory review of patient's medical history

Not avoidable: allergic or idiosyncratic reactions

Unevaluable

Activity	Time (minutes)
Present the classification of ADRs based on: <ul style="list-style-type: none"> • Frequency • Mechanism of occurrence • Predictability • Degree of severity • Avoidability using Ref. 047, slides 31-38.	15

- C. Predisposing factors of adverse drug reactions: age, gender, pregnancy, previous history of allergy or reaction, multiple drug therapy, ethnic and genetic factors and concomitant disease processes.
(Sources: Ref. 044, Ref. 051, Ref. 054)

Certain factors predispose to the ADRs. Listed below are such factors with a brief statement or an example for each:

Age: ADRs more likely in patients of 60 years and over

Gender: Women more likely to experience ADRs than men

Pregnancy: Some medications (teratogens) cause fetal malformation. Examples include: methotrexate (methylaminopterin), tetracyclines, thalidomide, coumarin anticoagulants, isotretinoin (Accutane®)

Previous history of allergy or reaction: even a small amount of drug can trigger an allergic reaction

Ethnic and genetic factors: may account for alterations in the handling of drugs and their effects

Multiple-drug therapy: chance of the drugs interacting with each other increases as the number of drugs given concomitantly increases

Concomitant disease processes: underlying renal or hepatic disease increase the risk of adverse drug reactions due to drugs eliminated by these organs

<i>Activity</i>	<i>Time (minutes)</i>
Present overview of predisposing factors of adverse drug reactions using Ref. 044 slides 22-31.	20
Demonstrate the on-line tool that shows pregnancy risk categories from FDA and provides capacity to search the category of any drug using Ref. 048 . Allow the students to suggest drugs for you to use in the search.	20
Summarize this topic by stressing that a large proportion of ADRs may be avoided in certain patient groups by preventing inappropriate prescribing or administration by awareness of individual patients' predisposing factors for ADRs.	5

D. Brief overview of strategies that minimize the occurrence or promote early detection of ADRs.

(Source: Ref. 006)

Monitoring Product Quality to identify products that are defective or counterfeit, deteriorated, or adulterated because of poor manufacturing practices inadequate distribution and storage, or tampering.

Educating Healthcare providers to reduce medication errors from illegible handwriting, use of dangerous abbreviations, overlooked interactions with other medicines, oral miscommunications, and sound-alike or look-alike products

Participating in post-marketing surveillance and regularly reviewing recent international PSURs (Periodic Safety Update Reports)

Instituting active surveillance methods using registries, sentinel sites, and follow-up of defined patient cohorts

Establishing mechanisms to communicate medicine safety information to health care professionals and the public

Activity	Time (minutes)
<p>Present the following five strategies: (10 minutes)</p> <ul style="list-style-type: none"> • Monitoring Product Quality - In the mid-1990s, almost 100 children in Haiti died from ingesting local manufactured pain relief syrup adulterated with diethylene glycol. • Educating Healthcare providers to reduce medication errors - U.S. Institute of Medicine in 2006 estimated that more than 1.5 million Americans are injured every year by preventable medication errors. • Participating in post-marketing surveillance and staying aware of post-marketing information resulting in changes to the recommended treatment guidelines. • Instituting active surveillance can be especially helpful for measuring rates of an ADR in a targeted population such as the frequency of AZT-associated anemia. (Source: Ref. 045 slide 4). • Establishing mechanisms to communicate medicine safety information to health care professionals and the public. Allows for rapid publication of new government policies on medicines and newly identified side effects. Additional example: Poll of 118 endocrinologists and diabetes educators 10 months after important change in the prescribing information for metformin showed 94% were unaware of the change. (Requires internet connection to internet) (Source: Ref. 049) <p>Ask students to cluster in groups of three to spend 10 minutes discussing and recording how they personally plan to minimize or prevent ADRs upon joining the pharmacy workforce after graduation.</p> <p>Call upon several students to share one of their plans with the entire class making sure that there is at least one plan related to each of the above. Then, summarize by stressing the importance their future roles will play in reducing ADRs. (10 minutes)</p>	30

Sources used in this session:

- Ref. 006 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. Sep. 2009.
- Ref. 044 Federal Ministry of Health, Nigeria. *Definitions and Classification of Adverse Events*. [PowerPoint slides]. 6 Jan 2011.
- Ref. 045 Federal Ministry of Health, Nigeria. *Active Surveillance* [PowerPoint slides]. 6 Jan 2011.
- Ref. 046 Aronson, J. K. & Ferner, R. E. Clarification of Terminology in *Drug Safety*. *Drug Safety*: 28.10 (2005): 851-870.
- Ref. 047 Stergachi, A. *Pharmacovigilance Training of Trainers: Definitions and Types of Adverse Events* [PowerPoint slides]. Rwanda. Sep. 2009.
- Ref. 048 FDA Categorization of Drug Risks to the Fetus. Web. Last update: 5 Oct. 2006. Web.
- Ref. 049 Silvio E. Inzucchi, S. E., Masoudi, F. A. & McGuire, D. K. (, ember). Metformin in Heart Failure. *Diabetes Care* 30.12 (Dec. 2007). Web.
- Ref. 050 The Uppsala Monitoring Centre. *Glossary of terms used in Pharmacovigilance*. Web. Aug. 2011.
- Ref. 051 Natalie Hurwitz, N. Predisposing Factors in Adverse Reactions to Drugs [Abstract]. *Br Med J*. 1.5643 (1 March 1969): 536–539. Web.
- Ref. 052 National Coordinating Council for Medication Error Reporting and Prevention. *What is a Medication Error?* Web.
- Ref. 054 University of Washington Medicine Department of Pharmacy Services' Drug Information Center. Teratogens List. Web.
- Ref. 055 Cross-Matching Exercise

Additional Reading and Resources:

- Ref. 043 Hartigan-Go, K. *Development plans for PV centres including everyday problems International Society of Pharmacovigilance (ISoP)*. [PowerPoint slides]. Sep 2008.
- Ref. 046 Aronson, J. K. & Ferner, R. E. Clarification of Terminology in *Drug Safety*. *Drug Safety*: 28.10 (2005): 851-870.
- Ref. 053 Franceschi, M., Scarcelli, C., Niro, V., Seripa, D., Paziienza, A. M., . . . Pilotto, A. Prevalence, Clinical Features and Avoidability of Adverse Drug Reactions as Cause of Admission to a Geriatric Unit: A Prospective Study of 1756 Patients. *Drug Saf*. 31.6 (2008): 545-56. Web.

Session 2.2: Medication Error as a Factor for Adverse Drug Events

Topics to cover in this session:

- A. Burden of medication error; causes of medication error
- B. Overview of common problem-prone areas with regard to medication errors
- C. Approaches to prevent medication errors

Objectives: By the end of the session, students will be able to:

- Highlight the burden of medication error in hospitals
- Analyze how system weakness contributes to medication errors in hospitals
- Highlight key strategies that can be used to prevent or minimize medication errors
- Narrate self-perception of his/her role in minimizing or preventing medication errors upon joining the pharmacy workforce after graduation

Content Summary and Process Overview / Instructional Methodology (Total Duration: 35 Minutes)

A. Burden of medication error; causes of medication error. (Sources: Ref. 062, Ref. 059 page 18, Ref. 064)

Medication error includes any error occurring in the medication use process.

One US study found that each preventable ADE that took place in a hospital added about \$8,750 (in 2006 dollars) to the cost of the hospital stay. Assuming 400,000 of these events each year, the total annual cost would be \$3.5 billion in this one group. Another study looked at preventable ADEs in US’s Medicare system enrollees aged 65 and older and found an annual cost of \$887 million for treating medication errors in this group. These figures do not take into account lost earnings or compensation for pain and suffering.

Most causes of medication errors can be attributed to the following three factors:

- Human factors: Heavy staff workload and fatigue, Inexperience, lack of training, poor handwriting, and oral orders
- Workplace factors: Poor lighting, noise, interruptions, excessive workload
- Pharmaceutical factors: Excessive prescribing; confusing medicine nomenclature; packaging, or labeling; increased number or quantity of medicines per patient; frequency and complexity of calculations needed to prescribe, dispense, or administer a medicine; lack of effective policies and procedures

<i>Activity</i>	<i>Time (minutes)</i>
Describe the enormity of the financial burden of medication errors in hospitals using example from US study quoted in Ref. 062 that each preventable ADE that took place in a hospital added about \$8,750 (in 2006 dollars) to the cost of the hospital stay, resulting in an estimated total annual cost of \$3.5 billion.	5
Ask students to think of possible factors that contribute to medicine errors. Then, show them the following so they can see how many of the factors they identified: Most causes of medication errors can be attributed to the following three factors: <ul style="list-style-type: none"> • Human factors: Heavy staff workload and fatigue, Inexperience, lack of training, poor handwriting, and oral orders • Workplace factors: Poor lighting, noise, interruptions, excessive workload • Pharmaceutical factors: Excessive prescribing, confusing medicine nomenclature, packaging, or labeling, increased number or quantity of medicines per patient, frequency and complexity of calculations needed to prescribe, dispense, or administer a medicine, lack of effective policies and procedures 	5

- B. Overview of common problem-prone areas with regard to medication errors.
(Sources: Ref. 060, Ref. 063 slide 9, Ref. 056 slides 14 and 16, Ref. 066, Ref. 065)

One study of where medication errors take place showed the breakdown as follows:

Prescribing and transcribing – 60%

- illegible and/or imprecise prescription
- incomplete, inadequate or incorrect instructions
- wrong indication, dose, duration, dilution, formulation
- identity of the patient unclear
- failure to consider a contra-indication (medical history, pre-existing condition, or interaction with a co-prescribed drug)

Administration – 30%

- wrong patient
- wrong dose, time, route of administration, site
- inadequate preparation before administration
- errors of manipulation : contaminants (air, others) when injected
- incompatible drugs mixed in the same injectable solution

Dispensing – 10%

Dispensing errors usually occur due to wrong drugs being dispensed because of the problem of sound-alike or look-alike medications.

High-risk drugs cause harm in 6% or more of reported medication errors (USP)

Top 10 drugs most frequently reported in Canada as causing harm because of medication error:

Insulin	Morphine
Hydromorphone	Heparin (unfractionated)
Fentanyl	Warfarin
Furosemide	Dalteparin
Metoprolol	Ramipril

These 10 drugs accounted for 199 of 465 harmful medication incidents that were voluntarily reported to ISMP (Institute for Safe Medication Practices) Canada over a 5-year period (2001 to 2005). Ref. 060

Activity	Time (minutes)
<p>Show students the percentages of medication errors that one study associated with:</p> <ul style="list-style-type: none"> • Prescribing and transcribing – 60% • Administration – 30% • Dispensing – 10% <p>Ask them to provide examples of each. Then, compare the examples they provided with the list shown in the content summary above.</p>	5
<p>Case Study</p> <p>If time permits, discuss one or both of these case studies about medication error from page 4 of Ref. 070</p> <p>The first example involves an insulin order written for “4 U NPH insulin.” However, because of poor handwriting, the “U” for “units” was mistaken for a zero, and the patient received 40 units of neutral protamine Hagedorn insulin.</p> <p>The second example shows a breakdown in communication that occurred when a physician gave a verbal order for insulin. Although the physician ordered 16 units of regular insulin, the nurse heard it as an order for 60 units; therefore, a 60-unit dose was administered.</p>	

C. Approaches to prevent medication errors. (Source: Ref. 059 pages 18 and 19, Ref. 070)

Broad interventions to reduce medication errors are:

Improving physician prescribing

- Institute educational programs that focus on the most common prescribing errors.
- Require legible handwriting by ordering physicians.
- Require complete spelling of a medicine's name.
- Use a standardized designation for doses (i.e., milligrams = mg, micrograms = mcg, and grams = g; use the word "units" rather than "U"; and use a leading zero for values less than 1 but not a trailing zero after a decimal, e.g., write 0.2 mg or 2 mg instead of .2 mg or 2.0 mg).
- Write the route of administration on all orders.
- Write out directions completely. Write "daily" instead of "QD" and "every other day" instead of "QOD."
- Limit the use of oral or telephone orders to emergency situations, and require that the order be read back to the prescriber.

Improving dispensing

- Separate the storage of drugs that have similar packages and names.
- Change the appearance of look-alike drug names on order entry screens and alter the sequence of the products so that look-alike names are not right next to each other on the screen.
- Apply uppercase lettering to different portions of drug names of drugs with similar names.

Improving drug administration

- Check the patient's identity.
- Ensure that dosage calculations are checked independently by another health care professional before the drug is administered.
- Ensure that the prescription, drug, and patient are in the same place in order that they may be checked against one another.
- Ensure the medication is given at the correct time.
- Minimize interruptions during drug rounds.

Correcting systems flaws that predispose to error

- Introduce a system to identify and record information about medication errors.
- Where feasible, institute pharmacy-based admixture of IV fluids. If ward personnel must perform IV admixture, there should be clear written procedures and skills certification of the personnel.
- Develop special procedures for high-risk drugs. These procedures should include written guidelines, checklists, and educational materials.
- When preparing to administer a medication, confirm the identity of the patient by reading the patient's wristband and talking to the patient or family member.

- To minimize the likelihood that a dose will be missed, standardize administration times and develop a policy to provide doses when a patient is off the floor.
- Analyze medicine names as new products are added to the formulary. For look-alike and sound-alike names, establish a policy requiring that prescribers write both brand and generic name.
- Use pharmacy staff effectively to monitor and manage medicine use and distribution.

Activity	Time (minutes)
Ask students to review the causes to determine three of the causes that are the easiest to deal with and will have the greatest impact on reducing medication error at the least cost. Ask a few students to share their choices and the reasons for their choices. Confirm or refute their responses.	10
Show Ref. 061 “What you can do to avoid medication errors” as a reminder that patients can play an important role in reducing medication error, too.	2
<p>Ask the students to vote by show of hands</p> <p>Which is better?</p> <ul style="list-style-type: none"> • 150 microgram of clonidine OR 0.15 mg • 0.25 mg of digoxin OR 250 microgram • 1 mg atropine OR 1.0 mg • .5 mg atropine OR 0.5 mg atropine <p>If time permits, ask students to identify what error might occur if the better choice is not used.</p> <p>(Source: Ref. 057, slide 45)</p>	5
<p>Ask students to interpret the following dates:</p> <ul style="list-style-type: none"> • Expiry date 12 09 04 • Expiry date 09 12 04 • Expiry date 25 09 04 <p>Stress the importance of using unambiguous dates. In the example above, it is easy to confuse December 9, 2004 with September 12, 2004.</p>	3
<p>Case Study</p> <p>If time permits, discuss case study from Ref. 069 highlighting a potentially fatal error associated with a morphine pump.</p>	

Case Study

If time permits, discuss case study from Ref. 067 describing using technology to reduce medication error.

The Physician order entry (POE) at Brigham and Women's Hospital. This computerized medication order entry system has the potential to prevent an estimated 84 % of dose, frequency, and route errors. Such a system eliminates illegible orders that lead to medication errors. Also, because the system requires the name of the medication, dosage, route, and frequency of administration to be entered, errors that arise from omission of critical information are eliminated. Programmed within the system are algorithms that check dosage frequency, medication interactions, and patient allergies. Once an order is entered, this computerized system also provides physicians with information about the consequences of therapy, benefits, risks, and contraindications.

Sources used in this session:

- Ref. 056 Moore, N. *Medication Errors*. Training Course in Pharmacovigilance. Hanoi. [PowerPoint slides]. Dec. 2010.
- Ref. 057 Hartigan-Go, K. *Patient Safety & Medication Errors International Society of Pharmacovigilance (ISoP)*. [PowerPoint slides]. 2009.
- Ref. 059 Rational Pharmaceutical Management Plus, Center for Pharmaceutical Management, & Management Sciences for Health. *Drug and Therapeutics Committee Training Course, Session 4, Assessing and Managing Medicine Safety: Participants' Guide*. 2007.
- Ref. 060 Institute for Safe Medication Practices Canada. Top 10 Drugs Reported as Causing Harm through Medication Error. *ISMP Canada Safety Bulletin*, 6.1 (Feb. 2006).
- Ref. 061 Institute of Medicine of the National Academies. What You Can Do To Avoid Medication Errors. *Fact Sheet*. Jul. 2006.
- Ref. 062 Institute of Medicine of the National Academies. Preventing Medication Errors. *Report Brief*. Jul. 2006.
- Ref. 063 Federal Ministry of Health, Nigeria. *Safety of Medicines in Nigeria; National Pharmacovigilance Training Curriculum: Medication Errors and Patient Safety* [PowerPoint slides]. Jan. 2011.
- Ref. 064 Institution for Safe Medication Practices. *Frequently Asked Questions (FAQ)*. Web.
- Ref. 065 Williams, D.J.P. Medication Errors. *J R Coll Physicians Edinb*, 37 (Jul 2007):343–346.
- Ref. 066 Olsson, S. *Current trends in pharmacovigilance – a global perspective*. WHO Collaborating Centre for International Drug Monitoring. [PowerPoint slides]. Web. 2005.
- Ref. 067 Agency for Healthcare Research and Quality. Reducing and Preventing Adverse Drug Events To Decrease Hospital Costs. Web. Mar 2001.
- Ref. 069 U.S. Food and Drug Administration. Strategies to Reduce Medication Errors: Working to Improve Medication Safety. Web. Last Updated: 12 Aug. 2011.
- Ref. 070 Grissinger, M. *Avoiding Medication Errors with Insulin Therapy*. May 2010.

Additional Reading and Resources:

- Ref. 058 Hartigan-Go, K. *Principles and Mechanisms of ADR* International Society of Pharmacovigilance (ISoP). [PowerPoint slides]. Dec. 2009.
- Ref. 068 U.S. Food and Drug Administration. Preventable Adverse Drug Reactions: A Focus on Drug Interactions. Web. Last Updated: 30 Apr 2009.

Session 2.3: Other Factors for Adverse Drug Events

Topics to cover in this session:

- A. Brief overview of the burden of substandard and counterfeit products, and the impact of low quality medicines
- B. Brief overview of therapeutic ineffectiveness and the factors contributing to it, including drug resistance

Objectives: By the end of the session, students will be able to:

- Briefly describe the burden of substandard and counterfeit products
- Articulate that treatment failure is an important issue in public health programs such as HIV/AIDS, malaria, and TB, and that it needs to be tracked for informing future treatment decisions

Content Summary and Process Overview / Instructional Methodology (Total Duration: 15 Minutes)

- A. Brief overview of the burden of substandard and counterfeit products, and the impact of low quality medicines. (Source: Ref. 074)

Substandard drugs are “genuine drug products which do not meet the quality specifications set for them”. **Counterfeits** are “deliberately and fraudulently mislabeled with respect to identity and/or source. Counterfeiting can apply to branded and generic products. Counterfeits may include products with correct or incorrect ingredients, without active ingredients, with insufficient active ingredient, or with fake packaging”. It is not always clear if poor-quality medicines are counterfeit or substandard, but it is important that they are correctly classified because they have different origins and different solutions.

It is difficult to estimate the extent of substandard and counterfeit products. However, The International Medical Products Anti-Counterfeiting Taskforce (IMPACT) has suggested that many developing countries of Africa, parts of Asia, and parts of Latin America have areas where >30% of the medicines on sale can be counterfeit. Other developing markets, however, have <10%.

Low quality medicines result in:

- Increased mortality and morbidity
- Engendering of drug resistance and loss of medicine efficacy
- Loss of confidence in health systems and health workers
- Economic loss for patients, their families, health systems, and the producers and traders in good-quality medicines
- Adverse effects from incorrect active ingredients
- Waste of enormous human effort and financial outlay in development of medicines, optimizing dosage, carrying out clinical trials, discussing policy change, and manufacturing medicines
- Increased burden for health workers, medicine regulatory authorities, customs officials and police officers

Activity	Time (minutes)
<p>Provide these examples of results of substandard and counterfeit medications being used (Sources: Ref. 071, Ref. 073, Ref. 074) and pose the follow-up questions.</p> <p>Gentamicin eye drops contaminated with gentamicin-resistant <i>Pseudomonas aeruginosa</i> led to severe eye infections.</p> <p>After hundreds of patients with visceral leishmaniasis failed to respond to 'miltefosine' in Bangladesh, capsules were found not to contain miltefosine.</p> <p>Placebo tablets containing no active ingredients were stolen and sold as a contraceptive medicine, leading, it was claimed, to unexpected pregnancy.</p> <p>23-year-old man with hyperparasitaemic falciparum malaria treated with oral artesunate. After his death from cerebral malaria, analysis of his medication revealed that the main active ingredient in this drug was acetaminophen. Artesunate was also present in the tablet but only 10 mg per tablet, instead of the 50 mg of artesunate present in the genuine product.</p> <p>Ask students to estimate the percentage of counterfeit artesunate (containing no or sub-therapeutic active ingredient) bought in South-East Asia. (Estimated to be-third to one-half.)</p> <p>An antidepressant (fluvoxamine) and a muscle relaxant (cyclobenzaprine hydrochloride) were labeled as anti-retrovirals in the Democratic Republic of Congo. Ask students to hypothesize about the possible results of this last example.</p>	10

B. Brief overview of therapeutic ineffectiveness and the factors contributing to it, including drug resistance. (Sources: Ref. 006 page 5, Ref. 072 slide 4, Ref. 074)

The scope of Pharmacovigilance is expanding to include therapeutic ineffectiveness which may result from the use of substandard or counterfeit products, non-adherence, drug interactions, and drug resistance. While reporting of therapeutic ineffectiveness can alert to substandard and counterfeit products, awareness of therapeutic ineffectiveness can also highlight non-adherence, drug interactions, and drug resistance. Such information can then be communicated to health care professionals and consumers for risk-benefit decision making. High level of therapeutic ineffectiveness may necessitate review and possible modification or change in the recommended treatment regimen if the underlying reason gets identified as drug resistance. If other factors listed above are in play, efforts should be made to remove or minimize them.

Anti-infectives containing sub-therapeutic amounts of the active ingredient (whether counterfeit or substandard) increase the risk of the selection and spread of drug-resistant pathogens. For diseases

treated with combination therapy (e.g. tuberculosis, HIV, falciparum malaria), poor-quality combination medicines risk the spread of resistance due to the poor-quality active ingredient and the 'unprotected' co-ingredient.

Activity	Time (minutes)
<p>Present the factors contributing to therapeutic ineffectiveness:</p> <ul style="list-style-type: none"> • substandard or counterfeit products • non-adherence • drug interactions • drug resistance <p>Summarize by stressing that anti-infectives containing sub-therapeutic amounts of the active ingredient (whether counterfeit or substandard) increase the risk of the selection and spread of drug-resistant pathogens.</p>	5

Sources used in this session:

- Ref. 006 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. Sep. 2009.
- Ref. 071 Newton, P. N., McGready, R., Fernandez, F., Green, M. D., Sunjio, M., Bruneton, C., White, N. J. Manslaughter by Fake Artesunate in Asia—Will Africa Be Next? *PLoS Medicine*, 3.6 (2006): 752-5.
- Ref. 072 Joshi, M. P. *A System-oriented Approach to Implementing Pharmacovigilance*. [PowerPoint slides]. 29 Sep. 2009.
- Ref. 073 World Health Organization. *The Safety of Medicines in Public Health Programmes: Pharmacovigilance an essential tool*. 2006.
- Ref. 074 Newton, P. N., Green, M. D., & Fernandez, F. Impact of Poor-Quality Medicines in the 'Developing' World. *Trends Pharmacol Sci*. 2010 March; 31(3-3): 99–101. doi: [10.1016/j.tips.2009.11.005](https://doi.org/10.1016/j.tips.2009.11.005)

Additional Reading and Resources:

- Ref. 075 Meyboom, R. H. B., Lindquist, M., Flygare, A., Biriell, C., & Edwards, I. R. The Value of Reporting Therapeutic Ineffectiveness as an Adverse Drug Reaction. *Drug Safety*, 23.2 (Aug. 2000): 95-99.
- Ref. 076 Meyboom, R. H. B., Egberts, A. C. G., Gribnau, F. W. J., & Hekster, Y. A. Pharmacovigilance in Perspective. *Drug Safety*, 21.6 (Dec. 1999): 429-447.

Session 2.4: Adverse Drug Events: Assessment of Severity and Causality

Topics to cover in this session:

- A. Assessing severity of ADRs (mild, moderate, severe, fatal)
- B. Methods of assessing causality of ADRs: WHO-UMC scale and Naranjo Algorithm

Objectives: By the end of the session, students will be able to:

- Distinguish ADRs of various severity (mild, moderate, severe and fatal)
- Briefly explain the WHO-UMC scale and Naranjo Algorithm for assessing causality of ADR

Content Summary and Process Overview / Instructional Methodology (Total Duration: 50 Minutes)

- A. Assessing severity of ADRs (mild, moderate, severe, severe life-threatening).
(Source: Ref. 080 Slide 9)

Based on their impact on the patient, ADRs are classified into the following four categories.

Grade 1 - Mild: transient or mild discomfort; no limitation in activity; no medical intervention/therapy required

Grade 2 - Moderate: limitation in activity - some assistance may be needed; no or minimal medical intervention/therapy required.

Grade 3 - Severe: marked limitation in activity, some assistance usually required; medical intervention/therapy required, hospitalization possible.

Grade 4 - Severe life-threatening: extreme limitation in activity, significant assistance required; significant medical intervention/therapy required, hospitalization or hospice care.

<i>Activity</i>	<i>Time (minutes)</i>
Open the class by briefly describing these three specific ADRs but do not share assessments of their severity. Mild - Hyperpigmentation in HIV-Infected Patients Receiving Emtricitabine Ref. 085 Moderate - Symptomatic hyperlactatemia in an HIV-positive patient Ref. 080 Severe -Fluconazole induced toxic epidermal necrolysis: a case report Ref. 086	5
Present the categories used in assessing severity of ADRs (mild, moderate, severe, severe life-threatening) and the characteristics of ADRs which fall into each of the categories.	5
Ask the students to assess the three ADRs in terms of severity and then to share the results of their assessments with the person next to them. Was every pair of students in agreement on all three assessments? If not, allow a few who disagreed to share the justifications for their assessments. Then show the answers to the class.	5

B. Methods of assessing causality of ADRs: WHO-UMC scale and Naranjo Algorithm.

Causality of ADRs refers to an assessment of relatedness between exposure to a medicine and an adverse event.

Factors determining causality (Source: Ref. 072_slide 37, Ref. 059 page 10)

Strength of the association: if the odds are known and are very high for an observed event, such as GI upset with aspirin, then the case is strengthened for causation.

Consistency of the observed evidence: When there is an association between a drug and an adverse reaction that has been demonstrated consistently over years of clinical practice, causality becomes more likely.

Temporality of the relationship: The closer the relationship of the administration of the drug and the occurrence of the ADR, the more likely that the drug may be the actual cause of the reaction. This is not always true as some adverse events may occur several days or weeks after the administration of the offending drug.

Dose-response relationship: Reaction more severe when the dose was increased, or less severe when the dose was decreased. (Not always true as very low doses of some drugs, e.g., penicillin, can elicit serious anaphylactic responses.)

Confounding factors: Alternative causes (other than the drug) that could on their own have caused the reaction. Confounding factors such as the administration of other medicines, food, and beverages can account for observed events. The existence of concurrent diseases and infections can also cause certain observed effects, so distinguishing them from the suspected medicine is difficult. Environmental factors, such as air pollutants, weather conditions, and exposure to allergens, may also play a role.

Two popular methods for Classifying Causality of an ADR: WHO-UMC and Naranjo Algorithm

WHO-UMC Causality Categories for causality assessment of the relationship between the intake of a medicine and an adverse reaction. Various causality terms and methods are in use but the ones in this method are most widely used. (Sources: Ref. 083, Ref. 077 slide 17)

Certain

- Event or laboratory test abnormality, with plausible time relationship to drug intake
- Cannot be explained by disease or other drugs
- Response to withdrawal plausible (pharmacologically, pathologically)
- Event definitive pharmacologically or phenomenologically (i.e. an objective and specific medical disorder or a recognized pharmacological phenomenon)
- Rechallenge satisfactory, if necessary

Probable/Likely

- Event or laboratory test abnormality, with reasonable time relationship to drug intake

- Unlikely to be attributed to disease or other drugs
- Response to withdrawal clinically reasonable
- Rechallenge not required

Possible

- Event or laboratory test abnormality, with reasonable time relationship to drug intake
- Could also be explained by disease or other drugs
- Information on drug withdrawal may be lacking or unclear

Unlikely

- Event or laboratory test abnormality, with a time to drug intake that makes a relationship improbable (but not impossible)
- Disease or other drugs provide plausible explanations

Conditional/Unclassified

- Event or laboratory test abnormality
- More data for proper assessment needed
- Additional data under examination

Unassessable/Unclassifiable

- Report suggesting an adverse reaction
- Cannot be judged because information is insufficient or contradictory
- Data cannot be supplemented or verified

Naranjo Algorithm (Source: Ref. 082)

Uses scoring based on answers to ten questions to assess the adverse drug reaction causality.

Question	Yes	No	Do not know or not done	Score
1. Are there previous conclusive reports on this reaction?	+1	0	0	
2. Did the adverse event appear after the suspected drug was administered?	+2	-1	0	
3. Did the adverse reaction improve when the drug was discontinued or a specific antagonist was administered?	+1	0	0	
4. Did the adverse reaction reappear when the drug was readministered?	+2	-1	0	
5. Are there alternative causes (other than the drug) that could on their own have caused the reaction?	-1	+2	0	
6. Did the reaction reappear when a placebo was given?	-1	+1	0	
7. Was the drug detected in the blood (or other fluids) in concentrations known to be toxic?	+1	0	0	
8. Was the reaction more severe when the dose was increased or less severe when the dose was decreased?	+1	0	0	
9. Did the patient have a similar reaction to the same or similar drugs in any previous exposure? +1 0 0	+1	0	0	
10. Was the adverse event confirmed by any objective evidence?	+1	0	0	

Naranjo scores of 9 or 10 indicate that an event was "definitely" an ADR; scores of 5-8 rate the likelihood as "probable"; scores of 1-4 are "possible"; and scores of less than 1 are "doubtful."

Activity	Time (minutes)
Introduce the topic by admitting that there are a variety of assessment scales and that none of the scales are perfect.	5
Show examples of WHO-UMC scale and the Naranjo Algorithm as examples of two popular scales. Then, ask the students to use an example of an actual ADR and each of those scales to assess the ADR's causality. (Example on Source: Ref. 072, slide 40). Use the on-line interactive Naranjo calculator, if computer access permits. (Source: Ref. 084)	25
Summarize by pointing out that the students activity highlighted the fact that successful causality assessment depends not only on the scale used, but also on the completeness of the information provided about the ADR.	5

Sources used in this session:

- Ref. 059 Rational Pharmaceutical Management Plus, Center for Pharmaceutical Management, & Management Sciences for Health. *Drug and Therapeutics Committee Training Course, Session 4, Assessing and Managing Medicine Safety: Participants' Guide*. 2007.
- Ref. 072 Joshi, M. P. *A System-oriented Approach to Implementing Pharmacovigilance* [PowerPoint slides]. 29 Sep. 2009.
- Ref. 077 Berdai, D. *Risk and crisis Management in Pharmacovigilance*. Hanoi. [PowerPoint slides]. 2009.
- Ref. 080 Antoniou, T., Weisdorf, T., & Gough, K. Symptomatic Hyperlactatemia in an HIV-Positive Patient: A Case Report and Discussion. *CMAJ*, 168.2 (21Jan. 2003).
- Ref. 081 Hanoi University of Pharmacy. *Introduction To Pharmacovigilance: Signal Evaluation: Assessing Causality and Characterizing Risk*. [PowerPoint slides]. 26 Mar 2009.
- Ref. 082 How Can I Recognize an Adverse Drug Event? Medscape Education. Web. 2008.
- Ref. 083 The Uppsala Monitoring Centre. The use of the WHO-UMC system for standardised case causality assessment. Web. 2011.
- Ref. 084 Adverse Drug Reactions Probability Scale: NARANJO Algorithm [Interactive Tool]. Web. From: Naranjo, C. A., et al. A method for estimating the probability of adverse drug reactions. *Clin. Pharmacol. Ther.*, 30.2 (1981): 239–45.
- Ref. 085 Rashbaum B. Evaluation of Hyperpigmentation in HIV-Infected Patients Receiving Emtricitabine. Poster Exhibition: The 3rd IAS Conference on HIV Pathogenesis and Treatment: Abstract no. TuPe2.4C15. 2005.
- Ref. 086 Ofoma, U. R. & Chapnick, E. K. Fluconazole Induced Toxic Epidermal Necrolysis: A Case Report. *Cases Journal* 2009, 2:9071 doi:10.1186/1757-1626-2-9071.

Additional Reading and Resources:

- Ref. 027 U.S. Food and Drug Administration. Reporting Serious Problems to FDA. Web. Last Updated: 23 Jun. 2011.
- Ref. 068 U.S. Food and Drug Administration. Preventable Adverse Drug Reactions: A Focus on Drug Interactions. Web. Last Updated: 30 Apr 2009.
- Ref. 078 Moore, N. *Adverse Drug Reaction Causality Assessment*. Hanoi. [PowerPoint slides]. 2009.
- Ref. 079 Moore, N. *Causality Assessment Imputology*. Hanoi. [PowerPoint slides]. 2009.

Session 3.1: Passive and Active Methods of Surveillance

Topics to cover in this session:

- A. Sources of ADE data: premarket safety data, spontaneous reports, Phase IV studies, scientific literature, product inquiries and complaints, unpublished manuscripts, internet
- B. Passive surveillance methods — roles of spontaneous reporting; strengths and limitations of spontaneous reporting; key data fields in Vietnam spontaneous reporting form: patient details, description of the adverse event or product quality problem, suspected drug(s) or vaccine(s), reporter details
- C. Brief introduction to active surveillance methods: case control study, cohort study, prescription events monitoring, registries, sentinel surveillance
- D. Strategies to improve ADE reporting and analysis (e.g., ADR form widely available, reporting as routine and normal part of administering healthcare, distribution network, feedback to reporters)

Objectives: By the end of the session, students will be able to:

- Explain strengths and limitations of spontaneous reporting
- Demonstrate competence and confidence in filling the various fields of the spontaneous reporting form currently used in Vietnam
- Through a personal narrative, demonstrate enthusiasm and conscientiousness (in his/her role as a health care worker) toward filling and sending spontaneous reporting form upon joining the pharmacy workforce after graduation
- Demonstrate correct understanding by telling that spontaneous reporting and active surveillance approaches are complementary methods
- Describe strategies to improve ADE reporting

Content Summary and Process Overview / Instructional Methodology (Total Duration: 200 Minutes)

- A. Sources of ADE data: premarket safety data, spontaneous reports, Phase IV studies, scientific literature, product inquires and complaints, unpublished manuscripts, internet. (Sources: Ref. 087, Ref. 072)

ADR information can be obtained from clinical trials safety data -both pre-marketing and post-marketing (Phase IV) studies, medical publications, WHO/UMC publications, newspapers, the internet and colleagues. The least reliable information is anecdotal while the most reliable is gained from clinical trials. There are mainly two methods of ADR reporting; passive spontaneous surveillance and active surveillance. Passive, spontaneous surveillance and active surveillance are complementary methods. Data collected by both methods are needed to best meet the PV goals of safeguarding public health and improving rational medicine use.

According to WHO, the following is required for ADR reporting: Identifiable source of information or reporter (who must be literate), Identifiable patient, Name (s) of suspected product (s) and Description of the suspected reaction(s)/event.

Activity	Time (minutes)
<p>Ask the students spend 5 minutes listing potential sources of ADE data. Then, show them the following list and provide a few moments for them to compare their lists.</p> <ul style="list-style-type: none"> • clinical trials safety data , both pre-marketing and post-marketing (Phase IV) studies • medical publications, • WHO/UMC publications • Newspapers • the internet • colleagues <p>Ask them to volunteer sources that were missing from their lists. Which sources were missing from their lists most often? (5 minutes)</p> <p>Summarize by stressing that the least reliable information is anecdotal while the most reliable is gained from clinical trials.</p> <p>Then, provide transition to the next topic by explaining that two complementary methods of ADR reporting; passive spontaneous surveillance and active surveillance. Stress that data collected by both methods are needed to best meet the PV goals of safeguarding public health and improving rational medicine use. (5 minutes)</p>	15

- B. Passive surveillance methods — roles of spontaneous reporting; strengths and limitations of spontaneous reporting; key data fields in Vietnam spontaneous reporting form: patient details, description of the adverse event or product quality problem, suspected drug(s) or vaccine(s), reporter details. (Sources: Ref. 087, Ref. 072, Ref. 090)

In passive spontaneous reporting, health care workers voluntarily submit suspected ADR reports to regulatory authorities followed by re-evaluation of risk and the benefits of the drugs. The advantages of passive spontaneous reporting are that it is simple, low cost and able to detect rare events if continuously done. The main problem with this method is underreporting. In passive surveillance, health professionals and others are encouraged to report adverse events, but no other active measures used. So, spontaneous reporting is dependent on the initiative and motivation of potential reporters. In spite of these limitations, spontaneous reporting is a key method of adverse events surveillance.

According to WHO, the following is required for ADR reporting: Identifiable source of information or reporter (who must be literate), Identifiable patient, Name (s) of suspected product (s) and Description of the suspected reaction(s)/event. The revised ADR reporting form in use in Vietnam since July 2011 contains all of those key data fields.

<i>Activity</i>	<i>Time (minutes)</i>
<p>Introduce passive spontaneous reporting by pointing out that it is dependent on the initiative and motivation of potential reporters. Highlight the advantages (it is simple, low cost and able to detect rare events if continuously done) and point out that the main problem with this method is underreporting. (5 min)</p> <p>Identify some of the reasons for under reporting such as common misconceptions (shown in Ref. 087 page 55) that: (5 minutes)</p> <ul style="list-style-type: none"> • Known reactions should not be reported • Serious ADRs are documented • Not sure if the drug is responsible for the ADR • Not absolutely certain drug caused ADR • One reported does not contribute to medical knowledge <p>Determine if any of the students previously held any of those misconceptions prior to taking this course. (10 minutes)</p>	20

<p>Show Vietnam's ADR reporting form (Ref. 090) and review fields that collect: patient details, description of the adverse event or product quality problem, suspected drug(s) or vaccine(s), reporter details. You can use Ref. 090 (interactive PDF that allows you to type into it) and show the students Ref: 148 – the DI&ADR on-line reporting system, if internet access is available.</p> <p>Alert to the instructor: Do NOT use the official, live DI&ADR on-line reporting system during the training sessions to avoid accidentally submitting practice ADRs into the system.</p> <p>Remind the students about what happens to the information submitted on these forms. (10 minutes)</p> <p>Provide several real-life example events and ask students to fill out the forms for those events. (20 minutes) Then show the correctly filled out forms so the students can verify that they filled out the form correctly. (10 minutes)</p> <p>Remind students that according to WHO, the following is required for ADR reporting: Identifiable source of information or reporter (who must be literate), Identifiable patient, Name (s) of suspected product (s) and Description of the suspected reaction(s)/event. (5 minutes)</p>	<p>45</p>
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C. Brief introduction to active surveillance methods: case control study, cohort study, prescription events monitoring, registries, sentinel surveillance. (Sources: Ref. 087, Ref. 045, Ref. 088)

Active surveillance (in contrast to passive surveillance) seeks to determine the ratio/number of ADRs through formal and continuous monitoring and collection of health outcomes.

Active surveillance methods include case control, cohort studies, prescription event monitoring, registries and sentinel surveillance. Active surveillance methods are more reliable but more expensive than passive surveillance methods.

Case control studies are epidemiologic studies in which the frequency of exposure to a drug in a group of patients who already have had a particular adverse event is compared to the frequency of exposure to that medication in a group of patients who did not experience that ADR. So, patient cases are recruited after occurrence of the ADR and are compared with control patients who did not experience the same ADR.

Cohort studies are epidemiologic studies in which the frequency of an ADR's occurring in a group that has been exposed to a medication of interest is compared to the frequency of that same ADR's occurring in a group that was not exposed to that same medication. The cohorts of patients must be followed, waiting for the ADR to appear.

Prescription events monitoring is a non-interventional cohort technique in which patients are identified from dispensed prescriptions. Questionnaires are posted to the prescribing doctor requesting detailed info including suspected ADRs since the first prescription for the study drug. This technique is most applicable for new drugs intended for long-term, widespread use. But, its limitations include poor physician- and patient-response rates and the unfocused nature of data collection which can obscure important signals.

Registries are classified according to how the populations are defined. Product registries include patients who have been exposed to medicinal products or medical devices. Health services registries consist of patients who have had a common procedure, clinical encounter, or hospitalization. Disease or condition registries are defined by patients having the same diagnosis. An example is a pregnancy exposure registry which identifies pregnant women and actively collects information on drug exposures during pregnancy and associated pregnancy outcomes.

Sentinel surveillance takes place through reviewing medical records or interviewing patients in a sample of sentinel sites. This surveillance method provides complete and accurate data, and information on sub-groups may be obtained. It is most efficient for drugs used mainly in institutional settings e.g., hospitals, nursing homes. But, it has the disadvantages of selection bias, small number of patients, and increased cost.

Activity	Time (minutes)
Use power point slides in Ref. 045 to present the topic of active surveillance.	45
<p>CASE STUDIES</p> <p>Discuss case from Ref. 088, page 13 “The use of a computerized database to monitor vaccine safety in Vietnam”</p> <p>Discuss case from Ref. 088, page 14 “Mortality and failure among tuberculosis patients who did not complete treatment in Vietnam: A cohort study”</p> <p>Discuss case from Ref. 088, page 23 “Risk factors for HIV infection in a gynaeco-obstetric population in Vietnam: a case-control study”</p>	

- D. Strategies to improve ADE reporting and analysis (e.g., ADR form widely available, reporting as routine and normal part of administering healthcare, distribution network, feedback to reporters).
(Sources: Ref. 072, Ref. 089)

Strategies for improving ADE analysis cannot take place in the absence of ADE reports, so it is essential to increase the reporting rate. Some approaches to increasing the rate of reporting include:

- Ensure that the ADR form widely is widely available by making ADR reporting forms available to each health facility nationwide. Define priorities for reporting and provide quick access to the PV system.
- Incorporate reporting as routine and normal part of administering healthcare by including it in health facility SOPs and by incorporating PV into the education of all healthcare workers.
- Establish and use a distribution network to foster communication and to increase ADR awareness among healthcare professionals and the public.
- Provide feedback to reporters to encourage them to continue to report ADRs.

Optimize opportunities to improve ADE analysis by exploiting opportunities for integrating PV functions into existing tools and software. Use statistical screening of data bases – data mining.

Activity	Time (minutes)
<p><i>Open the topic by stressing that</i></p> <p>Strategies for improving ADE analysis cannot take place in the absence of ADE reports, so it is essential to increase the reporting rate. Discuss some of the approaches to increasing the rate of reporting listed in the content summary. Ask the students to consider why providing feedback to reporters might increase the rate of reporting. (15 minutes)</p> <p>Discuss potential opportunities to improve ADE analysis by exploiting existing tools and software. (The existing tools will vary depending upon the work location. The goal is for the students to be aware of the value of considering what tools and software are in place and how they might be used to improve ADE analysis.) (10 minutes)</p> <p>If time permits, discuss statistical screening of data bases and data mining.</p> <p>End the topic by asking students to cluster in groups of 3 to share how they plan to contribute to the improvement of ADE reporting and analysis in Vietnam upon joining the pharmacy workforce after graduation. Ask some students to share the results of their conversations. (10 minutes)</p>	<p>20</p>

Sources used in this session:

- Ref. 045 Federal Ministry of Health, Nigeria. *Active Surveillance* [PowerPoint slides]. 6 Jan 2011.
- Ref. 072 Joshi, M. P. *A System-oriented Approach to Implementing Pharmacovigilance*. [PowerPoint slides]. 29 Sep. 2009.
- Ref. 087 "Pharmacovigilance: Quality, Safety and Efficacy of Medicines For Better Health Care: Curriculum and Implementation Guide." Ministry of Public Health and Sanitation & Ministry of Medical Services. Kenya. [PowerPoint slides]. Feb. 2009.
- Ref. 088 Hanoi University of Pharmacy. *Introduction To Pharmacovigilance: Active Surveillance and Formal Pharmacoepidemiology Methods*. [PowerPoint slides]. 26 Mar 2009
- Ref. 089 Hanoi University of Pharmacy. *Introduction To Pharmacovigilance: Signal Evaluation: Signal Generation and Strengthening*. [PowerPoint slides]. 26 Mar 2009
- Ref. 090 Ministry of Health; The National DI & ADR Centre. *Vietnam ADR Reporting Form*
- Ref: 148 The National DI & ADR Centre, Hanoi. Vietnam On-line ADR Reporting System. Interactive form. Web.

Additional Reading and Resources:

- Ref. 091 Cobert, B. L. & Biron, P. *Pharmacovigilance from A to Z: Adverse Drug Event Surveillance*. Malden: Blackwell Science, 2002. Print.

Session 4.1: Strategies to Improve Risk Communications, and Principles of Risk Management and Risk Minimization

Topics to cover in this session:

- A. Principles and methods of benefit-risk assessment
- B. The Erice Declaration on effective communication in PV
- C. Role of the National DI&ADR Center, DAV, hospital DTCs and DIUs and other stakeholders in communicating medicine safety information; relevant circulars from MOH relating to such roles for key MOH bodies
- D. Examples from other countries and organizations on communicating messages about medicine safety (e.g., “Dear Doctor” letters, medicine alerts, media statements, patient information leaflets, newsletters, and personal feedback to reporters)
- E. Selected examples from other countries and organizations regarding strategies and tools for risk management and minimization

Objectives: By the end of the session, students will be able to:

- Through a personal narrative, demonstrate commitment to communicating drug safety information ethically and effectively
- Cite actual examples of strategies, approaches or tools used in Vietnam or other countries or organizations to promote and support risk communication, management and minimization
- Through a personal narrative, demonstrate commitment to promoting safety and preventing risks, taking a “proactive” rather than a “reactive” approach for the safe use of medicines, planning and implementing “risk management” and “risk minimization” strategies upon joining the pharmacy workforce after graduation

Content Summary and Process Overview / Instructional Methodology (Total Duration: 150 Minutes)

- A. Principles and methods of benefit-risk assessment. (Sources: Ref. 014, Ref. 077, Ref. 096, Ref. 081, Ref. 091)

In drug surveillance, an ADR is deemed acceptable when its frequency and severity are sufficiently compensated for by the frequency and magnitude of the therapeutic benefit of the drug. Similar to the benefit/risk judgment made in clinical therapeutics for an individual patient, a benefit/risk judgment can be made in pharmacovigilance from a population point of view. These judgments are called benefit-risk assessments.

In general, the net benefit-risk profile for society must reflect not only how many patients are expected to benefit from a therapy and to what extent, but also the uncertainties associated with its benefits and risks. At the extremes (high risk, low benefit; low risk, high benefit) judgments are relatively easy but, between the extremes there is more uncertainty, and decision making can be more complex and difficult.

Signals of adverse reactions of medical importance that result in a benefit-risk reassessment usually arise from market experience through spontaneous reports, but may also surface in large post-marketing or other studies. For marketed products, the most recent international Periodic Safety Update Report (PSUR) is an essential source of data for such an investigation. Spontaneous case reporting systems may signal a problem but cannot provide quantitative information on the degree of risk associated with the suspect medicine.

One way to reduce the complexity of an overall analysis is to express each medicine's benefits and risks in terms of the adverse reaction's seriousness, duration and incidence and the disease's seriousness, chronicity (acute, chronic, or duration of disease) and the extent of its potential control or cure. It is then possible to focus on the selected adverse reactions. If needed, benefits may also be expressed separately for each of a drug's indications. The comparative method of benefit-risk assessment qualitatively compares the product in question with similar products to determine whether the benefits and risks appear similar. However, the data and standards for benefit-risk assessment on the "similar," usually older, drugs may not be satisfactory by today's standards.

Activity	Time (minutes)
<p>Guide the students through the flowchart “Overview of a Benefit-Risk Evaluation Process” on page 14 of Ref. 014. (10 minutes)</p> <p>Share the check list of “Points to consider in evaluation of benefits” on pages 31-33 of Ref. 014. Ask the students to group in pairs to discuss and identify what they feel are the highest priority items under each of the following categories in the check list:</p> <ul style="list-style-type: none"> • The epidemiology and natural history of the target disease • Purpose or intended outcome of the treatment • Evidence of benefits: degree of efficacy achieved in clinical trials and effectiveness in clinical practice • Alternative therapies <p>Ask some students to volunteer the results of their discussions and to indicate why they felt those items were of higher priority. (20 minutes)</p> <p>Review the suggested sequential overall approach for the evaluation of drug attributed risks on pages 51 – 52 of Ref. 014 (10 minutes)</p> <p>Summarize this topic by stressing that while the benefits of medicines are usually represented as well-defined outcomes, risks usually include a mixture of adverse reactions of different types.</p>	30

B. The Erice Declaration on effective communication in PV. (Source: Ref. 093)

The Erice declaration was drawn up at the International Conference on Developing Effective Communications in Pharmacovigilance in Erice, Sicily, 24-27 September 1997.

The conference was attended by health professionals, researchers, academics, media writers, representatives of the pharmaceutical industry, drug regulators, patients, lawyers, consumers and international health organisations. Major points in the declaration include:

- Drug safety information must serve the health of the public
- Information should be ethically and effectively communicated in terms of content and method
- Facts, hypotheses and conclusions should be distinguished
- Uncertainty should be acknowledged
- Information should be provided in ways that meet both general and individual needs
- Education in the appropriate use of medicines is essential for the public, patients and health care providers
- Education requires special commitment and resources
- Information on medicines directed to the public should be balanced with respect to risks and benefits
- All evidence needed to assess and understand risks and benefits must be openly available
- Constraints which hinder communications should be recognised and overcome

Activity	Time (minutes)
Present slides 4-7 of Ref. 093. (5 minutes) Ask the students to gather in groups of 3 to identify the points they feel should be included when communicating drug safety information to patients. (5 minutes) Then use slides 9-11 of Ref. 093 about the points included in the ERICE Declaration. (5 minutes) Ask the students to compare the points included in the ERIC Declaration with the points they identified. Ask the students to share the points missing on their lists with the class. (5 minutes)	20

- C. Role of the National DI&ADR Center, DAV, hospital DTCs and DIUs and other stakeholders in communicating medicine safety information; relevant circulars from MOH relating to such roles for key MOH bodies. (Sources: Ref. 097, Ref. 098, Ref. 026)

The role of stakeholders in Vietnam's PV and medicine safety system in communicating medicine safety information includes:

National DI&ADR Center - National Drug Information and Adverse Drug Reaction Center- As the hub for receiving pharmacovigilance data collected by the regional centers, the National DI&ADR Center provides drug information and advice on ADRs for clinical sites, pharmacy staff and the community and also establishes connections with international drug and ADR centers.

DAV- Drug Administration of Vietnam - Collaborates with the drug regulatory authorities of other countries and international agencies on pharmacovigilance, including reporting ADRs to WHO/Uppsala Monitoring Centre

MSA – Medical Services Administration - Provides guidance on the safe and appropriate use of medicines at health facilities training health care workers on the rational and safe use of medicines in health facilities

Hospital DTCs- Drug and Therapeutic Committees - Produce documentation and guidelines for drug use. Provide training to trainers on drug use and provide training (including in minority languages) for the public about rational drug use in collaboration with The Voice of Vietnam.

DIUs- Drug Information Units - Their functions include providing drug information and publishing leaflets and handbooks.

Activity	Time (minutes)
<p>Show page 3 in the in Ref. 098 to remind the students about Vietnam’s PV national stakeholders which were previously discussed in session 1.2. Highlight the roles some of those stakeholders play in in communicating medicine safety information, as shown in Section “C” of the content summary in this session. (5 minutes)</p> <p>Show page 13 in Ref. 097 to show the challenges faced by DTCs in Vietnam. Ask the students to consider what steps they might take after they join the pharmacy workforce to help reduce those challenges. Invite a few students to share their thought on this issue. (15 minutes)</p> <p>Show the students examples of Vietnam’s Ministry of Health circulars relating to the roles of key MoH bodies. (Sources: Ref. 103, Ref. 104, Ref. 105, Ref. 106, Ref. 107_or from MoH website, if available) (15 minutes)</p>	30

- D. Examples from other countries and organizations on communicating messages about medicine safety (e.g., “Dear Doctor” letters, medicine alerts, media statements, patient information leaflets, newsletters, and personal feedback to reporters).

Public communication on safety concerns over medicines and advice on how to prevent medicine-induced patient harm is a challenge for the overall success of those responsible for pharmacovigilance. A wide variety of communication mechanisms such as “Dear Doctor” letters, medicine alerts, media statements, patient information leaflets, medicine safety bulletins and newsletters are used to provide healthcare professionals and patients with appropriate and prompt information.

Activity	Time (minutes)
<p>Use Ref. 095 slides 3 – 11 to introduce the topic of communication.</p> <p>Show examples of communications from other countries from pages 11-18 of Ref. 094_and Ref. 101 – the FDA Drug Safety Communications website</p>	25

- E. Selected examples from other countries and organizations regarding strategies and tools for risk management and minimization. (Sources: Ref. 072_slides 79-84, Ref. 109)

Risk management for medicinal products is the set of pharmacovigilance activities and interventions designed to identify, characterize, prevent or minimize risks relating to medicinal products, including the assessment of the effectiveness of those interventions. Risk management represents a

fundamental paradigm shift from a passive information-oriented approach to one of action and accountability for the safe use of drugs within the marketplace. In line with that paradigm shift, FDA and EMA are giving heavier emphasis on “risk management” covering the entire life-span of a drug to minimize safety problems. For example, FDA’s Risk Management Framework includes: risk management activities, risk assessment, risk confrontation, risk intervention, risk communication, and risk management evaluation. A valuable tool for risk minimization is ISMP’s list of error – prone abbreviations, symbols, and dose designations.

Activity	Time (minutes)
<p>Introduce the topic of using pharmacovigilance for risk management by presenting relevant slides of the presentation in Ref. 096, which includes the RiskMAP and REMS requirement in the USA.</p> <p>Pose the questions on slide 39 about Rofecoxib’s Risk Management and facilitate a discussion among the students.</p> <p>If time permits, share page 24 of Ref. 108 which contains ANNEX B: METHODS FOR RISK MINIMISATION of European Medicines Agency’s Guideline on Risk Management Systems for Medicinal Products for Human Use.</p> <p>Summarize this topic by stressing that the tools for risk minimization can be divided into those where a reduction in risk is achieved primarily through the provision of information and education and those which seek to control the use of the medicine.</p> <p>Ask the students to cluster in pairs to discuss how they plan on taking a “proactive” rather than a “reactive” approach for the safe use of medicines, planning and implementing “risk management” and “risk minimization” strategies upon joining the pharmacy workforce after graduation. Invite some students to share the results of those discussions with the class.</p>	60

Sources used in this session:

- Ref. 014 CIOMS Working Group IV Benefit-Risk Balance for Marketed Drugs: Evaluating Safety Signals. Web. 1998.
- Ref. 026 The National DI & ADR Centre, Hanoi University of Pharmacy & Ministry of Health *National Capacity Assessment for Drug Information and Pharmacovigilance*. Submitted to World Health Organization (WHO). Dec. 2009.
- Ref. 072 Joshi, M. P. *A System-oriented Approach to Implementing Pharmacovigilance*. [PowerPoint slides]. 29 Sep. 2009.
- Ref. 077 Berdai, D. *Risk and crisis Management in Pharmacovigilance*. Hanoi. [PowerPoint slides]. 2009.
- Ref. 081 Hanoi University of Pharmacy. *Introduction To Pharmacovigilance: Signal Evaluation: Assessing Causality and Characterizing Risk*. [PowerPoint slides]. 26 Mar 2009.
- Ref. 091 Cobert, B. L. & Biron, P. *Pharmacovigilance from A to Z: Adverse Drug Event Surveillance*. Malden: Blackwell Science, 2002. Print.
- Ref. 092 Federal Ministry of Health, Nigeria. *Risk Management Strategies*. [PowerPoint slides]. 6 Jan. 2011.
- Ref. 093 Federal Ministry of Health, Nigeria. *Medicine Information and Risk Communication*. [PowerPoint slides]. 6 Jan. 2011.
- Ref. 094 Joshi M. *Medicine Information and Medicine Safety Bulletins*. U.S. Agency for International Development. 2010.
- Ref. 095 Hanoi University of Pharmacy. *Effective Communication in Pharmacovigilance Programs*. [PowerPoint slides]. 26 Mar 2009
- Ref. 096 Hanoi University of Pharmacy. *Use of Pharmacovigilance for Risk Management*. [PowerPoint slides]. 26 Mar 2009
- Ref. 097 Nguyen T. P. C. *Role of the Drug and Therapeutic Committee in Safe and Rational Use of Drugs in Vietnam*. Medical Service Department, Ministry of Health. [PowerPoint slides]. 2009.
- Ref. 098 Hanoi University of Pharmacy. *National Stakeholders and their Roles in Medicine Safety Activities*. [PowerPoint slides]. 26 Mar 2009
- Ref. 099 Ann Van Ermen, A. V. *Pharmacovigilance and Risk Management*. Belgian Centre for Pharmacotherapeutic Information and Belgian Centre for Pharmacovigilance. [PowerPoint slides]. 26 Aug. 2007..
- Ref. 101 U.S. Food and Drug Administration. 2011 Drug Safety Communications. Web. Last Updated: 10 Jan. 2012.
- Ref. 103 Vietnam Ministry of Health. *Circular No: 09 /2011/TT-BYT): Guidance on criteria and technical scope of ART treatment sites*. Hanoi, 26 Jan. 2011
- Ref. 104 Vietnam Ministry of Health. *Circular No: 22/2011/TT-BYT: Stipulating the Organisation and Operation of Hospital Pharmacies*. Hanoi, 10 Jun. 2011
- Ref. 105 Vietnam Ministry of Health. *Circular No: 23/2011/TT-BYT: Promulgating Instructions on Drug Use in Health Care Establishments with Patient Beds*. Hanoi, 10 Jun. 2011

- Ref. 106 Vietnam Ministry of Health. *Circular No: 47/2010/TT-BYT: Guidelines for the Export and Import of Drugs and Primary Packaging*. Hanoi, 26 Jan. 2011
- Ref. 107 Vietnam Ministry of Health, Vietnam Drug Administration. *Circular No: 2313/QLD-CL: Concerning the Issuance of the List of Good Pharmacy Practices” (GPP), “Good Distribution Practices” (GDP) and a Number of Procedures*. Hanoi, 11 May 2007.
- Ref. 108 European Medicines Agency, Committee for Medicinal Products for Human Use (CHMP). *Guideline on Risk Management Systems for Medicinal Products for Human Use*. Web. 6 Sep. 2005.
- Ref. 109 Institute for Safe Medication Practices. *List of Error-Prone Abbreviations, Symbols, and Dose Designations*. Web. 2011.

Additional Reading and Resources:

- Ref. 100 Karwoski, C. B. *Practical Experience with Risk Management Plans in the US*. *Drug Information Association Annual Meeting*. [PowerPoint slides]. 2006.
- Ref. 102 Bahri, P., Mol, P. G. M., Theophile, H., et al. *Communication in Drug Safety: A report from an interactive debate held at the 10th Annual Meeting of the International Society of Pharmacovigilance (ISoP), 2010*. Web. *Drug Safety, 34.10, (Oct. 2011): 881-882*.

Session 5.1: Importance of PV in Public Health Programs (PHPs), Burden of ADEs in PHPs, Strategies to Improve Adverse Events Reports in PHPs

Topics to cover in this session:

- A. Importance of PV in PHPs (HIV/AIDS, TB, Malaria, Immunization): strengths, challenges and mutual benefits
- B. Epidemiology of adverse events and drug-related morbidity and mortality in PHPs (HIV/AIDS, TB, Malaria, Immunization); problem of treatment failure in PHPs
- C. Improving adverse event reporting within PHPs (HIV/AIDS, TB, Malaria, Immunization)

Objectives: By the end of the session, students will be able to:

- Explain why the conduct of PV is critical for a “safe” and rational use of medicines in the major PHPs such as HIV/AIDS, malaria, TB, and Immunization
- Show awareness of the significant problem of ADEs in PHPs by describing the burdens of ADRs and treatment failures
- Describe locally feasible measures that can help improve adverse event reporting within PHP’s HIV/AIDS, TB, Malaria, and Immunization programs.

Content Summary and Process Overview / Instructional Methodology (Total Duration: 50 Minutes)**A. Importance of PV in PHPs (HIV/AIDS, TB, Malaria, Immunization): strengths, challenges and mutual benefits. (Source: Ref. 110, Ref. 003, Ref. 112)**

Public health programs (PHPs) provide prevention, treatment, and control of infectious diseases such as malaria, TB, HIV/AIDS through the administration of medicines and vaccines.

The importance of PV in Public health programs is reflected in the fact that PV programs and public health programs are mutually beneficial. Public health programs provide a valuable opportunity for PV activities by offering cohorts of patients under controlled conditions to be monitored for safety over a period of time. In turn, that enhanced PV enables detection, evaluation and prevention of adverse events in those PHPs. The synergy between PHPs and PV results in a stronger spontaneous reporting system, particularly when establishing active surveillance components in public health programs for HIV/AIDS, Malaria, Tuberculosis and Immunization. Some of the strengths of PHPs include:

- They are well established programs using a limited number of drugs or vaccines
- The quality of product being used can be assured
- There are large populations involved
- They usually operate according to standard guidelines
- They are often well-funded with national and international support

Some of the challenges PHPs might encounter include:

- Disease may not be well-diagnosed/presumptive treatment
- Use fast-tracked medicines which may not have been sufficiently studied in some patient groups
- Self-medication
- Inadequate patient information
- Co-morbid conditions, nutrition, special patient groups
- Drug resistance
- Drug interactions, alternative therapies
- Poor medication adherence

Incorporating PV into PHPs can identify preventable/modifiable risk factors for drug-related harm, and identify new, previously unknown adverse drug reactions to medicines used in public health programs. The results can be improved clinical practice guidelines that are more locally relevant and evidence-based and a culture of drug safety awareness among health professionals. The knowledge gained from the PHP-based PV can inform future therapeutics research into safety of medicines used in public health programs.

Activity	Time (minutes)
Present Page 106 – 113 of Ref. 003 (slides #s 4 -22). When discussing the final bullet on slide 21, highlight the differences between the situation in Vietnam and the situation as described in Kenya.	25

B. Epidemiology of adverse events and drug-related morbidity and mortality in PHPs (HIV/AIDS, TB, Malaria, Immunization); problem of treatment failure in PHPs. (Sources: Ref. 003, Ref. 112)

Most data on burden of ADR are from resource-rich countries such as New Zealand, Australia, US, UK, and France, and very few are from resource-constrained countries. Very few developing countries have optimally functional reporting schemes and are members of the WHO collaborating center on drug monitoring. But, it is not appropriate to extrapolate data from developed countries. The burden of ADRs in resource limited settings may differ from resource-rich countries because of:

- High prevalence of HIV/AIDS, TB, Malaria and other comorbid conditions
- Risk-benefit generalization may not apply
- Poor medicine labeling, off-label use
- Traditional medicines and associated adverse events and interactions
- Genetic make-up, nutrition status
- Regular monitoring for early signs of toxicity often not well-established

ADRs are a significant cause of morbidity and mortality in PHPs. Potential ADRs associated with anti-TB drugs include: liver toxicity, neurotoxicity, Lupus syndrome and ocular toxicity. Potential ADRs associated with anti-retrovirals include: hypersensitivity, pancreatitis, neuropathy, disfiguring fat distribution, and severe skin reactions. And potential ADRs associated with anti-malarial drugs include: neuromuscular conditions such as dystonia and dyskinesia.

ADRs that occur in PHPs affect treatment adherence which increases the risk of drug resistance and erodes public confidence in PHPs resulting in wasted financial resources and suboptimal outcomes. Therapeutic ineffectiveness, or treatment failure, is a particularly important issue in public health programs such as HIV/AIDS, malaria, and TB. PHPs should collect data about the percentage of patients undergoing treatment whose regimen was modified because of treatment failure to inform future treatment guideline decisions.

Activity	Time (minutes)
<p>Show slide 21 of Ref. 112 to point out the countries providing the majority of ADR data. Ask the students to cluster in twos to spend 5 minutes listing some reasons why it is not appropriate to extrapolate ADR data from developed countries to resource limited settings. Invite students to share the reasons and create a list based on their contributions. Then add any additional reasons that might have been overlooked by the students.</p>	15
<p>If time permits, discuss this case study, “WHO, the Global Fund, and medical malpractice in malaria treatment” in Ref. 114 about drug resistance and treatment failure associated with malaria treatment. The opinion article written in 2004 states that “Most African countries reluctantly cling to chloroquine, sulfadoxine-pyrimethamine, or the insignificantly better combination of chloroquine and sulfadoxinepyrimethamine, because ACT is ten times more expensive and, therefore, unaffordable to them.” That was taking place even though there were links to drug resistance, treatment failure and deaths from malaria. Ask the students if they think this situation still taking place. Then, share the results of this study in Ref. 118 conducted in 2007 which shows that three years later, surprisingly, the situation had not changed.</p>	

C. Improving adverse event reporting within PHPs (HIV/AIDS, TB, Malaria, Immunization). (Sources: Ref. 110, Ref. 111)

In order to improve adverse event reporting within PHPs, practical and standardized guidance for reporting adverse events should be provided to the PHP staff members, and ADR forms must always be available at convenient places at all the patient treatment/management facilities. If possible, ADR reporting forms that have been adapted for the specific PHP should be used. Training in pharmacovigilance should be provided for key PHP staff. And, the PV activities within the PHP should be conducted in collaboration with the national pharmacovigilance system. Additionally, instituting mandatory ADR reporting by pharmaceutical manufactures improves information collection by drug regulatory authorities.

The guidance for reporting adverse events should tell the PHP staff to record:

- all new events even if minor
- change in a pre-existing condition
- abnormal changes in laboratory tests
- accidents
- all deaths with date and cause
- possible interactions with pharmaceutical or traditional medicines; (remember oral contraceptives, tobacco, alcohol or other commonly ingested products which the patient may not realize are “medicines” or interacting products.)

When providing guidance for clinicians and other prescribers the simplest advice is to request that any potentially medicine-related adverse clinical event that is recorded in the patient record should also be recorded and reported through an adverse event reporting form. The guidance should also provide reassurance that clinician does not need to use any special terminology.

If PHPs use ADR reporting forms that have been adapted to protocols of the specific HIV/AIDS, TB, Malaria, or immunization program, it will be easier for the staff to fill out the form and will also result in more accurate data.

There are some general features that should characterize all forms:

- All dates should be in a standard format that is noted on the form (e.g. dd-mm-yyyy).
- Abbreviations for medicines should be standardized.
- The forms should include units for all laboratory values. The organizers should ensure that all clinics use the same units for recording the results of a given test. If this is not the case, the forms should have an option that allows the local site staff to indicate the unit

Training courses in pharmacovigilance for key personnel, and the PV activities within the PHP should be conducted in collaboration with the national pharmacovigilance system.

<i>Activity</i>	<i>Time (minutes)</i>
Ask students to suggest strategies that can help improve or stimulate ADR reporting. Then, show them the list in the content summary. Share the list of general standardization features that should characterize all forms. Show the form on page 24 of Ref. 111 and, if time permits, ask them to comment on possible benefits of the fact that this form has been modified for the specific ARV PHP.	10

Sources used in this session:

- Ref. 003 "Pharmacovigilance: Quality, Safety and Efficacy of Medicines For Better Health Care: Participants' Manual." Ministry of Public Health and Sanitation & Ministry of Medical Services. Kenya. [PowerPoint slides]. Feb. 2009.
- Ref. 110 Karema, C. *Pharmacovigilance Training of Trainers: Integrating Pharmacovigilance into Public Health Program (PHP)*. Rwanda. [PowerPoint slides]. Sep. 2009.
- Ref. 111 World Health Organization. *Pharmacovigilance for Antiretrovirals in Resource-Poor Countries*. 2007.
- Ref. 112 The Uppsala Monitoring Centre. *Implementing Pharmacovigilance in Public Health Programs*. [PowerPoint slides]. 2009
- Ref. 114 Attaran, A., Barnes, K. I., Curtis, C., d'Alessandro, U., Fanello, C. I., Galinski, M. R., . . . Watkins, W. M. WHO, the Global Fund, and medical malpractice in malaria treatment. *The Lancet*, 363, (17 Jan. 2004): 237–40.
- Ref. 118 Frosch, A. E. P., Venkatesan, M. and Laufer, M. K. Patterns of chloroquine use and resistance in sub-Saharan Africa: a systematic review of household survey and molecular data. *Malar J.* 2011; 10: 116. Web. Published online 2011 May 9. doi: 10.1186/1475-2875-10-116.

Additional Reading and Resources:

- Ref. 113 Strengthening Pharmaceutical Systems (SPS) Program. *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. Web. 2009.

Seminars

Topic /Time	Activity
<p>Spontaneous Reporting 200 minutes</p>	<p>Following the path of a spontaneous report from its inception through the DI&ADR center.</p> <ul style="list-style-type: none"> • Review the topic of “Spontaneous Reporting” to remind students of what they learned about it in session 3.1. (20 minutes) • Ask the students to fill out a variety of mock ADR forms (45 minutes) • Have invited speaker from DI&ADR Center present what happens to an ADR form (step-by-step) from the time it is filled out and once it reaches the DI&ADR Center. Have the speaker demonstrate the kinds of reports that are produced from the DI&ADR Center database and explain the value that can be gained from the reports and analysis. Students should be encouraged to ask the questions so that they get the best possible picture of a spontaneous ADR report’s lifecycle within the DI&ADR Center. (120 minutes) • Ask the students to consider and discuss how they might apply concepts they learned during this seminar when they join the workforce. (15 minutes)

Topic /Time	Activity
Causality Assessment 200 minutes	<p>Groups of students present the case scenarios and the group's assessment of causality using the WHO or Naranjo scale.</p> <ul style="list-style-type: none"> • Review the topic briefly to remind students of what they learned about causality assessment in session 2.4 (15 minutes) • Present this case: "Adverse Drug Reactions in Clinical Practice: a Causality Assessment of a Case of Drug-Induced Pancreatitis" in Ref. 117 as an example of causality assessment made from a medical case. (25 minutes) • Provide students with cases from the DI&ADR Center on which the patient names have been masked. Ask the students to assess causality of the cases provided using the WHO and the Naranjo scales. (35 minutes) • Divide the students into 3 groups and ask each group to select a case scenario to present. (One group to present a case with "certain" causality, one group to present a case with "probable/likely " causality and one group to present a case with "possible" causality.) Tell the students that their presentations should take about 15 min /presentation (about 7 slides) plus 5 minutes for Q&A for each presentation for a total of 20 minutes per group. (10 minutes) • Provide time for students meet in their groups to work on selecting their cases and planning their presentations - conferring with the instructor, if needed. (30 minutes) • Students present the cases and their causality assessments. (60 minutes) • Ask students for feedback on their experiences in creating the cases and preparing the presentation and summarizes important issues brought out in the presentations. (25 minutes)

Topic /Time	Activity
Risk Management 200 minutes	<p>Group problem solving using Nominal Group Technique* (NGT) structured brainstorming.</p> <ul style="list-style-type: none"> • Review the topic of Risk Management briefly to remind students of what they learned about Risk Management in session 4.1.(15 minutes) • Present introductory information about Tysabri (Natalizumab) in Ref. 116 with a focus on the warning box, and then present the first 16 slides of Ref. 115 Review of Tysabri Risk Minimization Action Plan (RiskMAP) BY Division of Drug Risk Evaluation Office of Drug Safety (35 minutes) • Explain that at the next meeting a structured brainstorming session will be conducted to enable the class to identify issues that the sponsor of Tysabri might have addressed to improve the RiskMAP. • Explain the NGT (Nominal Group Technique) process and facilitate the initial brainstorming through the recording step • Facilitate “discussion for clarification” • Facilitate categorization (if indicated) and prioritization and summarize the results (30 minutes) • Then, show the students slides 17-24 of Ref. 115, which list the additional issues that FDA’s Office of Drug Safety thought the sponsor should have addressed in the RiskMAP. (10 minutes) • Ask the students to consider and discuss how they might apply concepts they learned during this seminar when they join the workforce. (10 minutes) <p>*Step-by-step guidance on how to facilitate this specific session is provided on the following pages. Generic guidance on facilitating NGT is provided in Appendix 2. Review of the generic guidance in Appendix 2 is recommended before using the step-by-step guidance on following page.</p>

Sources used in this session:

- Ref. 115 Wysowski, D. *Review of Tysabri Risk Minimization Action Plan (RiskMAP)*. FDA Division of Drug Risk Evaluation, Office of Drug Safety. Peripheral and Central Nervous System Drugs Advisory Committee Meeting. [PowerPoint slides]. March 7-8, 2006
- Ref. 116 National Center for Biotechnology Information, U.S. National Library of Medicine. *Natalizumab Injection*. Web. 2011.
- Ref. 117 Farcas, A & Bojita, M. Adverse Drug Reactions in Clinical Practice: a Causality Assessment of a Case of Drug-Induced Pancreatitis. *J Gastrointestin Liver Dis. September 2009: Vol.18 No 3, 353-358.*

Facilitating structured brainstorming to identify issues the sponsor of Tysabri (Natalizumab) might have addressed to improve their RiskMAP.

Silent Brainstorming

- Before the class, write the following question on a hidden page of a flipchart: ***What additional issues might the sponsor of Tysabri (Natalizumab) have addressed to improve the RiskPAP?***
- Explain to the students that you are about to show them a question and that they will have 2 minutes to write a list of brief answers to that question on their papers. (This is silent brainstorming – no calling out.)
- Uncover the question on the covered flipchart. Read it to them and then tell them that their 2 minutes have started.
- Watch the time carefully and alert them when they have 1 minute left and then when they have 30 seconds left.

Recording

- Start at one side of the room and ask the first student to provide one response from his/her list. Write that response on the flipchart as #1.
- Ask the next student to give you one response from his/her list. Write that response as #2.
- Continue to circle the room in this fashion (usually several times) collecting issues the sponsor of Tysabri (Natalizumab) might have addressed to improve the RiskPAP.
- While Recording is going on, do not permit any discussion of the issues.
- Leave lots of space between the responses to allow for later clarification. As each page is filled, hang it on the wall and begin another page.
- Be on the lookout for a response that is really a compound response. Take only one portion and ask the participant to wait with the second portion.
- When there are no more responses, the recording is completed.

Discussion for Clarification

- Return to each numbered issue and read it aloud and ask if there are any questions about it.
- If there are questions or need for clarification, direct them to the student who contributed that issue.
- If there are recommendations to add information to clarify the issue or to combine the issue with another, ask the student who contributed that issue if they agree with that course of action.
- If no participants ask questions about an issue that appears to need clarification, pose the question yourself

Continued...

Categorization

(Sometimes, no categorization is required. But, if the issues identified seem to fall into categories, don't skip this step.)

- Start with a flipchart page containing a list of letters – A through D.
- Then, ask the participants to identify some potential category names that are appropriate for the responses. Assign those category names to A, B, etc. Then, go through the hanging flipchart pages and assign the appropriate letter to each item to indicate its category.
- If there is an issue left over without a category, that issue may be in a category by itself, so that is one more letter to add to the category list.

Conducting the Prioritization

- Hand out the voting sheets and give the students the following directions:
 - Take the next 10 minutes to walk around the room and review all of the issues.
 - Select the 3 issues which you feel are the most important for the sponsor of Tysabri (Natalizumab) to have addressed to improve the RiskPAP.
 - Then, rank them as your 1st, 2nd and 3rd choices based on their importance.
 - The voting sheet has a spot for your first choice (which gets 5 votes) your second choice (which gets 3 votes) and your third choice (which gets 1 vote). When you hand in your completed voting sheet it should simply have one item number on each on each of the lines. (Example of Voting Sheet in Appendix 2.)
- Draw prioritization grid on the flip chart while everyone is voting. Put marks in each box for the votes and then total the votes. (Example of Prioritization Grid in Appendix 2).
- Highlight the issues which were given the highest total scores. (Usually 3-5 items will have many more votes than the rest.)
- Read each of those items aloud so that the students can see what they, as a group, thought were the most important issues for the sponsors to have included in the RiskMAP.

Annex 1: Guidance on Enhancing the Objectivity of Student Assessment

While essay questions are a popular mechanism of student assessment at the university level, it is most difficult to perform objective student assessment based on written responses to essay questions.

The answers to multiple choice, true/false, cross-matching, and fill-in-the-blank questions are unambiguous and thus allow for a much higher level of objectivity on the part of the Instructor.

Short-answer questions allow for the instructor to challenge the student to create a response rather than to simply select the answer, while still helping the instructor to retain a high level of objectivity. Some examples of short-answer-questions are:

- Give three examples of prescribing errors that lead to medication errors.
- What is the function of the National DI&ADR Center?
- Which source of ADR information is the most reliable?
- What country has the highest ADR reporting rate?
- Define the criteria for each grade of severity of ADR below.
 - Grade 1. Mild
 - Grade 2. Moderate
 - Grade 3. Severe
 - Grade 4. Severe Life-Threatening

In situations where essay questions are being used, the level of objectivity can be increased by alerting the students about the components that will be expected in their written responses and the objectivity can be further enhanced by letting the students know how each of those components will be weighted in the grading.

An additional technique, Objectively Structured Practical Examination (OSPE) is a multi-station, multi-task assessment process. At each station, the student is observed performing a task. The grading mechanism for each station is structured to maintain objectivity. For example, score sheets might be used with partial scores having been pre-determined for situations where a student only partially performs the assigned task.

Using a combination of the assessment techniques described above can aid the instructor to incorporate as much objectivity as possible into the student assessment process.

Source used in this section:

- Ref. 301 "Objective Structured Clinical Exam (OSCE) & Objective Structured Practical Exam (OSPE)". Boursicot, K., Ware, J. & Hazlett, C. Trainer the Trainer Assessment Workshops run by IDEAL International Consortium in Hong Kong & Muscat. [PowerPoint Slides]. 2010.

Annex 2: Test Questions

1. All of the following are addressed by pharmacovigilance EXCEPT: (circle answer)
 - A. adverse effects
 - B. drug interactions
 - C. poor quality and counterfeit products,
 - D. illicit drug abuse
 - E. medication use errors
 - F. lack of efficacy

2. The country with the highest ADR reporting rate is: (circle answer)
 - A. Uganda
 - B. New Zealand
 - C. Haiti
 - D. United States
 - E. China

3. Match the organization with the function:

<ol style="list-style-type: none"> A. Ministry of Health (MOH) _____ B. National DI&ADR Center _____ C. DAV- Drug Administration of Vietnam _____ D. MSA – Medical Services Administration _____ 		<ol style="list-style-type: none"> 1. Monitors product quality 2. Governance and guidance of the health, healthcare and health industry of Vietnam 3. Provides guidance on the safe and appropriate use of medicines at health facilities 4. Responsible for Vietnam’s database of PV and drug information
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4. In VN, new herbal remedies must be registered and manufactured according to the same GMP rules as conventional pharmaceuticals.

___ TRUE ___ FALSE

5. Anti-infectives containing sub-therapeutic amounts of active ingredient as a result of counterfeiting are more likely increase the risk of selection and spread of drug-resistant pathogens than non-counterfeit substandard anti-infectives containing sub-therapeutic amounts of active ingredient.

___ TRUE ___ FALSE

6. All of the following are pharmacovigilance activities EXCEPT:

- A. Reporting ADRs
- B. Analyzing ADR reports
- C. Educating healthcare professionals about ADRs
- D. Monitoring pharmaceutical pricing policies
- E. Monitoring ADRs

7. A/B/O blood type is known to be a predisposing factor for ADRs.

___ TRUE ___ FALSE

8. All of the following organizations play a role in Vietnam’s pharmacovigilance and medicine safety systems:

- Drug Administration of Vietnam (DAV)
- Medical Services Administration (MSA)
- FDA Office of Drug Safety
- Public Health Programs
- National DI&ADR Center

___ TRUE ___ FALSE

9. Which of the following problem-prone areas is most responsible for medication errors? (circle answer)

- A. Administration
- B. Dispensing
- C. Prescribing and transcribing

10. Give 3 examples of prescribing errors that lead to medication errors:

- 1. _____
- 2. _____
- 3. _____

11. Passive surveillance (in contrast to active surveillance) seeks to determine the ratio/number of ADRs through formal and continuous monitoring and collection of health outcomes.

___ TRUE ___ FALSE

12. At which grade of severity of ADR is medical intervention/therapy usually first required? (circle answer)

Grade 5. Mild

Grade 6. Moderate

Grade 7. Severe

Grade 8. Severe Life-Threatening

13. WHO-UMC and Naranjo Algorithm are methods for assessing which characteristic of ADRs. (circle answer)

A. Reaction Type

B. Severity

C. Causality

D. Risk vs. Benefit

14. According to WHO, which of the following are not required for ADR reporting? (circle all answers)

A. Identifiable source of information or reporter

B. Identifiable patient,

C. Patient's family medical history

D. Name(s) of suspected product (s)

E. Name of prescriber of the product

F. Description of the suspected reaction(s)/event.

15. Spontaneous Reporting is a key element in Active Surveillance.

___ TRUE ___ FALSE

16. Which of the following sources of ADR information is the most reliable? (circle answer)

A. Medical publications

B. Clinical Trial data

C. Colleagues

D. Internet

E. Anecdotal

17. The main focus of the Erice declaration is effective communications in pharmacovigilance.

TRUE FALSE

18. Why is PV in PHPs important? (circle answer)

- A. PV enables detection, evaluation and prevention of adverse events in those PHPs
- B. PHPs offer cohorts of patients under controlled conditions to be monitors for safety over a period of time which enhances PV
- C. PV programs and public health programs are mutually beneficial
- D. All of the above

19. Patients should be given education about the appropriate use of their medications.

TRUE FALSE

20. What is the term used to refer to the probability of harm being caused, usually expressed as a percent or ratio of the treated population? (circle answer)

- A. Financial risk
- B. Risk management
- C. Uncertainty
- D. Risk

21. One of the reasons adverse events are collected on marketed medications is: (circle answer)

- A. WHO / UMC Monitoring Centre requires it
- B. Events with relatively low frequency may not be seen during pre-marketing clinical trials
- C. Doctors and patients have input that they do not have during pre-marketing clinical trials.
- D. The product's approved labeling may change after the medication is on the market.

22. Which of the following is an example of an ambiguous date:

- A. 12/12/12
- B. 11/12/12
- C. 16/05/12
- D. January 23, 2012

23. Financial burdens from poor quality medicines, ADRs and medication errors can be _____ by effective PV systems. (circle answer)
- A. Eliminated
 - B. Somewhat reduced
 - C. Greatly reduced
 - D. None of the above
24. Communication in pharmacovigilance is provided only from health program managers, decision-makers, authorities and Policy-makers to patients and healthcare providers.
- ___ TRUE ___ FALSE
25. All of the following are included in the FDA's categorization of drug risks to the fetus EXCEPT: (circle answer)
- A. Controlled studies in women fail to demonstrate a risk to the fetus in the first trimester (and there is no evidence of a risk in later trimesters), and the possibility of fetal harm appears remote.
 - B. Studies in animals or human beings have demonstrated fetal abnormalities, or there is evidence of fetal risk based on human experience or both, and the risk of the use of the drug in pregnant women clearly outweighs any possible benefit. The drug is contraindicated in women who are or may become pregnant.
 - C. Studies of children born to women who took the medication in the first trimester, and studies of their grandchildren, reveal that there are no risks from it for women who are or may become pregnant.
 - D. There is positive evidence of human fetal risk, but the benefits from use in pregnant women may be acceptable despite the risk (e.g., if the drug is needed in a life-threatening situation or for a serious disease for which safer drugs cannot be used or are ineffective).

Annex 3: Test Answers

1. D
2. B
3. A-2, B-4, C-1, D-3
4. TRUE
5. FALSE
6. D
7. FALSE
8. FALSE
9. C
10. poor handwriting; unclear oral orders; incomplete instructions; wrong indication, dose, duration, dilution, formulation; identity of the patient unclear; failure to consider a contraindication.
11. FALSE
12. Grade 3
13. C
14. C, E
15. FALSE
16. B
17. TRUE
18. D
19. TRUE
20. D
21. B
22. B
23. C
24. FALSE
25. C

Annex 4: How to Facilitate Structured Brainstorming Sessions

Using an interactive, learner-centered instructional technique in a classroom setting

Steps in the structured brainstorming process

- Explanation of the process to participants (the first time it is used with a class)
- Brainstorming responses to a question
- Recording responses
- Discussion for clarification
- Categorization (optional)
- Prioritization

Structured brainstorming - components and typical times

Time	Activity	Done by
15 minutes	Explanation of the process to participants	Facilitator
5 minutes	Brainstorming responses to the focus question	All
30 minutes	Recording	Facilitator / All
1 hour	Discussion for clarification	Facilitator / All
10 minutes	Categorization	Facilitator / All
20 minutes	Prioritization	Facilitator / All
10 minutes or more	Review of results and discussion	Facilitator

Optimal conditions

- Number of participants between 5 and 20
- U-shaped table or arrangement so students can see each other
- Flip chart
- Lots of space to hang pages from the flipchart on the walls

Explaining the process to the participants

The first time you use this process with your class, it is important to explain the process so the students will know what to expect. Use the text on the following pages to explain each portion of the process and to establish ground rules.

Text to use when explaining the brainstorming step

At the start of each structured brainstorming session I will provide you a very short amount of time in which you are to generate written answers to a specific question. The first part of the process (the actual “brainstorming”) is conducted in silence.

Your written answers should be in bullet format rather than lengthy statements.

The reason for the short amount of time is so that you don’t have time to self-censor. This allows the group to generate a broader range of answers to the question.

Text to use when explaining the recording step

During the recording step, I will ask each of you to provide one of the responses from your paper, which I will write on the flipchart. I will keep going around the room until all of the answers have been recorded on the flip chart. (If someone has already provided an answer that you have on your list, please cross it off of your list.)

In the event that your answer consists of two items tied together, I'll take one portion of your response and ask you to hold the other portion until the next round. When you have no more answers on your list, you can just "pass". But even though you have "passed", if you think of another item during the next round, you provide your answer.

During the recording step, there is to be no comment or critique of any items provided

Text to use when explaining the discussion for clarification step

During round robin recording, there was no critique permitted of any answers. However, that does not mean that all responses are equally good. Discussion for clarification allows us to weed out as well as clarify the answers.

During this step, I will read each answer and ask if there is any need for clarification. Questions must be addressed to the originator of the answer – only the originator of the answer can clarify the answer.

If the originator of the answer provides clarifying information, I will record the clarifying information. Or, the originator of the answer may decide that the answer is flawed and should be removed. Only the originator of the answer can ask that it be removed

The same words can mean different things to different people, so in this step another thing we are doing is making sure that we all agree that the words mean the same thing.

During the discussion for clarification, it is also possible that we will discover that there is a hierarchical relationship between 2 of the answers and that one is actually a subset of the other. At that point, I will move the answer that is the subset and combine it with the broader answer.

Once all of the answers have been discussed and clarified and in some cases combined, it may be clear that they fall into different categories. If so, we will categorize them in a later step.

Conducting the Session

Conducting the Brainstorming

- Read the question written on the flipchart. (Keep it hidden until this moment and then uncover it.)
- Tell the participants that they have a specific, short amount of time to answer the question. (1.5 minutes usually works well. Up to 2.5 minutes for more difficult questions.)
- Watch the time carefully and alert them when they have 1 minute left and then when they have 30 seconds left.

Conducting the Recording

- Start at one side of the room and ask the first participant to provide 1 response from his/her list. Write that response on the flipchart as #1.
- Ask the next participant to give you 1 response from his/her list. Write that response as #2.
- Leave lots of space between the responses to allow for clarification
- Be on the lookout for a response that is really a compound response. Take only one portion and ask the participant to wait with the second portion.

Conducting the Discussion for Clarification

- Return to each numbered item and read it aloud. Ask if there are any questions
- If there are questions or need for clarification, direct them to the original contributor of that item
- If there are recommendations to add information to clarify the item or to combine the item with another, ask the originator of the item if they agree with that course of action.
- If no participants ask questions about an item that appears to need clarification, pose the question yourself

Conducting the Categorization (Sometimes, no categorization is required.)

- Start with a flipchart page containing:

A =

B =

C =

D =

- Then, ask the participants to identify some potential category names that are appropriate for the responses. Assign those category names to A, B, etc. Then, go through the hanging flipchart pages and assign the appropriate letter to each item.

- If there is an item left over without a category, the item may be in a category by itself, so that is one more to add to the category list.

Conducting the Prioritization

- Hand out the voting sheets and provide the criterion on which to base the prioritization
- Give the participants the following directions:

Take the next 10 minutes (amount of time can vary a little) to walk around the room and review of the items.

Select the 3 items which you feel are the best based on the criterion provided. Then, rank them as your 1st, 2nd and 3rd choices.

The voting sheet has a spot for your first choice (which gets 5 votes) your second choice (which gets 3 votes) and your third choice (which gets 1 vote).

Your completed voting sheet should simply have one item number on each on each of the lines.

VOTING SHEET
5 votes for item # _____
3 votes for item # _____
1 vote for item # _____

- Draw prioritization grid (see next page) on the flip chart while everyone is voting.
- Ask for 2 volunteers. One to read the votes and one auditor to watch you write the votes on the grid, to ensure they are recorded correctly. To avoid confusion, it's best if the reader always reads the sheets in the following way:

#x got 5 votes, #y got 3 votes, #z got 1 vote

- Put marks in each box for the votes and then total them up.

Prioritization Grid

Item #	5 votes	3 votes	1 vote	Total Votes

Working with brainstorming results

- Highlight the items which were given the highest total scores. (Usually 3-5 items will have many more votes than the rest.)
- Read each of those items aloud so that the participants can see what they, as a group, thought were the most important items based on the criterion given.
- These items can then serve as a basis for additional, focused discussion or future assignments.