Pharmacovigilance in India(PvPI), and EU regulations

Module 9 Topic 4

DCGI requirements for AE reporting

- Unsuspected adverse event is communicated from

1.Sponsor to regulatory authorities within 14 days

2. Investigator to sponsor within 24 hours

3. Investigator to ethics committee within 7 days

Deadlines for India

- A PSUR shall be submitted every 6 months for the first 2 years after approval. For the subsequent 2 years, PSURs are submitted annually.
- All cases involving serious, unexpected adverse reactions, must be reported to the authorities within 15 days of the initial receipt of information by the applicant.

CDSCO Guidance SAEs in CTs

- As per the regulations (Schedule Y of Drugs & Cosmetics Rules), all Unexpected SAEs have to be reported to CDSCO within 14 calendar days.
- All the sections of the covering letter should be completed. When some information is not available at the time of report e.g. causality assessment by medical monitor of Sponsor / CRO, compensation provided for study related injury or death, the same has to be provided as a follow-up report
- Causality assessment by investigator and the medical monitor of Sponsor /CRO. **The assessment report should clearly mention whether the SAE occurred is related or not related (Situations like unlikely, possibly, suspected, doubtful etc should not be used).**
- Whether the outcome is fatal
- **Details of compensations provided for injury or death. In case no compensation has been paid, reason for the same should be submitted**
- CDSCO Draft Guidance May 2011

Pharmacovigilance Programme of India (PvPI)

Steering Committee

Chairman: Drugs Controller General (India)

Members:	HOD Pharmacology (AIIMS)
	Nominee DG, ICMR
	ADG Extended Program Immunization
	Under Secretary (Drug Control)
	Nominee VC of Medical University
	Nominee MCI
Member Secretary	OIC New Drugs

Indian Pharmacopoeia Commission, Gaziabad , will be National Coordinating Centre

Objectives

To monitor Adverse Drug Reactions (ADRs) in Indian population

To create awareness amongst health care professionals about the importance of ADR reporting in India

To monitor benefit-risk profile of medicines

Generate independent, evidence based recommendations on the safety of medicines

Support the CDSCO for formulating safety related regulatory decisions for medicines

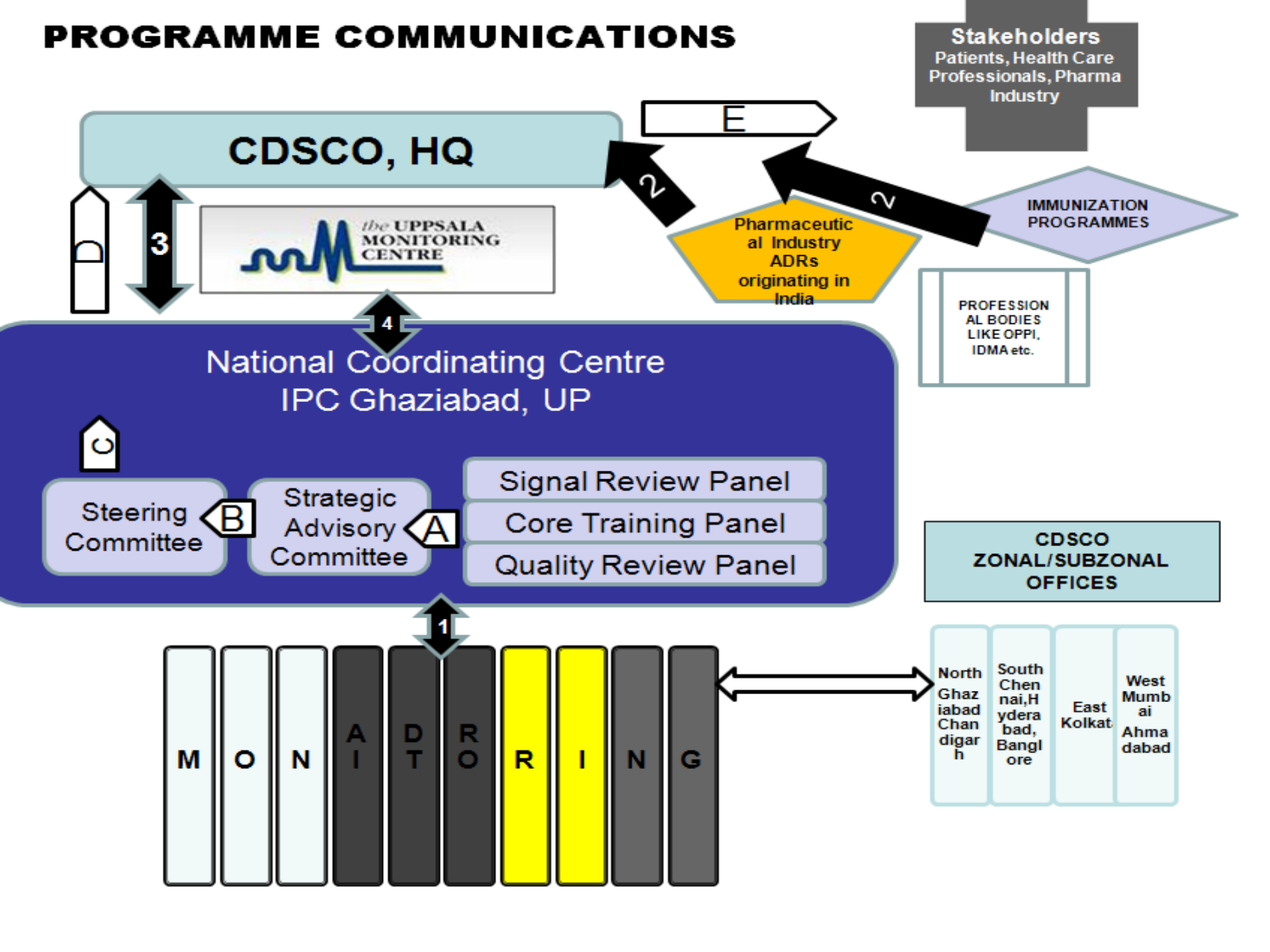
Communicate findings with all key stakeholders

Create a national centre of excellence at par with global drug safety monitoring standards

Governance

- PvPI will be administered and monitored by the following two committees:
- I. Steering Committee
- II. Strategic Advisory Committee
- Technical support will be provided by the following committees:
- I. Signal Review Panel
- II. Core Training Panel
- III. Quality Review Panel

PROGRAMME COMMUNICATIONS



ADR Monitoring Centers

Medical institutes/central institutes/ autonomous institutes like ICMR will also be inducted into the programme as AMCs on voluntary basis, and will not be provided any support from CDSCO.

Public and corporate hospitals will be inducted on a voluntary basis, and will not be provided any support from CDSCO.

Function - Medical Colleges

Collection of ADR reports Perform follow up with the complainant to check completeness as per SOPs

Data entry into Vigiflow

Reporting to PvPI National Coordinating

Centre (PvPI NCC) through Vigiflow with the source data (original) attached with each ADR case

Training/ sensitization/ feedback to physicians through newsletters circulated by the PvPI NCC

Functions – Other Centers

Collection of ADR reports

Perform follow up with the complainant to check completeness as per SOPs

Report the data to CDSCO HQ

Function - National Coordinating Center

Preparation of SOPs, guidance documents & training manuals

Data collation, Cross-check completeness,

Causality Assessment etc as per SOPs

Conduct Training workshops of all enrolled centers

Publication of Medicines Safety Newsletter

Reporting to CDSCO Headquarters

Analysis of the PMS, PSUR, AEFI data received from CDSCO HQ

CDSCO

- Take appropriate regulatory decision & actions on the basis of recommendations of PvPI NCC at IPC Ghaziabad.
- Propagation of medicine safety related decisions to stakeholders
- Collaboration with WHO-Uppsala Monitoring Center – Sweden
- Provide for budgetary provisions & administrative support to run National PvPI

Collaboration with WHO

Training of the staff at the PvPI national coordinating centre at IPC *Ghaziabad*, the ADR Monitoring centers in medical colleges across the country

Usage of UMC's Vigiflow software (for medicines) and Paniflow (for vaccines) at no cost to PvPI.

Access to Vigibase, which contains worldwide medicines safety data

Access to early information about potential safety hazards of medicines (worldwide data)

Technical collaboration for a regular publication that will be issued by the PvPI National Coordinating Centre

Safety Database

- Vigiflow software provided by WHO-Uppsala Monitoring Centre will be utilized as the safety database, where all data originating from India will be maintained in a secure and confidential manner.

Pharmacovigilance
Guidance Document

for

Marketing Authorization Holders of Pharmaceutical Products

सत्यमेव जयते

Published by

Indian Pharmacopoeia Commission
National Coordination Centre - Pharmacovigilance Programme of India
in Collaboration with Central Drugs Standard Control Organization
Ministry of Health & Family Welfare
Government of India

PV guidance document covers

- PvPI, scope, spread, communication, responsibilities. Divided in the following modules
- Module l - Pharmacovigilance System Master File
- Module 2 - Collection, Processing & Reporting of Individual Case Safety Reports
- Module 3 - Preparation & Submission of Periodic Safety Update Report
- Module 4 - Quality Management System at MAH
- Module 5 - Audits & Inspections of Pharmacovigilance System at MAH
- Module 6 - Submission of Risk Management Plan

PV ICH E2E Guidelines

EU Regulations

- New **pharmacovigilance legislation** (Regulation (EU) No 1235/2010 and Directive 2010/84/EU) was adopted by the European Parliament and European Council in December 2010.
- Accompanied by the **implementing regulation # 520/2012, a** legally binding act, published by the European Commission in **19 June 2012** that provides details on the operational aspects for the new legislation:
- Things have been changed from passive to proactive
- PV plan including risk management plan will now be a part of new drug applications
- A new set of guidelines (Good PV Practice) for the conduct of pharmacovigilance in the EU is under development.
- These guidelines are organised into 16 modules, the first seven GVP modules came into force on 2 July 2012

(GVP Modules, a Summary. Clinical Research Advisor sep 2012)

Pharmacovigilance System Master File

- A detailed description of the pharmacovigilance system used by the marketing authorisation holder with respect to one or more authorised medicinal products.
- To be maintained electronically.
- Not submitted along with mkting application
- Can be reviewed by authorities anytime
- Reduced documentation
- Will help do away with DDPS(Detailed Description Of Pharmacovigilance System) over time
- Tool for QPPV to
  - oversee and manage system
  - Ensure compliance with requirements
  - Identify risks and help mitigate them

Major elements of the PV master file:

- Lists products , route of authorisation of each product, presence on the market and indication of special monitoring measures
- Information about QPPV – job description, qualifications etc, contact details, backup arrangements and national contacts if present.
- Organisational structure and sites of PV activities, including third parties.
- Location, functionality and responsibility for computer systems.
- Contracts and agreements for key activities.
- Description of the key processes, data handling and records of the pharmacovigilance system
- Description of the quality system.
- Description of record keeping and archiving.
- Change log, Notification of significant changes as reqd.

http://www.ottosen.com/pharmacovigilancesystemsmasterfiles download dec12

Qualified Person for PV (QPPV)

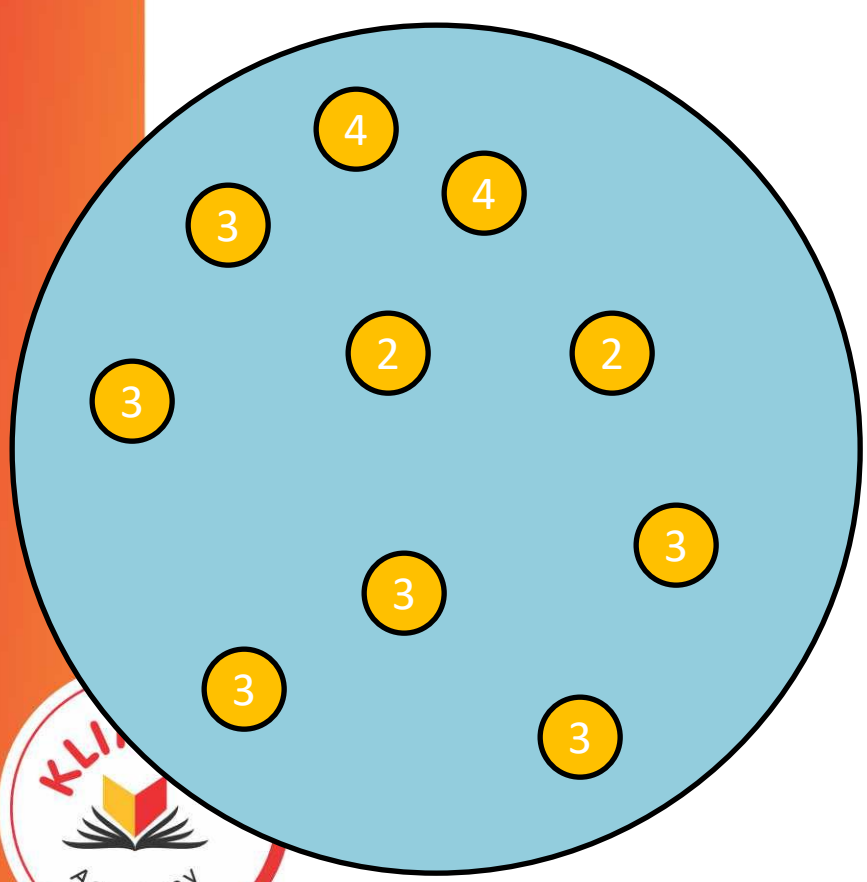
- Establishing and maintaining a pharmacovigilance system
- Preparing PV reports as defined by regulations
- Answering requests from Health Authorities
- Providing Health Authorities with any other information relevant to product safety
- Responsible for overall pharmacovigilance for all medicinal products of the company and specifically for:
- Having an overview of the safety profiles and any emerging safety concerns for the company's drugs
- Acting as a single contact point for the Health Authorities on a 24-hour basis

EU Guidance on PV

- Background :
- The decision to approve a drug is based on its having a satisfactory balance of benefits and risks within the conditions specified in the product labeling. This decision is based on the information available at the time of approval.

Example

New Drug with Benefit/Risk Ratio =4



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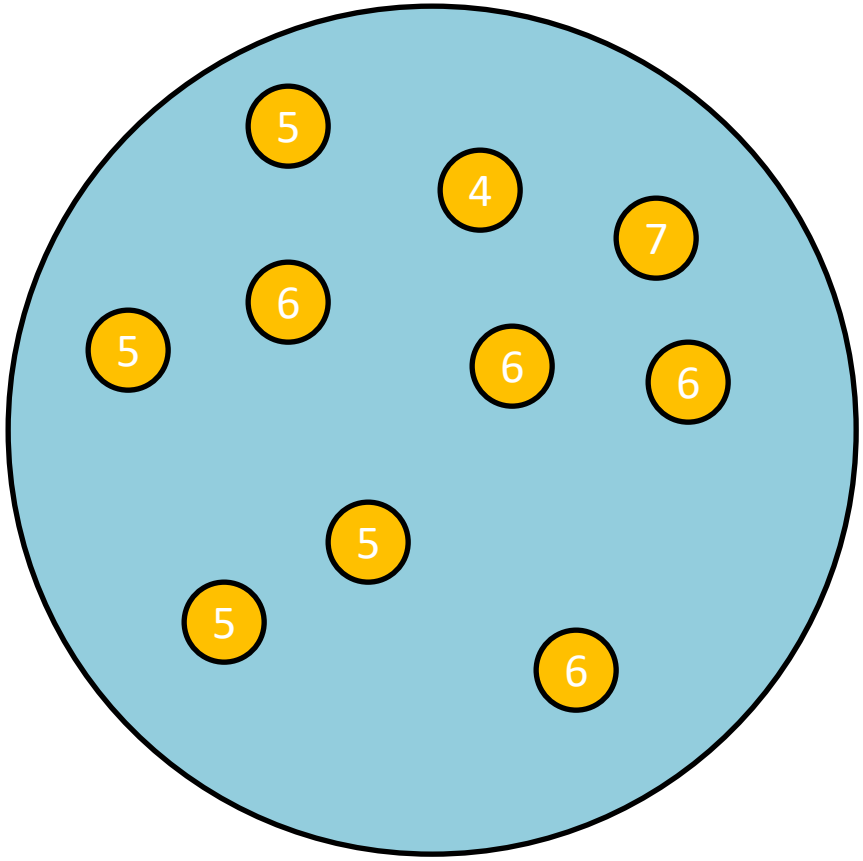


2010

Explanation

- A new Drug with a Benefit /Risk ratio of 4, was approvable in 1980, when most other drugs for the same indication in the market had a poorer B/R ratio.
- In 2010 when most drugs in the market have a ratio more than 4, the new drug with a ratio of 4 may not be approvable.

Post Marketing

- Once a product is marketed, new information will be generated, which can have an impact on the benefits or risks of the product; evaluation of this information should be a continuing process, in consultation with regulatory authorities
- The benefit-risk balance can be improved by reducing risks to patients through effective PV that can enable information feedback to the users of medicines in a timely manner.
- Also by curtailing the type of users to exclude those at high risk

Active Surveillance

- Active surveillance, in contrast to passive surveillance, seeks to ascertain completely the number of adverse events via a continuous pre-organised process.

- This may be achieved by selecting sites or particular adverse events.

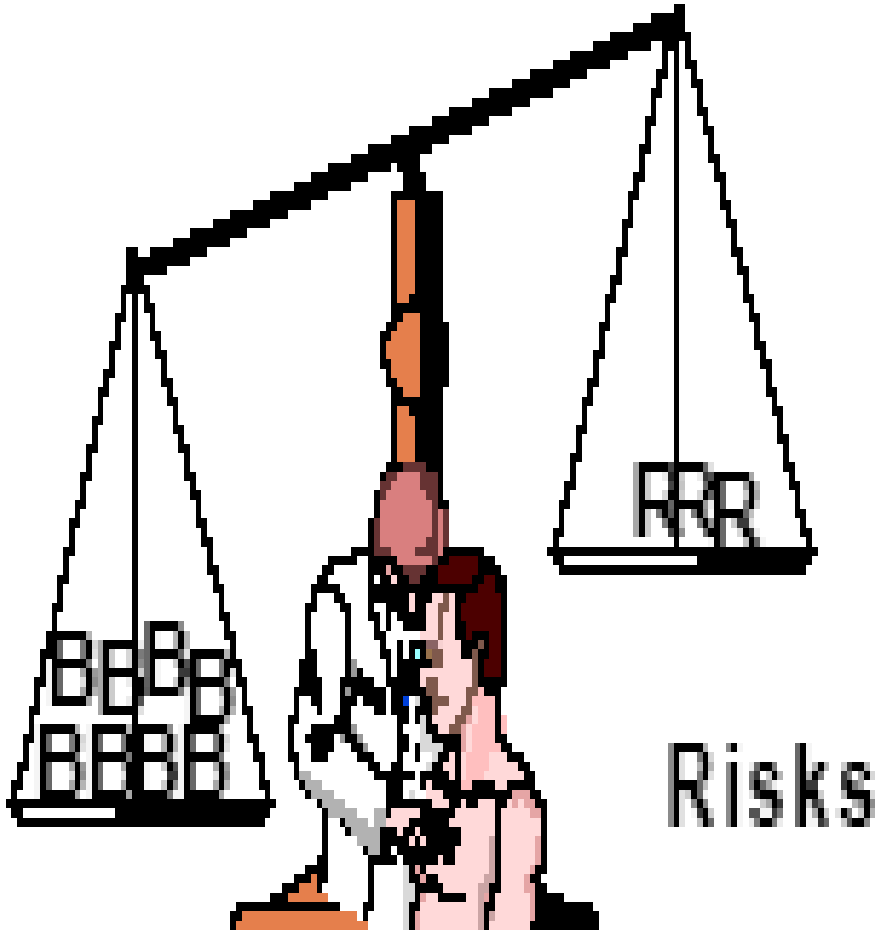
MODULE #	Module title (EU Good PV practice Modules)
I	Pharmacovigilance systems and their quality systems
II	Pharmacovigilance system mast file
III	Pharmacovigilance inspections
IV	Pharmacovigilance audits
V	Risk management systems
VI	Management and reporting of adverse reactions to medicinal products
VII	Periodic safety update report
VIII	Post-authorisation safety studies
IX	Signal management
X	Additional monitoring
XI	Public participation in pharmacovigilance
XII	Continuous pharmacovigilance, ongoing benefit-risk evaluation, regulatory action and planning of public communication
XIII	?? Incident management plan
XIV	International cooperation
XV	Safety communication
XVI	Risk minimisation measures: tools and effectiveness indicators

Why Manage Risk Proactively?

- Regulatory Expectation
  - US, Europe, ICH E2E
- Company Perspective
  - to understand the risk profile
  - to protect the company's asset
- Patient perception
  - expect safe and effective drugs
  - do not fully understand risks
- Need to change prescribing behaviour: labelling not always sufficient

Overall Objectives of Risk Management

Planning Benefit - Risk Optimization



Risk Management Definition

Risk Management

=

Risk Assessment

+

Risk Minimization

Risk Management Strategy

- Product Risk Management Plan

  Plan identifying the risks associated with a medicinal product, methods to further clarify the safety profile and ways to minimise risk to individual patients in clinical use

- Three elements

  Pharmacovigilance specification

  Pharmacovigilance Plan

  Risk Minimisation “toolkit”

Pharmacovigilance Specification

- A structured method of documenting the established risks of a drug and the potential for unidentified risks at the time of marketing authorisation

Risk Management Plan

Purpose

Assessing risks by focused evaluation to close gaps in knowledge systematically (PM commitments - continued development - targeted populations)

- looking for potential risks (class effects)

- following observed events

- characterizing outcomes that are mulifactorial

Advance planning and communication of evaluation for new products

Method

Integration of incremental data acquisition starting in development, systemizing postmarketing commitments and new indication projects for the newly released compound

Continued integration of all available data requires start at phase 1

Risk Minimisation activities

- Could be as simple as a direction to “shake well before use”
- Warnings, precautions, contraindications mentioned in the PI
- Gathering data about a potential risk and updating PI on an ongoing basis