Pharmacovigilance in India(PvPI), and EU regulations

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 new drugs and clin trials Rules 2019, 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 **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CDSCO Draft Guidance May 2011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

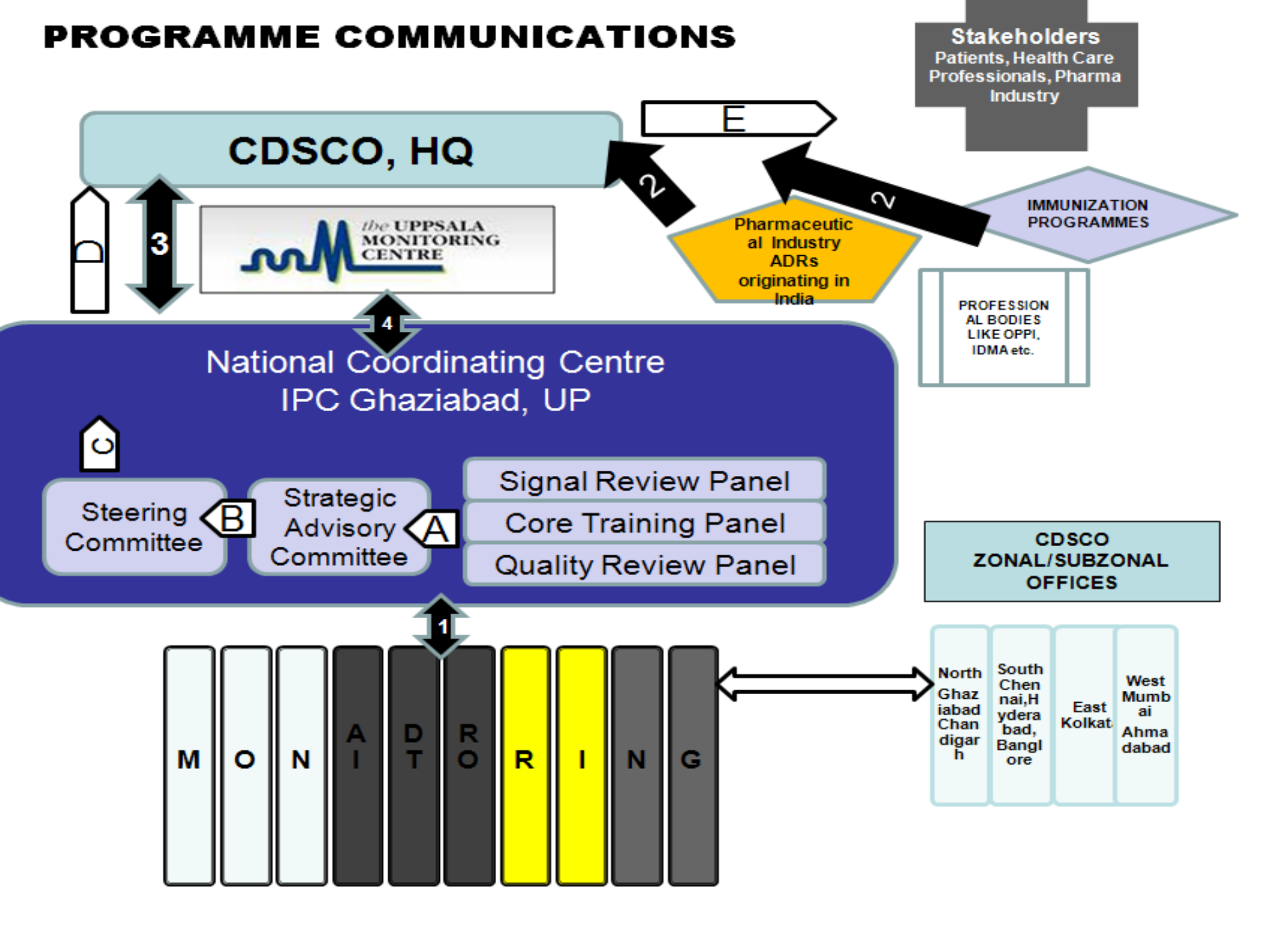
Objectives

- 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

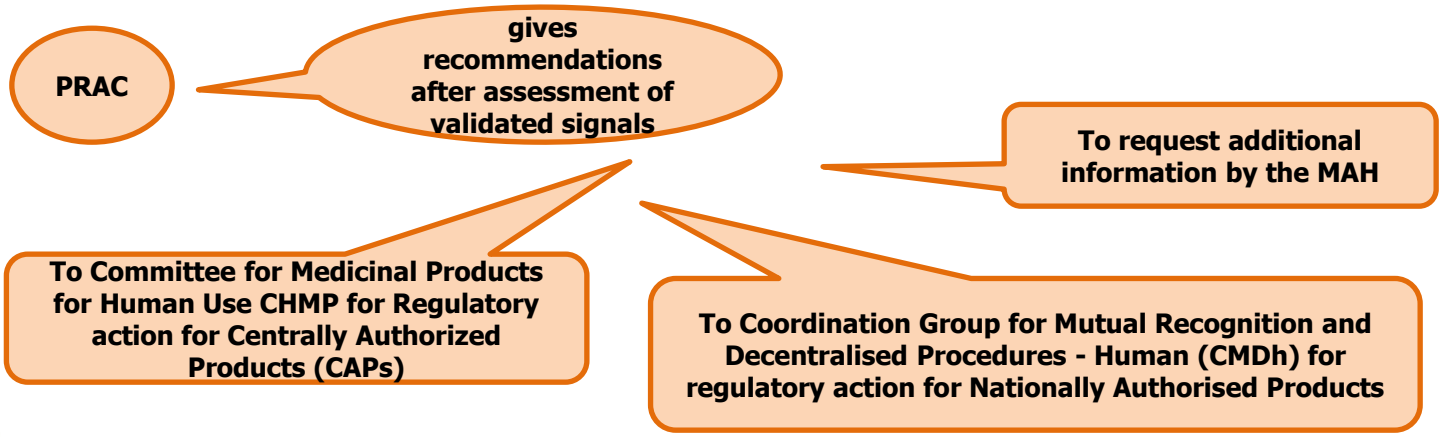
EU guidelines

European Medicines Agency (EMA)

- The EMA is a **decentralised agency of the EU**, responsible for the **scientific evaluation of medicines** developed by pharmaceutical companies **for use in the EU.** It began operating in 1995.
- EMA works in close co-operation with WHO.
- The EMA is the hub of a **European medicines network** comprising:
  - over 40 national regulatory authorities
  - the European Commission
  - the European Parliament
  - other decentralised EU agencies
- EMA approves products for marketing and supervises them across their lifecycle.
- It works through various committees
- For PV they have the PRAC (Pharmacovigilance Risk Assessment Committee)
- They also maintain **Eudravigilance**

EMA and PRAC

The Pharmacovigilance Risk Assessment Committee (PRAC) is the committee at the European Medicines Agency that is responsible for assessing and monitoring all safety issues for human medicines.



- PRAC members are nominated by EU Member States
- All members serve on the Committee for a period of three years which is renewable once.

EudraVigilance

- It is a data processing network and management system for reporting and evaluating suspected adverse reactions during the development and following the marketing authorizations of medical products in the European Economic Area (EEA).
- The first operating version was launched in December 2001.
- The system is in full compliance with the specifications of the ICH. It includes:
  - a fully automated safety and message processing mechanism using XML-based messaging;
  - a large reference pharmacovigilance database incorporating an extensive query and tracking and tracing capability.

EMA: Legislations

The legislations that touch most on Pharmacovigilance are as under:

- **Regulations:** Directly applicable and binding in all EU member states without the need for any additional national implementation legislation (unlike the use of the word *regulation* in the US).
- **Directives:** Bind the member states to the objectives of the legislation within a certain time period but allows each member state to create its own form of national law to achieve it.
- **Guidelines and opinions:** Non-binding and similar to FDA guidance.

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)

Good Pharmacovigilance Practices (GVP)

- Good pharmacovigilance practices (GVP) are a set of measures drawn up to facilitate the performance of pharmacovigilance in the EU.
- GVP apply to marketing-authorisation holders (MAHs), the EMA and EU Member States. They cover medicines authorised centrally as well as at national level.
- The guideline on GVP is divided into chapters that fall into two categories:
  - Modules covering major pharmacovigilance processes (GVP modules I to XVI)
  - Product- or population-specific considerations.

GVP Modules (1)

Module	Module Title	Summary
I	PV systems and quality systems	Guidance for the establishment and maintenance of quality assured pharmacovigilance systems for marketing authorization holders, competent authorities of Member States and the Agency.
II	Pharmacovigilance system master file	provides requirements for the pv system master file, including its maintenance, content and associated submissions to competent authorities, applicable from July 2012,
III	Pharmacovigilance inspections	planning, conduct, reporting and follow-up of pharmacovigilance inspections in the EU and outlines the role of the different parties involved.
IV	Pharmacovigilance audits	Guidance on planning and conducting the legally required audits, and in respect of the operation of the EU regulatory network,

GVP Modules (2)

Module	Module Title	Summary
V	Risk management systems	This module includes the principles of risk minimization, and details of routine risk minimization measures.
VI	Management and reporting of ARs	collection, data management and reporting of suspected adverse reactions (serious and non-serious) associated with medicinal products for human use
VII	Periodic safety update report	Guidance for PSURs which are pv documents intended to provide an evaluation of the risk-benefit balance of a medicinal product
VIII	Post-authorisation safety studies	Concerns PASS defined as any study relating to an approved product conducted with the aim of identifying, characterising or quantifying a safety hazard, confirming the safety profile, or of measuring the effectiveness of risk management measures.

GVP Modules (3)

Module	Module Title	Summary
VIII Addendum 1	Post-authorisation safety studies:	Member States requirements for transmission of information on non-interventional post-authorisation safety studies
IX	Signal Management	This module provide guidance and requirements on structures and processes involved in signal management.
X	Additional monitoring	general principles for assigning additional monitoring status to medicinal products and on communication and transparency aspects.
XV	Safety Communication	guidance to MA holders, competent authorities in Member States and the EMA on how to communicate and coordinate safety information in the EU.
XVI	Risk-minimisation measures	Selection of tools and effectiveness indicators

EU-QPPV

- QPPV(Qualified Person for Pharmacovigilance is an individual named by a pharmaceutical company as the main person responsible for ensuring that the company meets its legal obligations for the monitoring of the safety of the product on the market.

QPPV roles and responsibilities:

- Single point of contact for the authorities in member states and the agency on a 24-hr. basis and also for PV inspections. Shall reside in EU
- Is responsible for the overall functioning of the PV system including its quality system (e.g. SOPs, contractual arrangements, database operations, compliance data regarding quality, completeness and timeliness of expedited reporting and submission of periodic update reports, audit reports and training of personnel in relation to pharmacovigilance).

Responsible for ensuring conduct of pharmacovigilance and submission of all pharmacovigilance-related documents in accordance with the legal requirements and GVP

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

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

PV under US FDA

Food and Drug Administration (FDA)

The Food and Drug Administration (FDA) is an agency within the U.S. Department of Health and Human Services. The FDA has its headquarters at Silver Spring, Maryland and consists of offices and Centers.Founded in 1906

FDA’s Responsibilities

- FDA is mainly responsible for
  - protecting the public health by assuring the safety, effectiveness, quality, and security of human and veterinary drugs, vaccines and other biological products, and medical devices. The FDA is also responsible for the safety and security of most of our nation’s food supply, all cosmetics, dietary supplements and products that give off radiation. and
  - regulating tobacco products.
- FDA's responsibilities extend to the 50 United States, the District of Columbia, Puerto Rico, Guam, the Virgin Islands, American Samoa, and other U.S. territories and possessions
- Centre for Drug Evaluation and Research (CDER) has different requirements for the three main types of drug products: new drugs, generic drugs and over-the-counter drugs

FD&C Act & Title 21 of the Code of Federal Regulations

- **Title 21** of CFR governs food and drugs within the United States for the FDA, the Drug Enforcement Administration (DEA), and the Office of National Drug Control Policy (ONDCP)
- It is divided into three chapters-
  - Chapter I: Food and Drug Administration
  - Chapter II: Drug Enforcement Administration
  - Chapter III: Office of National Drug Control Policy

US FDA

Various Centers are: (like committees in EU)

- Center for Drug Evaluation and Research (CDER)
- Center for Biologics Evaluation and Research (CBER)
- Center for Devices and Radiological Health (CDRH)
- Center for Food Safety and Applied Nutrition
- Center for Tobacco Products
- Center for Veterinary Medicine
- National Center for Toxicological Research

Reporting System - MedWatch

- MedWatch is the FDA's reporting system for adverse events
  - **Purpose**: Detect safety hazard signals
- The MedWatch system collects reports of adverse reactions and quality problems (E.g.; All type of clinical and spontaneous reports and special scenarios like lack of effect, pregnancy, medication error)
- Healthcare professionals, Consumers, and Patients can report voluntarily
- Voluntary AE Reporting can be conducted in following ways:
  - Online, phone,
  - Mail,
  - Fax ,
  - MedWatch 3500 Form.

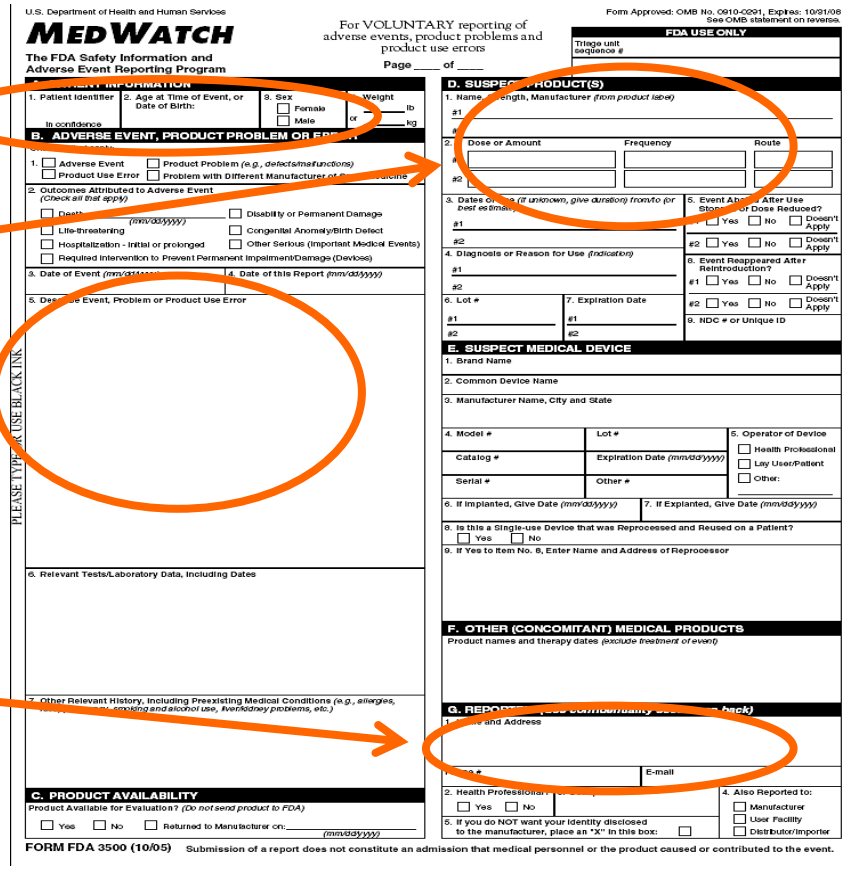
Reporting In to MedWatch - How to report

Patient

Product

Description of Event or Problem

Reporter



U.S. Department of Health and Human Services

MEDWATCH

The FDA Safety Information and Adverse Event Reporting Program

For VOLUNTARY reporting of adverse events, product problems and product use errors

Page ____ of ____

Form Approved: OMB No. 0910-0291, Expires: 10/31/08
See OMB statement on reverse.

FDA USE ONLY
Triage unit
Sequence #

A. PATIENT INFORMATION
1. Patient Identifier
2. Age at Time of Event, or Date of Birth:
3. Sex ☐ Female ☐ Male
Weight ____ lb or ____ kg
In confidence

B. ADVERSE EVENT, PRODUCT PROBLEM OR ERROR
1. ☐ Adverse Event ☐ Product Problem (e.g., defects/malfunctions)
☐ Product Use Error ☐ Problem with Different Manufacturer of Same Medicine
2. Outcomes Attributed to Adverse Event (Check all that apply)
☐ Death (mm/dd/yyyy)
☐ Disability or Permanent Damage
☐ Life-threatening
☐ Congenital Anomaly/Birth Defect
☐ Hospitalization - Initial or prolonged
☐ Other Serious (Important Medical Events)
☐ Required Intervention to Prevent Permanent Impairment/Damage (Devices)
3. Date of Event (mm/dd/yyyy)
4. Date of this Report (mm/dd/yyyy)
5. Describe Event, Problem or Product Use Error
6. Relevant Tests/Laboratory Data, Including Dates
7. Other Relevant History, Including Preexisting Medical Conditions (e.g., allergies, pregnancy, smoking and alcohol use, liver/kidney problems, etc.)

C. PRODUCT AVAILABILITY
Product Available for Evaluation? (Do not send product to FDA)
☐ Yes ☐ No ☐ Returned to Manufacturer on: (mm/dd/yyyy)

D. SUSPECT PRODUCT(S)
1. Name, Strength, Manufacturer (from product label)
#1
#2
2. Dose or Amount | Frequency | Route
#1
#2
3. Dates of Use (if unknown, give duration) from/to (or best estimate)
#1
#2
4. Diagnosis or Reason for Use (Indication)
#1
#2
5. Event Abated After Use Stopped or Dose Reduced?
#1 ☐ Yes ☐ No ☐ Doesn't Apply
#2 ☐ Yes ☐ No ☐ Doesn't Apply
6. Lot #
#1
#2
7. Expiration Date
#1
#2
8. Event Reappeared After Reintroduction?
#1 ☐ Yes ☐ No ☐ Doesn't Apply
#2 ☐ Yes ☐ No ☐ Doesn't Apply
9. NDC # or Unique ID

E. SUSPECT MEDICAL DEVICE
1. Brand Name
2. Common Device Name
3. Manufacturer Name, City and State
4. Model # | Lot # | Catalog # | Expiration Date (mm/dd/yyyy) | Serial # | Other #
5. Operator of Device ☐ Health Professional ☐ Lay User/Patient ☐ Other:
6. If Implanted, Give Date (mm/dd/yyyy)
7. If Explanted, Give Date (mm/dd/yyyy)
8. Is this a Single-use Device that was Reprocessed and Reused on a Patient? ☐ Yes ☐ No
9. If Yes to Item No. 8, Enter Name and Address of Reprocessor

F. OTHER (CONCOMITANT) MEDICAL PRODUCTS
Product names and therapy dates (exclude treatment of event)

G. REPORTER (Please Type or Use Black Ink)
1. Name and Address
Phone #
E-mail
2. Health Professional? ☐ Yes ☐ No
3. Occupation
4. Also Reported to: ☐ Manufacturer ☐ User Facility ☐ Distributor/Importer
5. If you do NOT want your identity disclosed to the manufacturer, place an "X" in this box: ☐

FORM FDA 3500 (10/05) Submission of a report does not constitute an admission that medical personnel or the product caused or contributed to the event.

Guidances on PV in USA

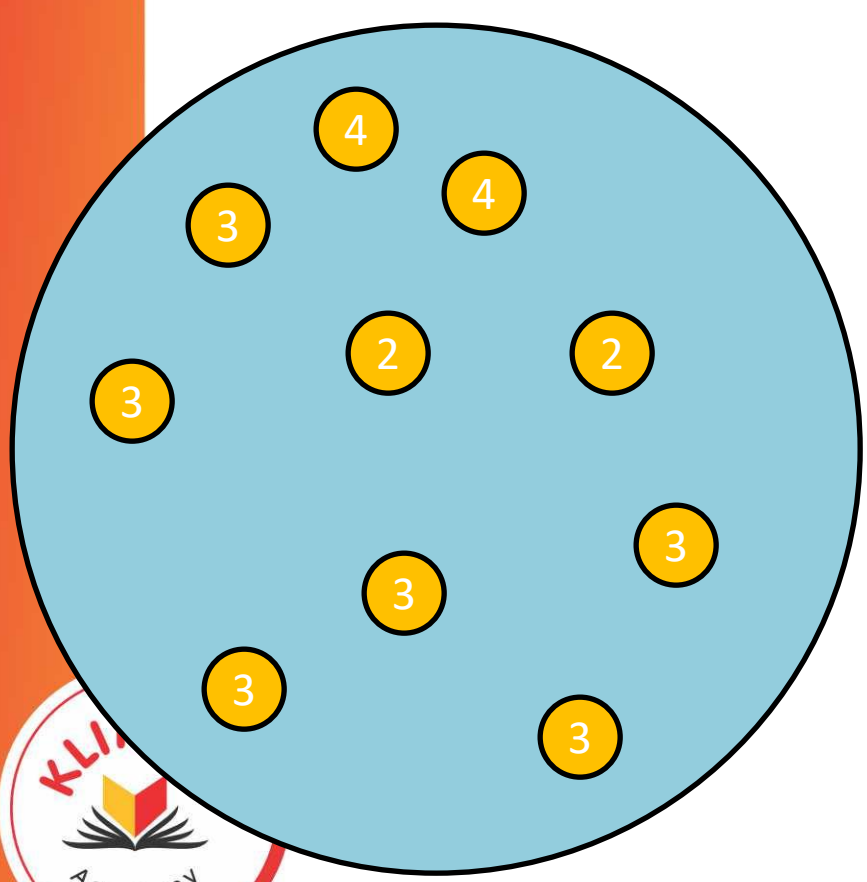
- As in other countries FDA also insists on reporting, analysis, risk management and risk minimisation. Some of its guidances are
- E2E – PV planning
- Risk Minimisation
- Good PV practice

EU Guidance on PV planning

- 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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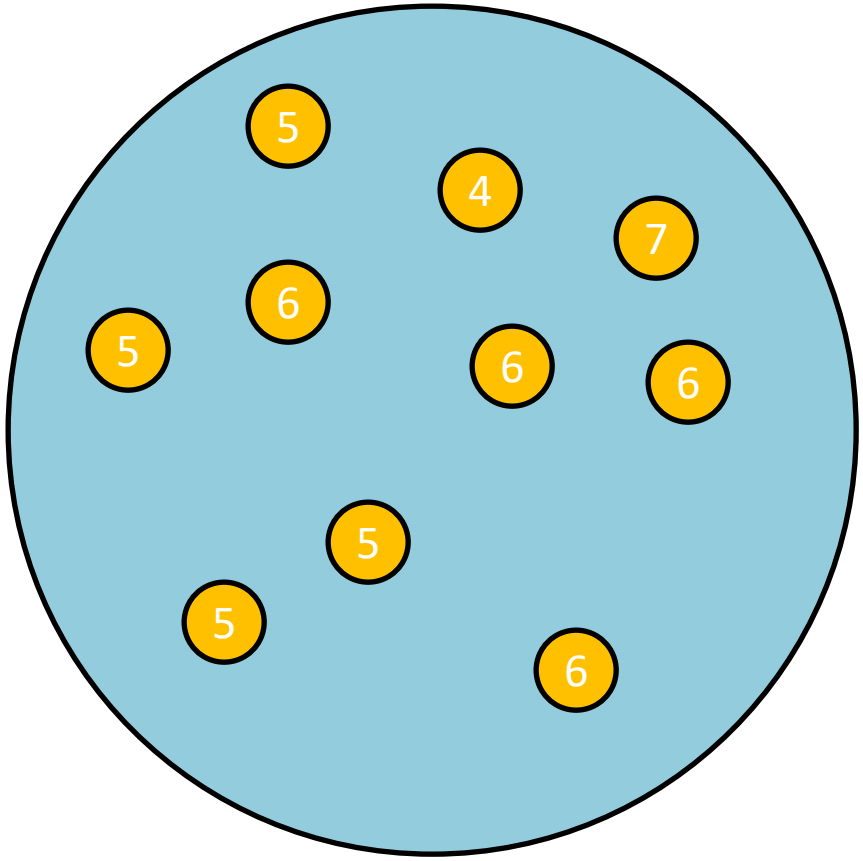


2010

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

ICH E_2E

PV planning as per E2E is divided into the following sections

- Safety Specification;
- Pharmacovigilance Plan;
- Pharmacovigilance Methods.

Safety specification

- Summary of the important identified risks of a drug, important potential risks, and important missing information, populations potentially at-risk (where the product is likely to be used), and outstanding safety questions which warrant further investigation
- Intended to help industry and regulators identify any need for specific data collection
- To facilitate the construction of the PV Plan

Elements of SS

- Non Clinical
  - Toxicity
  - General pharmacology (cardiovascular, including QT interval prolongation; nervous system; etc.);
  - Drug interactions;
  - Other toxicity-related information or data.
- Clinical
  - The extent of the world-wide exposure;
  - Any new or different safety issues identified;
  - Any regulatory actions related to safety.

Elements of SS

Possible risks in populations not studied

- Children;
- The elderly;
- Pregnant or lactating women;
- Patients with relevant co-morbidity such as hepatic or renal disorders;
- Patients with disease severity different from that studied in clinical trials;
- Sub-populations carrying known and relevant genetic polymorphism;
- Patients of different racial and/or ethnic origins.

Elements of SS

- Adverse Drug Effects
- Those observed in clinical studies
- Those not observed in clinical studies, but could be expected on the basis of class effects

Elements of SS

Drug Interactions

Drug-Drug Interactions

Drug Food Interactions

Drug environment interactions

Elements of SS

Epidemiology of the Indication

- Incidence, prevalence
- Gender
- Age groups at risk
- Racial or ethnic peculiarities

Principles of PV Plan

- Planning of pharmacovigilance activities throughout the product life-cycle;
- Science-based approach to risk documentation;
- Effective collaboration between regulators and industry;
- Applicability of the Pharmacovigilance Plan across the three ICH regions.
- Products yet to be marketed
  - Initiate plan well before making an NDA, dialogue with regulators.
- Products already in the market
  - Collect safety information and set up a pharmacovigilance plan if one is not in place

Routine PV Plan

- Systems and processes that ensure that information about all suspected adverse reactions that are reported are collected and collated in an accessible manner;
- The preparation of reports for regulatory authorities:
- Expedited adverse drug reaction (ADR) reports;
- Periodic Safety Update Reports (PSURs).
- Continuous monitoring of the safety profile of approved products including signal detection, issue evaluation, updating of labeling, and liaison with regulatory authorities;
- Other requirements, as defined by local regulations.

PV Methods

- Passive Surveillance
- Stimulated Reporting
- Active Surveillance
- Comparative Observational Studies
- Targeted Clinical Investigations
- Descriptive Studies.

Passive Surveillance

- Spontaneous Reports- Unsolicited communication by healthcare professionals or consumers to a company, regulatory authority or other organisation (e.g., WHO, Regional Centres, Poison Control Centre) that describes one or more ADRs in a patient who was given one or more medicinal products and that does not derive from a study or any organized data collection scheme
- Assist in identifying and quantitating risks
- Provide information on at risk groups, risk factors and clinical features of risks
- Often incomplete and underreported

Case Series

- A number of case reports on a single drug reporting similar adverse events are known as a case series.
- A case series often provides evidence of association between the drug and the adverse effect while helping in identifying the population at risk, and associated factors. It may be used for generating a hypothesis too!

Stimulated Reporting

- Reporting by health professionals who have been encouraged and facilitated to report adverse events.
- Generally refer to a particular setting (hospital or an epidemic) for a limited period of time(generally in the early marketing phase).

Active Surveillance

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

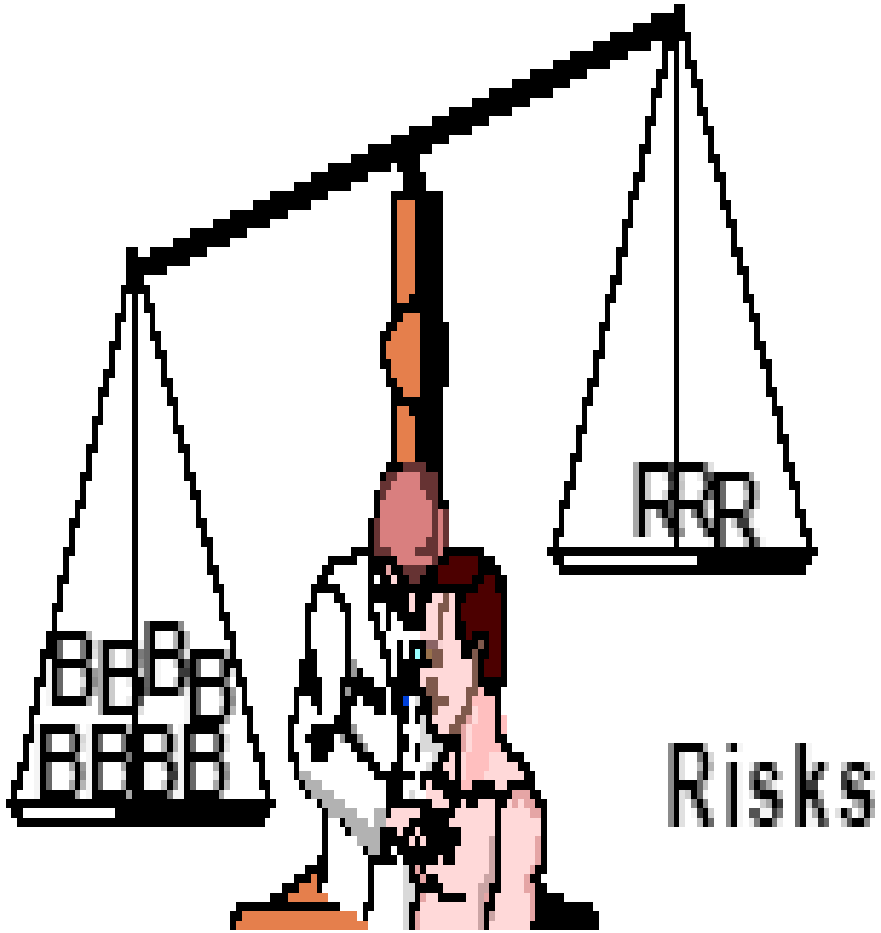
- This may be achieved by selecting sites or particular adverse events.

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”

Basic Components of a Risk Management Plan

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