Regulatory Requirements and Guidelines

An Overview of National Regulatory Requirements for Pharmacovigilance

Objectives

- Provide overview of Pharmacovigilance systems in different countries
- Discuss the varying regulations and requirements for several Asian based countries
- Gather further understanding of Pharmacovigilance requirements in Course Participant's countries

Group Discussion

What are your local Pharmacovigilance Regulations?

Local Pharmacovigilance Regulations

- Is there a Centralised adverse event database?
- Electronic or postal lodgment of adverse event information?
- Reporting timelines?
- Minimum report requirements?
- Access to AEs from overseas distributors?

- ICH
- European Union
- Australia
- ASEAN Countries
- Challenges for Developing Countries

Pharmacovigilance in Western World

- Pharmacovigilance systems in Western World countries were initiated following early medical mishaps
  - Thalidomide use resulting in birth defects (primarily phocomelia)
  - Elixir of sulfanilamide contaminated with diethylene glycol
- These events lead to introduction of National Legislation (US FD&C Act) and the WHO system for voluntary reporting of adverse events
- The International Conference on Harmonization (ICH) is viewed as the gold standard for regulatory guidelines and processes

ICH

- Cooperation of Regulatory Authorities and Pharmaceutical Companies to discuss scientific and technical aspects o drug registration
- Harmonisation of regulatory requirements was first initiated within the European Union. Its success prompted the collaboration between EU, Japanese and US FDA
- ICH evolved to become an instrumental driver of regulatory standards and guidelines

ICH PhV Guidelines

- ICH Guidelines have been implemented by many developed countries Regulatory Agencies
  - Australian TGA, US FDA, EMA, etc
- Provide a harmonized definition and methodology, including Pharmacovigilance activities
  - Country specific requirements may be implemented over those described in the ICH guidelines
- Web site: www.ich.org

A valuable resource for future reference!

ICH PhV Guidelines

- ICH Pharmacovigilance Guidelines:
  - E2A Clinical Safety Data Management: Definitions and Standards for Expedited Reporting
  - E2B(R3) Clinical Safety Data Management: Data Elements for Transmission of Individiual Case Safety Report
  - E2C(R2) Periodic Benefit-Risk Evaluation Report
  - E2D Post-approval Safety Data Management: Definitional and Standards for Expedited Reporting
  - E2E Pharmacovigilance Planning
  - E2F Development Safety Update Report

ICH PhV Guidelines

- ICH Guidelines are not intended to specifically direct the process of pharmacovigilance activities
  - Aid in the successful implementation of local regulatory requirements for AE recording, analysis and reporting
  - Guidelines should be considered in combination with local regulatory requirements
- Pre-reading material included ICH Guideline E2E *Pharmacovigilance Planning*

Any specific questions on Guideline E2E?

Pharmacovigilance Planning

- The ICH document is intended to guide in the development of a safety specification and Pharmacovigilance Plan
- Safety Specification is a summary of the risk associated with a therapeutic good (drug, biotechnology product, vaccine, etc)
  - Important Identified Risks
  - Important Potential Risks
  - Important Missing Information
- Provide a framework to determine areas where specific data collection is required

Coincides with the Pharmacovigilance Risk Management Plan to be discussed later

Pharmacovigilance Planning

- Pharmacovigilance Plan discusses the key elements of the Safety Specification as Ongoing Safety Concerns
- Identifies how any additional data intended to address missing information within the Safety Specification
- Describes the systems and processes that ensure all adverse reactions that are reported to the Company are collected, reported, investigated and reported to the Regulatory Authorities.

ICH E2E

- Provides a concise summary of Pharmacovigilance Methods to guide Company processes and systems
- Includes:
  - Passive Surveillance
  - Active Surveillance
  - Stimulated Reporting
  - Comparative Observational Studies
  - Targeted Clinical Investigations

ICH Guidelines

- Should not be read in isolation of local regulatory requirements
- Provides information on best practice and international standards supporting drug development programs
- Valuable source of reference material

European PhV Requirements

- All medicines in the EU are required to follow mandatory steps to monitor their ongoing safety and effectiveness
- Legal framework of pharmacovigilance or medicines marketed in the EU is provided by Regulations (EC) No. 726/2004 and 2012/1027/EU (centrally authorized medicines), along with Directive 2001/83/EC and 2012/26/EU for nationally approved medicines (including medicines approved via Mutual Recognition procedures)
- European Medicines Agency (EMA) has released Good Pharmacovigilance Practice (GVP) guidelines to facilitate PhV activities

European PhV Requirements

- Process Steps in Pharmacovigilance
  - Data collection and management
  - Signal Detection
  - Safety Issue Evaluation and Decisions
  - Periodic Benefit Risk Assessment
  - Regulatory action/Risk Minimisation
  - Communication with stakeholders and the public
  - Audit, both of the outcomes of actions taken and the key processes involved

European PhV Requirements

- European Regulations apply to
  - Pharmaceutical Companies
  - Regulators
    - National Medicines Agencies, e.g.
      - MHRA
      - ANSM
      - BPharm
      - MEB
    - European Medicines Agency
- Requirements are not applied to Patients, Doctors and other healthcare professionals

EU AE Reporting

- Only valid Individual Case Safety Report (ICSR) should be reported.
- The clock for reporting of valid ICSR commences as soon as the information creating the minimal reporting criteria has been received by either the MAH or the Regulatory Authority

  ➢**Day Zero**
- Serious ICSR's generally must be reported within 15 days of date of receipt
  - Includes events reported within and outside the EU
- Non-serious ICSR's shall be reported within 90 days from date of receipt

Australian PhV Requirements

- Australian regulatory Agency: Therapeutic Goods Administration (TGA)
- Similar to the EU, MAHs must follow well defined regulations relating to the collection, evaluation and reporting of adverse events
- Regulatory requirements are specified within the *Therapeutic Goods Act 1989* (Cth)
- Therapeutic Goods Regulations, along with Therapeutic Goods Orders, standards and guidelines details how the Act requirements are to be implemented

Database of Adverse Events

- Australia has implemented a Database of Adverse Event Notifications (DAEN)
  - Searchable database containing the adverse events received by the Agency
  - Provides information about AE for medicines and vaccines used in Australia
  - Does not contain all the safety information relating to a drug
  - Provides the Agency with data to complete signal detection
  - Database accessed via internet (http://apps.tga.gov.au/PROD/DAEN/daen-entry.aspx).

AE Reporting

- Reporting of Adverse Events may be made by anyone
  - Pharmaceutical Industry
  - Doctor/Healthcare Professional
  - Patient/Consumer
  - Parent/Guardian
- Report can be lodged via email, online portal or post

AE Reporting

- MAH must report information in relation to any medicine for
  - All serious unexpected and serious expected adverse reactions (AR) occurring in Australia and are associated with the use of the medicine
  - All serious unexpected and serious expected ARs reported in the worldwide literature, that become known to the MAH, occurred in Australia and are associated with the use of the medicine
  - All clinical and medically relevant information in relation to serious ARs occurring in Australia that becomes available to the sponsor as a result of follow-up activities
  - a suspected increase in the frequency of serious ARs to the medicine, including the basis on which the frequency assessment has been made

Reporting Serious Adverse Reaction

- All serious AR must be reported no less than 15 days from day zero
  - Day zero for a serious AR starts on the day that the four minimum data elements are received
  - These four elements are:
    - An identifiable patient
    - One or more identifiable reporter(s)
    - One or more suspected reaction(s); and
    - One or more suspected medicine(s)

Significant Safety Issue

- A significant safety issue may include:
  - Withdrawal or suspension of availability of the product
  - Addition of a contraindication, warning or precaution statement to the label
  - Modification of an existing contraindication, warning or precaution statement in the PI or label for safety reasons
  - Modification or removal of an indication for safety reasons
- Must be reported within 72 hours (3 days)
  - Day zero is based on the time of awareness of the issue

ASEAN Pharmacovigilance Requirements

- Association of Southeast Asian Nations
  - Includes Indonesia, Malaysia, the Philippines, Singapore, Thailand, Brunei Darussalem, Vietnam, Laos PDR, Myanmar

ASEAN Pharmacovigilance Requirements

- In each of the ASEAN countries, Pharmacovigilance Centres have been established
- Each countries has initiated documented requirements for the conduct of Pharmacovigilance activities
- Requirements continue to evolve and become more robust
- Countries have each established an approved Individual Case Safety Report (ICSR) form

ASEAN Pharmacovigilance Requirements

- Mandatory reporting of Adverse Events resides with the Marketing Authorisation Holder (MAH) in Malaysia, Singapore and the Philippines
- In Malaysia, it is mandatory for Healthcare Professionals to also report Adverse Events

Surveillance Systems

- Each country has a Passive Adverse Event Surveillance system, with all excluding Laos PDR also established an active surveillance system
- Active surveillance systems vary
  - Follow up of patients from private and public sectors
  - Intensive monitoring of selected products, including anti-retrovirals
  - Active monitoring of adverse events following immunizations occurring within large public hospitals

Signal Monitoring

- Each country has ability to review signals based on event reports received
- Some actions are directed by National Regulatory Authority, whilst others will apply outcomes from more developed countries
- Outcomes of signal monitoring can include:
  - Product suspension and recall
  - Registration cancellation or withdrawal
  - Publication of safety alerts

ICSRs reported

- Summary of ICSRs received per year per million of population reported to National Pharmacovigilance Centres

Country	ICSR/year/million population
Cambodia	2.0
Indonesia	6.9
Laos PDR	4.1
Malaysia	419.3
The Philippines	41.1
Singapore	3,610.3
Thailand	781.2
Vietnam	84.9

As taken from Suwankesawong et al, 2016

Overview

- Half of the ASEAN countries have a PV system that meets WHO requirements for a function
- Legislative requirements differ between the various countries
- Resources availability impacts on the development of Pharmacovigilance systems
- Communication of safety alerts poses significant issue with some countries

Challenges for Developing Countries

- In 2013, a study was published by the US Agency for International Development (USAID) comparing the pharmacovigilance systems for developing countries
- Countries considered were:
  - Bangledesh
  - Cambodia
  - The Philippines
  - Nepal
  - Thailand

Citation:
Systems for Improved Access to Pharmaceuticals and Services (SIAPS) Program. 2013. Comparative Analysis of Pharmacovigilance Systems in Five Asian Countries. Submitted to the US Agency for International Development by the Systems for Improved Access to Pharmaceuticals and Services (SIAPS) Program. Arlington, VA: Management Sciences for Health.

Pharmacovigilance in Developing Countries

- Access to medicines in Developing Countries continue to improve
- Pharmacovigilance systems however were seen as fragmented, poorly resourced and may impact on public safety
- As seen with ASEAN countries, PV systems in the countries reviewed varied greatly
- Study reported that risk assessment and risk management was identified as the weakest component

What is the view from Course Participants on current Pharmacovigilance Systems in home Country?

Pharmacovigilance in Developing Countries

- Each country evaluated as part of review have regulatory framework, regulatory registers for approved products and Governance structures
- A National PV centre is established
  - The resourcing of these centres may not be adequate
  - Suwankesawong[1] reported staff numbers
    - Cambodia – 2 persons
    - The Philippines – 4 staff
    - Thailand – 13 staff

1. Suwankesawong W., Dhippayom T., Tan-Koi WC, Kongkaew C., Pharmacovigilance activities in ASEAN countries *Pharmacoepidemiology and Drug Safety 2016 doi: 10.1002/pds.4023*

Pharmacovigilance in Developing Countries

- Challenges with drug safety programs include inability to address incidences of falsified or substandard products in the market in the region
- The supply of falsified or substandard products will increase the number and severity of adverse events
- The need to generate and share reliable data may hinder the timely risk management and regulatory decisions

Governance of PV system

- Cambodia, the Philippines and Thailand were found to have legal provisions mandating pharmaceutical industry to report suspected adverse events to the National PV centres
- The Philippines and Thailand also specify timelines for reporting serious events for marketed products
  - Thailand: 24 hours (fatal event)
    7 days (unexpected event with fatal outcome) and 15 days for other serious AEFI
  - Philippines: 7 days
- For non-serious events, Philippines require reporting within 30 days

Signal Generation and Management

- All countries (excl Bangladesh) have a local database for collating PV data, along with standard dictionary/terminology for reporting events
- Reporting of events can be via electronic (Cambodia, Nepal, Philippines and Thailand) or via post (Bangladesh, Philippines and Thailand)
- Consumer reporting forms, product quality and medication error reporting forms available in Philippines and Thailand
- A lack of available reporting forms in some countries affects optimal safety reporting
- Significant under reporting of adverse events observed in all countries excluding Thailand

Adverse Event Reporting

Summary of Expected vs Actual Reporting of AEs (as taken from publication)

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

Adverse Event Reporting

- Only Thailand met the WHO recommendation of AE reporting
  - Optimal National Pharmacovigilance Centre should send over 200 reports per million inhabitants per year (http://who-umc.org/DynPage.aspx?id=108476&mn1=7347&mn2=7252&mn3=7322&mn4=7558)
- Cambodia and Thailand completed causality assessments on more than half of AEs reported
  - Allows further assessment and evaluation of signals
- Active surveillance limited amongst countries
- Thailand and Nepal regularly publish medicines safety bulletins
  - Distribution of bulletins to healthcare facilities remains a challenge

Overview

- Pharmacovigilance systems in Western countries are well established and highly regulated
- Developing countries are continuing to improve PV systems to achieve greater patient safety
- Despite National procedures continuing to be developed, Companies can enhance their PV systems to increase reporting of adverse event and signal detection
  - This will improve risk evaluation and management
- Development of a consistent and harmonized system should remain a goal