Module 3: Regulatory Aspects of Pharmacovigilance

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

US FDA

- In **1912**, the law was changed to cover false and fraudulent claims made for drugs. However, the law did not mandate safety and, in effect, unsafe products could be and were marketed.
- In **1937**, a company in US marketed elixir of sulfanilamide, which contained diethylene glycol (similar to antifreeze). More than 100 people died from this product. Because the law did not require safety testing for drugs, the company had done none.
- As a result, the Federal Food, Drug and Cosmetic Act was passed into law in **1938** giving authority to the U.S. Food and Drug Administration (FDA) to oversee the safety of food, drugs, and cosmetics

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:

- 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.

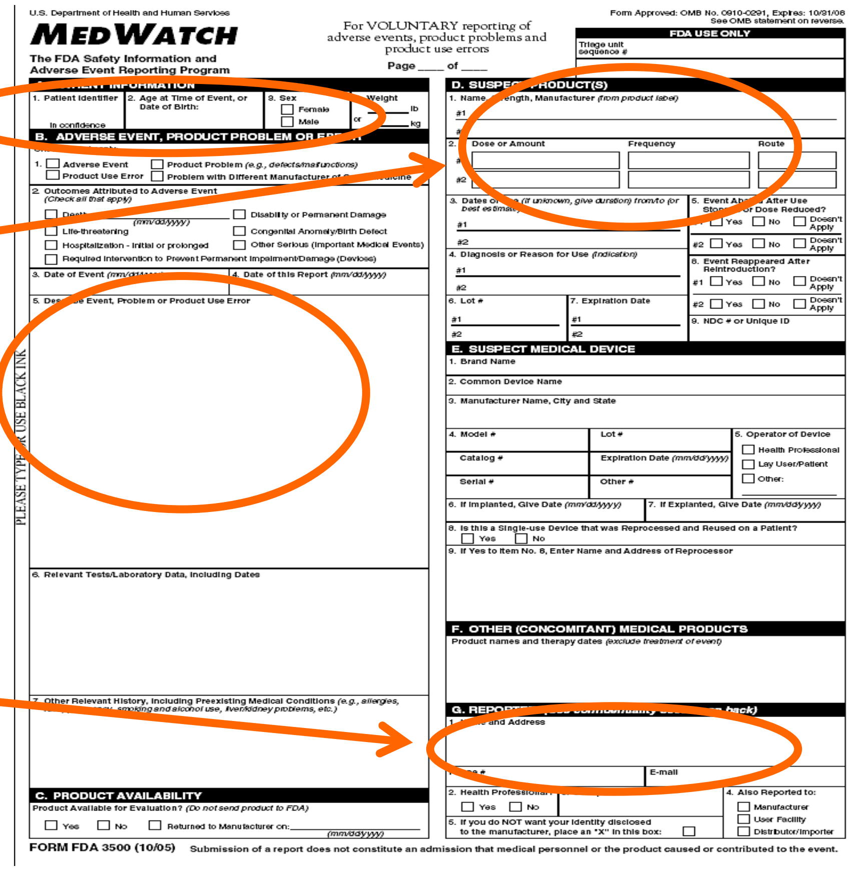
Reporting In to MedWatch - How to report

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 — In confidence
2. Age at Time of Event, or Date of Birth:
3. Sex — ☐ Female ☐ Male
4. Weight ____ lb or ____ kg

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, race, 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 (See confidentiality section on back)

1. Name and Address
Phone # | E-mail
2. Health Professional? ☐ Yes ☐ No
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: ☐

PLEASE TYPE OR USE BLACK INK

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.

European Medicines Agency (EMA)

The European Medicines Agency is a **decentralised agency of the European Union**, located in **London** responsible for the **scientific evaluation of medicines** developed by pharmaceutical companies **for use in the European Union.** It began operating in 1995.

EMA works in close co-operation with WHO and its procedure to protect and promote public and animal health through the evaluation and supervision of medicines throughout the European Union to provide a level of confidence that the product is safe and effective.

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

What does the EMA do?

Scientific Evalution for Marketing Authorization:

Most of the EMA's **scientific evaluation** work is carried out by its **scientific committees**, which are made up of members from European Economic Area (EEA) countries (Member States and EFTA), as well as representatives of patient, consumer and healthcare-professional organisations.

Safety monitoring of medicines: The EMA is responsible for coordinating the EU's safety-monitoring or 'pharmacovigilance' system for medicines

Pharmacovigilance Risk Assessment Committee (PRAC)

Provides recommendations on the safety of human medicines

The Committee for Medicinal Products for Veterinary Use (CVMP)

And its Pharmacovigilance Working Party deal with safety issues for veterinary medicines.

What does the EMA do? (Contd.)

Developing and Maintaining EudraVigilance:

EudraVigilance and **EudraVigilance Veterinary**, the EU reporting and data-storage systems for side-effect reports, and for supporting signal-identification activities in the EU, including coordinating the EU rapid-alert and incident-management systems for responses to new safety data.

Referrals:

An evaluation conducted by EMA committee following a referral from the European Commission or a Member State. Referrals are used to address particular issues, such as safety concerns, over the safety or benefit-risk balance of a medicine, to resolve disagreements between Member States on issues related to the authorisation of medicines or to give an opinion on an issue of Europe-wide interest.

Inspections:

The Agency is responsible for coordinating inspections requested by its committees in connection with the assessment of marketing-authorisation applications or referrals.

Source:http://www.ema.europa.eu/ema/index.jsp?curl=pages/about_us/general/general_content_000091.jsp&mid=WC0b01ac0580028a42

Marketing Authorisation process (Europe)

CTA: Clinical Trial Application is filed to the national competent authority (NCA) of the state to conduct the clinical trial within EU.

After the evaluation and approval of CTA, **Clinical Trials** are conducted.

Post phase I, Phase II and Phase III Clinical Trials, **Marketing Authorization Application (MAA**) is filed.

Marketing Authorization is granted post which **Phase IV/ PASS/PMS studies** are conducted.

Marketing Authorization Application (MAA)

Centralised Procedure (via the agency (EMA), which results in a single marketing authorisation valid throughout EU and EEA for 5 years, extension may be applied 3 months before expiry)

- Applications are submitted directly to the Agency
- Evaluation by the Agency's Scientific committees takes up to 210 active days plus 'clock stops', at the end of which the committee adopts an **opinion** on whether the medicine should be marketed or not.
- This opinion is then transmitted to the **European Commission,** which has the ultimate authority for granting marketing authorisations in the EU.
- When license is recommended, EPAR (European Public Assessment Report) is produced and MA is issued.

Nationalised Procedure (where individual EU Member States authorise medicines for use in their own **territory**)

- This type of authorization is granted on country-by-country basis by the **national competent authorities**, in each member state
- For medicines that fall outside the scope of the centralised procedure and intended for one market

For companies to get authorisation in more than one country

Decentralised Procedure (to obtain marketing authorizations in several member states for products with no previous MA in any of the member states) of EU

- An application is submitted to competent authorities of each of the member states where authorization is sought
- Quality/Efficacy/Safety/Administrative info along with the list of CMS (concerned Member states) and the member state to act as Reference Member state(RMS)
- **Draft Assessment report** on the medicinal product prepared and the **CMS and RMS validate the application** (14 days)
- RMS to prepare draft SmPC, labelling and package leaflet within 120 days which can be approved within 90 days

Mutual Recognition Procedure (to obtain marketing authorizations in multiple member states for products with previous MA in one of the member states of EU

- Application is evaluated by RMS (90 days instead of 120 days)
- After marketing authorization is granted, product may be marketed (Phase IV trials) where new uses or new populations, long term effects etc. can be explored.

Scientific Committees

Seven scientific committees, with members from all 31 states are as follows:

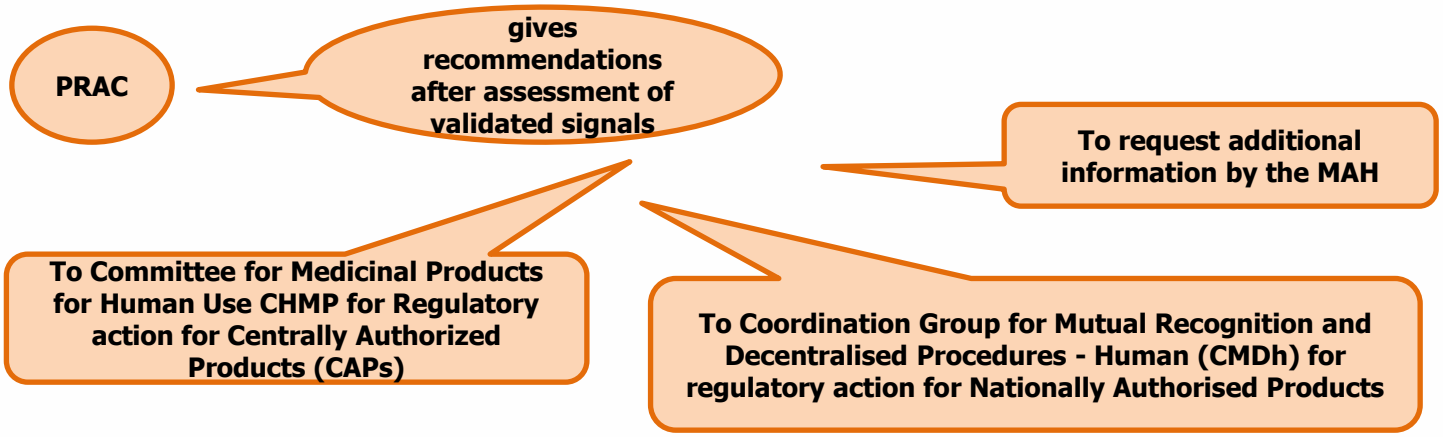
- **CHMP**: Committee for medicinal products for human use
- **PRAC**: Pharmacovigilance risk assessment committee
- **CVMP**: Committee for medical products for veterinary use:.
- **COMP**: Committee for orphan medical products: responsible for reviewing applications from people or companies seeking 'orphan-medicinal-product designation'.
- **HMPC**: Committee for herbal medical products:
- **PDCO**: Paediatric committee: To assess the content of paediatric investigation plans (PIPs) and adopt opinions on them.
- **CAT**: Committee for advanced therapies: for assessing the quality, safety and efficacy of gene therapy/somatic cell therapy/tissue-engineered/combined advanced-therapy medicines, and to follow scientific developments in the field.

CHMP

- In the '**centralised**' **procedure**, it is responsible for **initial assessment of medicines**
- Also responsible for several **post-authorisation and maintenance activities**, including the **assessment of any modifications or extensions ('variations**') to an existing marketing authorisation.
- In the '**mutual-recognition' and 'decentralised' procedures**, the CHMP arbitrates in cases where there is a disagreement between Member States
- Assessments are purely on scientific criteria and detrmine if the medicines meet Q/S/E requirements
- The CHMP can issue an 'urgent safety restriction' (USR) to inform healthcare professionals about changes as to how or in what circumstances the medication may be used
- The CHMP publishes a European public assessment report (EPAR) for every centrally authorised medicine that is granted a marketing authorisation
- Scientific assessment work conducted by the CHMP is subject to an internal peer-review system to safeguard the accuracy and validity of opinions reached by the Committee

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.

PRAC - Composition

The **Pharmacovigilance Risk Assessment Committee (PRAC)** is composed of:

- a chair and a vice chair, elected by serving PRAC members;
- one member and an alternate nominated by each of the 28 Member States;
- one member and an alternate nominated by Iceland and by Norway;
- six independent scientific experts nominated by the European Commission;
- one member and an alternate nominated by the European Commission after consultation of the European Parliament to represent healthcare professionals;
- one member and one alternate nominated by the European Commission after consultation of the European Parliament to represent patients organisations.

PRAC (Role)

- Responsible for **assessing all aspects of the risk management** of medicines for human use. This includes the **detection, assessment, minimisation and communication** relating to the risk of adverse reactions, while taking the therapeutic effect of the medicine into account.
- For the **design and evaluation of post-authorisation safety studies** and pharmacovigilance audit
- **To prepare recommendations on any questions relating to pv activities** related to a medicine for human use **and on risk-management systems**,.
- **Providing advice** either to the CHMP, CMDh, EMA Secretariat, Management Board and European Commission, as applicable.

The Pharmacovigilance Risk Assessment Committee (PRAC) meets once a month. The meetings of the PRAC are not public. The Agency publishes the agendas and minutes of the meetings. After each PRAC meeting, the Agency also publishes a table highlighting the main decisions taken in the meeting.

PRAC (Tasks)

PRAC tasks common to both centrally and non-centrally authorised products:

(i) For urgent Union procedures, Article 31 and Article 20 procedures triggered for safety reasons: the PRAC shall issue a recommendation.

(ii) For PSUR single assessment: the PRAC shall issue a recommendation.

(iii) For PASS protocols: issue a letter of endorsement or objection.

(iv) For PASS study results: the PRAC shall issue a recommendation.

(v) For signals: the PRAC shall issue a recommendation.

(vi) For establishment and subsequent **updating of the list of EU Reference Dates** (EURD) and the frequency of PSURs :shall be consulted.

(vii) For the **updating of the list of medicinal products requiring additional monitoring**: the PRAC shall be consulted.

(viii) For "for cause" pharmacovigilance inspections: shall issue an advice.

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.

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 their 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 detailed guidance regarding the requirements for the pv system master file, including its maintenance, content and associated submissions to competent authorities, applicable from July 2012,
III	Pharmacovigilance inspections	Guidance on the 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 authorised in the European Union (EU).
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 authorised medicinal product conducted with the aim of identifying, characterising or quantifying a safety hazard, confirming the safety profile of the medicinal product, 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	This module provides general principles for assigning additional monitoring status to medicinal products and on communication and transparency aspects.
XV	Safety Communication	This Module provides guidance to marketing authorisation holders, competent authorities in Member States and the European Medicines Agency on how to communicate and coordinate safety information in the EU.
XVI	Risk-minimisation measures	Selection of tools and effectiveness indicators

GPV - Product or Process-Specific Considerations

The chapters on product- or population-specific considerations are currently under development. They are being released for public consultation one by one. The first GVP considerations chapter (see below) was published in December 2013, i.e. GVP P I on pharmacovigilance for vaccines for prophylaxis against infectious diseases.

- Product- or population-specific considerations I: Vaccines for prophylaxis against infectious diseases
- Product- or population-specific considerations II (PII): Biological medicinal products.

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 NCAs in member states and the agency on a 24-hr. basis and also for PV inspections. Shall reside in EU or EEA
- 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

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.

Regulatory Authorities in the EU and EEA

• Austria	Austrian Agency for Health and Food Safety
• Belgium	Federal Agency for Medicines and Health Products (FAMHP)
• Bulgaria	Bulgarian Drug Agency
• Croatia	Agency for Medicinal Products and Medical Devices of Croatia
• Cyprus	Ministry of Health- Pharmaceutical Services
• Czech Republic	State Institute for Drug Control
• Denmark	Danish Health and Medicines Authority
• Estonia	State Agency of Medicines
• Finland	Finnish Medicines Agency (FIMEA)
• France	National Agency for the Safety of Medicine and Health Products

Source: http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/general/general_content_000155.jsp

Regulatory Authorities in the EU and EEA

- Germany Federal Institute for Drugs and Medical Devices (BfArM)
- Greece National Organization for Medicines
- Hungary National Institute of Pharmacy
- Iceland Icelandic Medicines Agency
- Ireland Irish Medicines Board
- Italy Italian Medicines Agency
- Latvia State Agency of Medicines
- Liechtenstein Office of Health/ Department of Pharmaceuticals
- Lithuania State Medicines Control Agency
- Luxembourg Ministry of Health
- Malta Medicines Authority

Source: http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/general/general_content_000155.jsp

Regulatory Authorities in the EU and EEA

• Netherlands	Medicines Evaluation Board
• Norway	Norewegian Medicines Agency
• Poland	Office for Registration of Medicinal Products, Medical Devices and Biocidal Products
• Portugal	National Authority of Medicines and Health Products
• Romania	National Medicines Agency
• Slovakia	State Institute for Drug Control
• Slovenia	Agency for Medicinal Products and Medical Devices of the Republic of Slovenia
• Spain	Spanish Agency for Medicines and Health Products
• Sweden	Medical Products Agency
• United Kingdom	Medicines and Healthcare Products Regulatory Agency (MHRA)

Brexit and UK PV

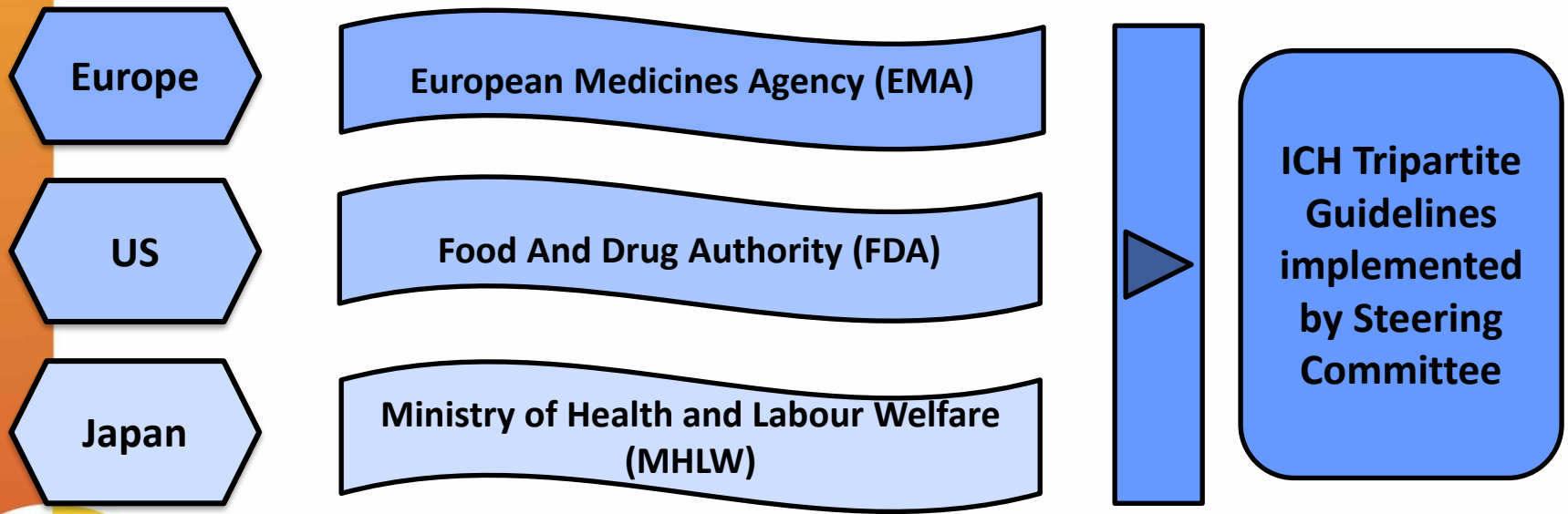
- The MHRA has a Brexit taskforce that has been and continues to take the time to look in detail at all areas of pharmaceutical legislation and take into account the needs of all stakeholders.
- Post-Brexit UK pharmacovigilance processes will be simpler than EU PV processes.
- The Brexit section of the MHRA website is titled ‘Making a success of Brexit’, and it has made it clear it is looking for the best options and opportunities available for the safe and effective regulation of medicines and devices in the UK post-Brexit.
- The existing EU rules will be converted into UK pharmacovigilance law at the moment of exit, with changes where necessary to make sure the rules work in the UK.
- The current PV legislation would remain in UK law as ‘secondary legislation’ and would be transferred into ‘primary legislation’ at a later date.

JAPAN - MHLW

- The Ministry of Health, Labor and Welfare is one of the cabinet level Ministries in the Japanese government
- This government body provides regulations on maximum residue limits for agricultural chemicals in foods, basic food and drug regulations, standards for foods, food additives, etc
- Japan – AE reporting system: **Institute for Safe Medication Practices (ISMP)**
  - Institute for Safe Medication Practices (ISMP) is a national, confidential medication error reporting system, that distributes hazard alerts and other medication safety information to 6,00,000 providers every other week.
  - **What is reported**: ISMP is a focused system for adverse drug events and hazards in medication delivery and management.
  - **Who reports**: Reports are accepted from HCPs, organizations or patients.
  - **How they report**: Reports from organizations or professionals can be submitted online, electronically, by telephone, mail or fax

ICH and the Regulatory Agencies/Bodies

International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) launched in 1990, is a unique undertaking that brings together the regulatory authorities of



and experts from the pharmaceutical industry in the three regions to discuss scientific and technical aspects of product registration.

International Conference on Harmonization (ICH)

- The **International Conference on Harmonization** of Technical Requirements for Registration of Pharmaceuticals for Human Use is a unique project that brings together the regulatory authorities of Europe, Japan and the USA and experts from the pharmaceutical industry in the three regions to discuss scientific and technical aspects of product registration
- To increase international harmonization of technical requirements to ensure that safe, effective, and high quality medicines are developed and registered in the most efficient and cost-effective manner
- ICH does not have "offices" as such because it is a voluntary cooperative effort of cosponsors from these three regions
- The ICH Secretariat is based in Geneva

International Conference on Harmonization (ICH)

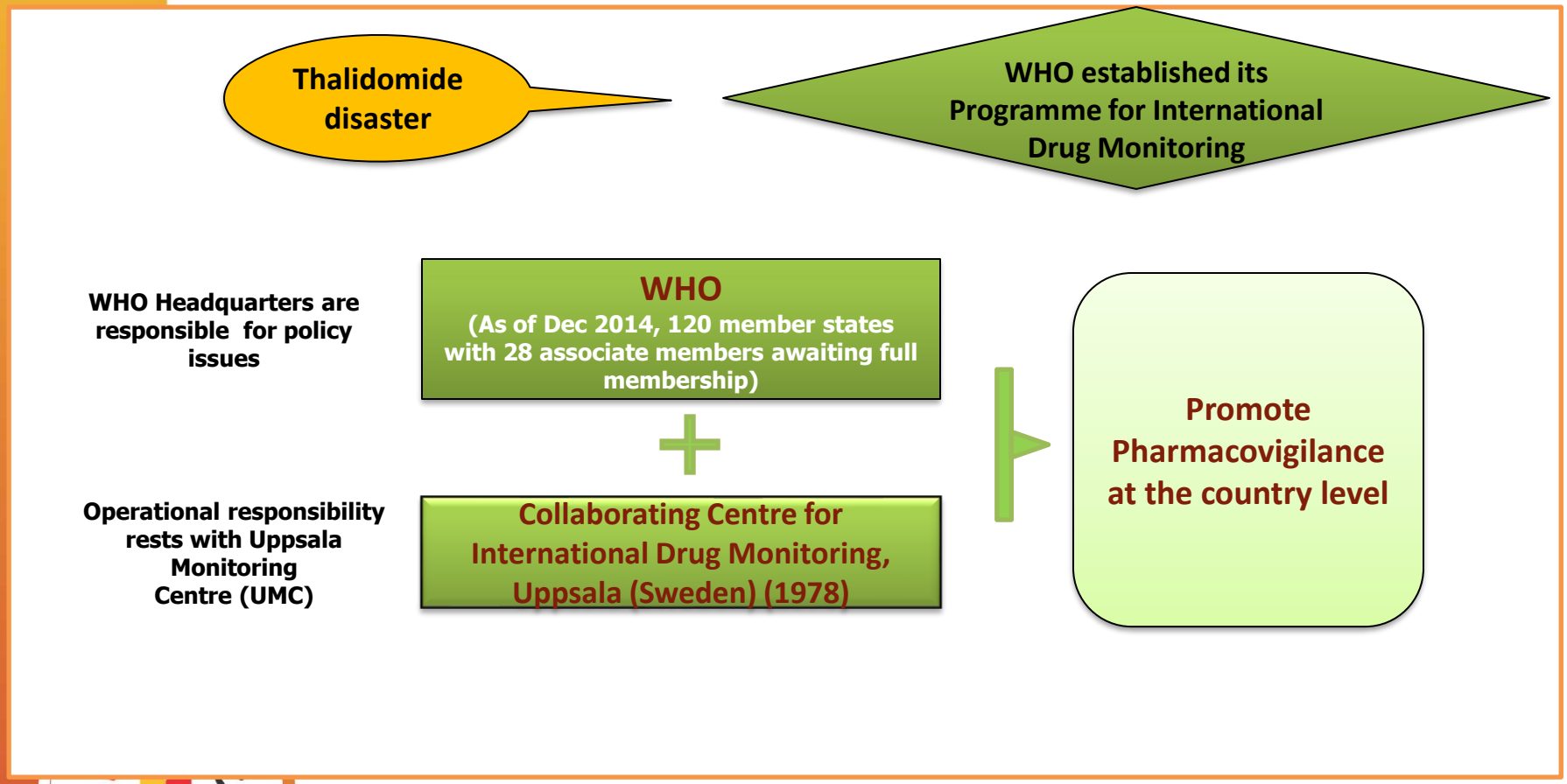
The ICH Topics are divided into four major categories and ICH Topic Codes are assigned according to these categories

- Quality: *Those relating to chemical and pharmaceutical Quality Assurance (Stability Testing, Impurity Testing, etc.)*
- Safety: Those relating to in vitro and in vivo pre-clinical studies (Carcinogenicity Testing, Genotoxicity Testing, etc.)
- Efficacy: *Those relating to clinical studies in human subject (Dose Response Studies, Good Clinical Practices, etc.)*
- Multidisciplinary: *Cross-cutting Topics which do not fit uniquely into one of the above categories (MedDRA, ESTRI, M3, CTD, M5)*

Important ICH Guidelines

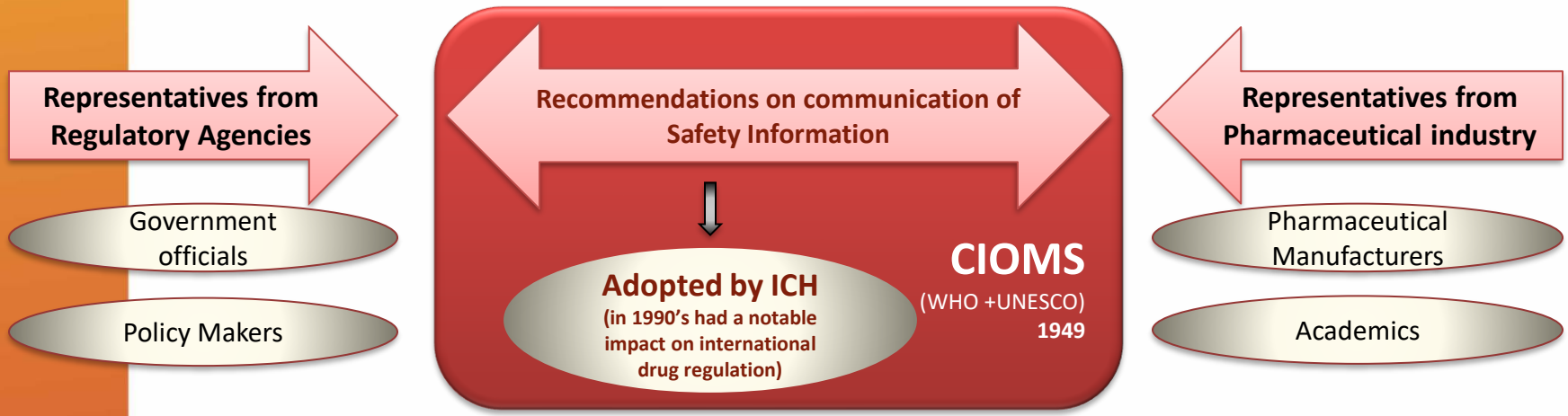
- **E2A:** Clinical safety data management: definitions and standards for expedited reporting
- **E2B (R3):** Clinical safety data management: Data Elements for Transmission of Individual Case Safety Reports
- **E2B(R3) IWG: Implementation:** Electronic Transmission of Individual Case Safety Reports
- **E2C (R2):** Periodic benefit-risk evaluation report
- **E2D:** Post-approval safety data management: definitions and standards for expedited reporting
- **E2E:** Pharmacovigilance planning
- **E2F:** Development safety update report
- **M1-MedDRA:** Medical Dictionary for Regulatory Activities
- **M8:** Electronic Common Technical Document (eCTD)

Role of WHO in PV



CIOMS

The Council for International Organizations of Medical Sciences (CIOMS) is a **nongovernmental and non-profit organization** established jointly by the **WHO and UNESCO in 1949**, with a mandate to collaborate with the United Nations and its specialized agencies.



CIOMS Programmes

To achieve its objectives, CIOMS has initiated and coordinates the following programmes:

- **Bioethics**
- **Health Policy, Ethics and Human Values**
- **Drug Development and Use (in collaboration with WHO)**

  - Safety Requirements for the Use of Drugs:

  Initiated in 1980s in the light of the benefits that society as a whole derives from modern drugs and vaccines

  -Assessment and Monitoring of Adverse Drug Reactions and Pharmacogenetics:

  CIOMS working groups have proposed recommendations within several areas

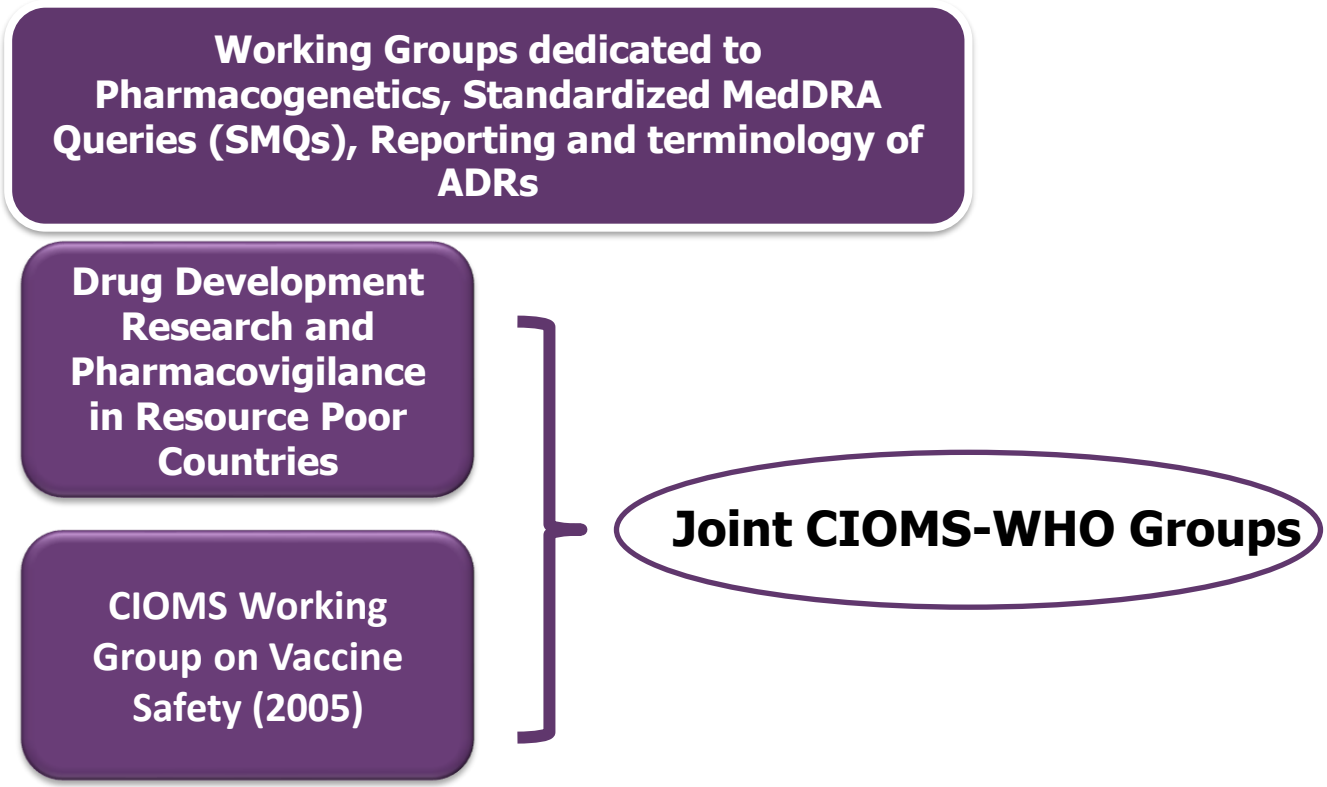
  International Nomenclature of Diseases

CIOMS Working Groups

In 1986, the Council for International Organizations of Medical Sciences (CIOMS), which since 1977 had functioned as a forum for discussion between international drug regulatory authorities and pharmaceutical companies, set up a working group on International Reporting of Adverse Drug Reactions to explore means of coordinating and standardizing the reporting of ADRs.

- I: CIOMS I form and international reporting of ADRs (1990)
- II: Periodic Safety Updates: PSURs, ICH-E2C, ICH-E2A (1992)
- III: Core clinical safety information on Drugs (1995) including New proposals for IB (1998-99)
- IV: Benefit Risk Balance for Marketed Drugs (1998)
- V: Current Challenges in PV (2001)
- VI: Management of Safety information from Clinical Trials (2005)
- VII: Development Safety Update Report (2006)
- VIII: Signal Detection (2010)
- IX: Toolkit for Medicinal Product Risk Management (April 2010)
- X: Applying good meta-analysis practices to clinical safety data (2011)

Other Working Groups



WEBSITE: http://www.cioms.ch/

PvPI India Pharmacovigilance Program

- The Central Drugs Standard Control Organization (CDSCO), Directorate General of Health Services under the aegis of Ministry of Health & Family Welfare, Government of India in *collaboration with Indian Pharmacopeia commission, Ghaziabad* is initiating a nation-
wide Pharmacovigilance programme for protecting the health of the patients by assuring drug safety. The programme shall be coordinated by the *Indian Pharmacopeia commission, Ghaziabad* as a National Coordinating Centre (NCC). The centre will operate under the supervision of a Steering Committee.

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

Goal

To ensure that the benefits of use of medicine outweighs the risks and thus safeguard the health of the Indian population.

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

- The Pharmacovigilance Programme of India will be administered and monitored by the following two committees:

I. Steering Committee

II. Strategic Advisory Committee

Support

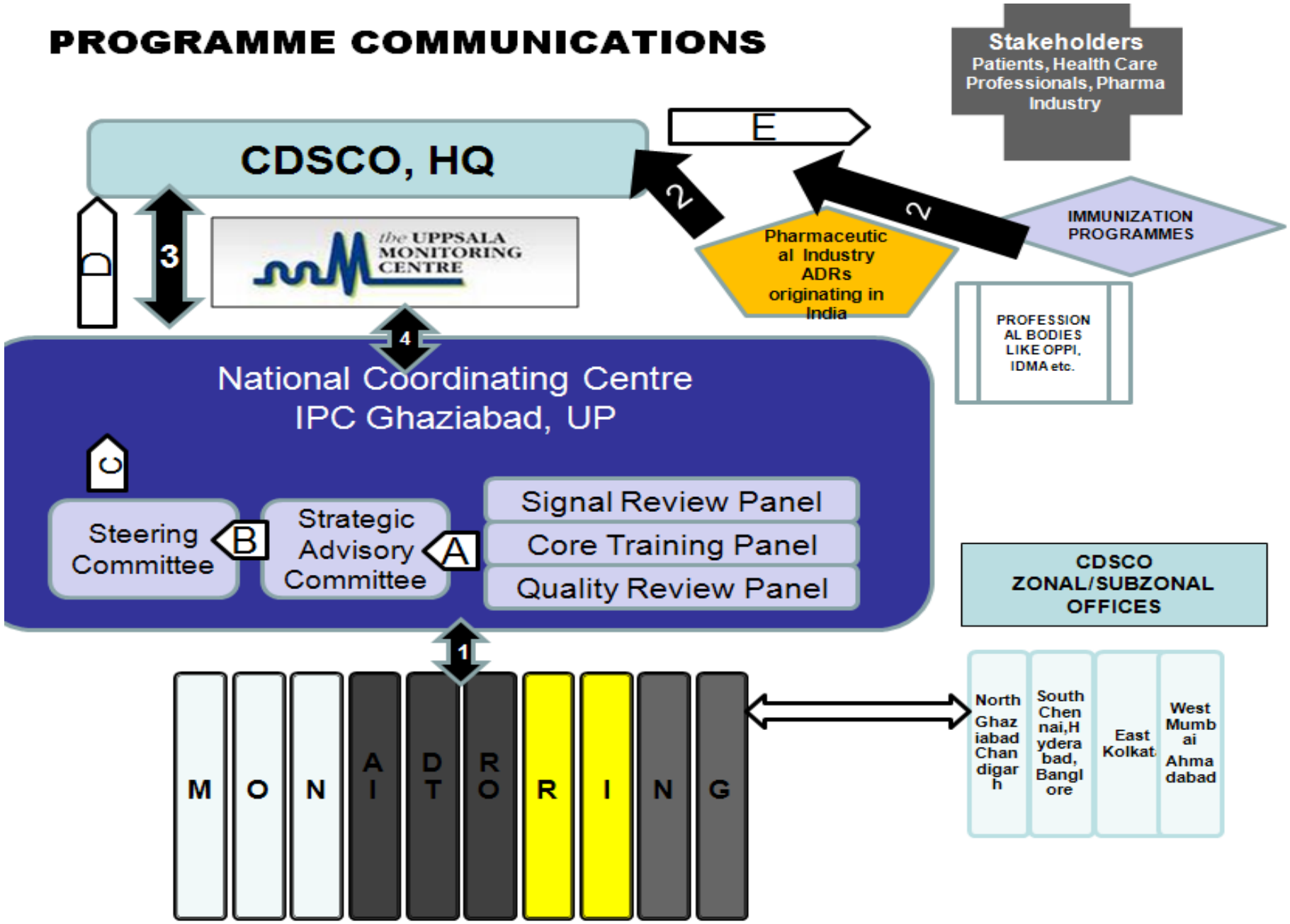
- Technical support will be provided by the following committees:

I. Signal Review Panel

II. Core Training Panel

III. Quality Review Panel

PROGRAMME COMMUNICATIONS



ADR Monitoring Centers

- MCI Approved Medical Colleges & Hospitals
- Private Hospitals
- Public Health Programmes
- Autonomous Institutes (ICMR etc.)

Collaboration with WHO & UMC

- WHO and UMC work with and/or provide technical support to more than 94 countries worldwide. The long term objective of the PvPI is to establish a **'Centre of Excellence'** for Pharmacovigilance in India. To achieve this objective, the PvPI National Coordinating Centre will collaborate with the WHO Collaborating Centre - Uppsala Monitoring Centre (UMC) based in Sweden.

Collaboration

- 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)

Collaboration

- Technical collaboration
  for Pharmacovigilance Programme of India
- Technical collaboration for a regular publication that will be issued by the PvPI National Coordinating Centre for distribution to the ADR Monitoring centers and other stakeholders.
- CDSCO Headquarters has held several meetings with UMC over the past few years to discuss the potential role and approach for technical collaboration.

SOPS

I. Roles and responsibilities of different personnel in PvPI
II. Training of programme personnel (including post training assessments & certifications)
III. Centre management (including infrastructure, manpower, status reports)
IV. Processing and reporting of suspected adverse drug reactions
V. Compliance and quality assurance in the programme
VI. Regulatory decision making
VII. Communication amongst various stakeholders

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

Zonal PV Centres

- Provide procurement, financial and administrative support to ADR monitoring centers
- Report to 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

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.

Risk Management

- Ensure availability and management of funds
- Conduct frequent training and awareness of Pharmacovigilance
- Detect and respond to under reporting of Adverse Drug Reactions
- Ensure quality of filled ADR forms
- Proper supervision of functioning of the centers
- Feed back to the Health Care Professionals

SUSPECTED ADVERSE DRUG REACTION REPORTING FORM

For VOLUNTARY reporting of Adverse Drug Reactions by healthcare professionals

CDSCO
Central Drugs Standard Control Organization
Directorate General of Health Services,
Ministry of Health & Family Welfare, Government of India,
FDA Bhavan, ITO, Kotla Road, New Delhi
www.cdsco.nic.in

(AMC/NCC Use only)
AMC Report No.
Worldwide Unique no.

A. Patient Information

1. Patient Initials _____

2. Age at time of Event or date of birth
---

3. Sex ☐ M ☐ F

4. Weight ____Kgs

B. Suspected Adverse Reaction

5. Date of reaction stated (dd/mm/yyyy)

6. Date of recovery (dd/mm/yyyy)

7. Describe reaction or problem

12. Relevant tests / laboratory data with dates

13. Other relevant history including pre-existing medical conditions (e.g. allergies, race, pregnancy, smoking, alcohol use, hepatic/ renal dysfunction etc)

14. Seriousness of the reaction

- ☐ Death (dd/mm/yyy)____
- ☐ Life threatening
- ☐ Hospitalization-initial or prolonged
- ☐ Disability
- ☐ Congenital anomaly
- ☐ Required intervention to prevent permanent impairment / damage
- ☐ Other (specify)

15. Outcomes

- ☐ Fatal
- ☐ Continuing
- ☐ Recovering
- ☐ Recovered
- ☐ Unknown
- ☐ Other (specify)____

C. Suspected medication(s)

S.No	8. Name (brand and /or generic name)	Manufacturer (if known)	Batch No./ Lot No. (if known)	Exp. Date (if known)	Dose used	Route used	Frequency	Therapy dates (if known give duration)		Reason for use of prescribed for
								Date started	Date stopped	
i.										
ii.										
iii.										
iv.										

Sl.No As per C	9. Reaction abated after drug stopped or dose reduced					10. Reaction reappeared after reintroduction				
	Yes	No	Unknown	NA	Reduced dose	Yes	No	Unknown	NA	If reintroduced dose
i.										
ii.										
iii.										
iv.										

11. Concomitant medical product including self medication and herbal remedies with therapy dates (exclude those used to treat reaction)

D. Reporter (see confidentiality section in first page)

16. Name and Professional Address :_____

_____

Pin code : _____ E-mail _____

Tel. No. (with STD code): _____

Occupation _____ Signature _____

17. Causality Assessment	18. Date of this report (dd/mm/yyyy)

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

Conclusions

The stronger the national system of pharmacovigilance and ADR reporting, the more likely it is that reasonable regulatory decisions will be made for the early release of new drugs with the promise of therapeutic advances.

Legislation governing the regulatory process in most countries allows for conditions to be placed on approvals, such as a requirement that there should be detailed pharmacovigilance in the early years after a drug's release.