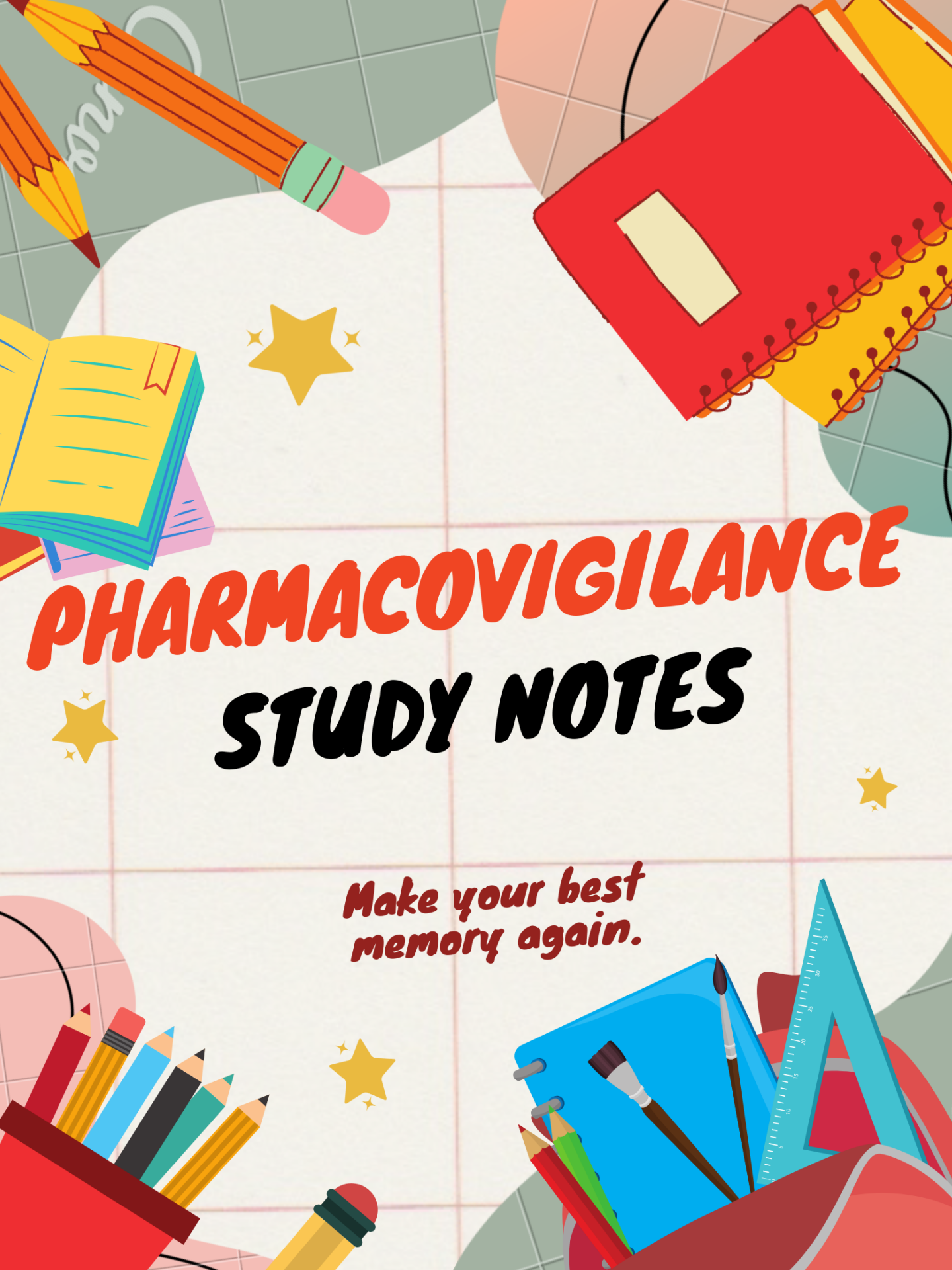

PHARMACOVIGILANCE
STUDY NOTES
Make your best
memory again.

Contents:

[A] Drug and disease classification –

- Anatomical, Therapeutic and Chemical Classification of Drugs (ATC)
  - In the ATC system the active substance is divided into different groups according to the organ or system on which they act and their therapeutic, Pharmacological and chemical properties.

➢ ATC / DDD Methodology

- Drug utilization research uses the Anatomical Therapeutic Chemical (ATC) as the classification system and Defined Daily Dose (DDD) as a unit of measure.

- DDD is the assumed average maintenance dose per day for a drug used for its main indication in adults.
- The methodology is endorsed by WHO and is recommended as the international standard for drug utilisation monitoring and research.

➢ Why ATC/DDD ?

- ATC/DDD methodology facilitates the presentation and comparison of drug consumption statistics at international, national and regional levels despite differences in nomenclature (both branded & generic), packing sizes, pricing and customary dosages.
- This methodology is useful for valid presentation & comparison of drug utilization within and across countries to support better outcomes & quality use of medicines.

➢ **General Principles for ATC Classification**

- Drugs are classified based on their main therapeutic use
- Only one ATC code for each ROA (route of administration).
- Several ATC code: if clearly different therapeutic uses reflected in different
  - Routes of administration (e.g. topical, systemic)
  - Strengths

➢ **ATC Groups**

In the Anatomical Therapeutic Chemical (ATC) classification system, the active substances are divided into different groups according to the organ or system on which they act and their therapeutic, pharmacological and chemical properties.

Drugs are classified in groups at five different levels.

1. **ATC 1st level**
   - The system has **fourteen main anatomical or pharmacological groups** (1st level). The ATC 1st levels are shown in the figure.
2. **ATC 2nd level**
   - Pharmacological or Therapeutic subgroup
3. **ATC 3rd & 4th levels**
   - **Chemical, Pharmacological or Therapeutic subgroup**
4. **ATC 5th level**
   - **Chemical substance**

The 2nd, 3rd and 4th levels are often used to identify **pharmacological subgroups** when that is considered more appropriate than **therapeutic or chemical subgroups**.

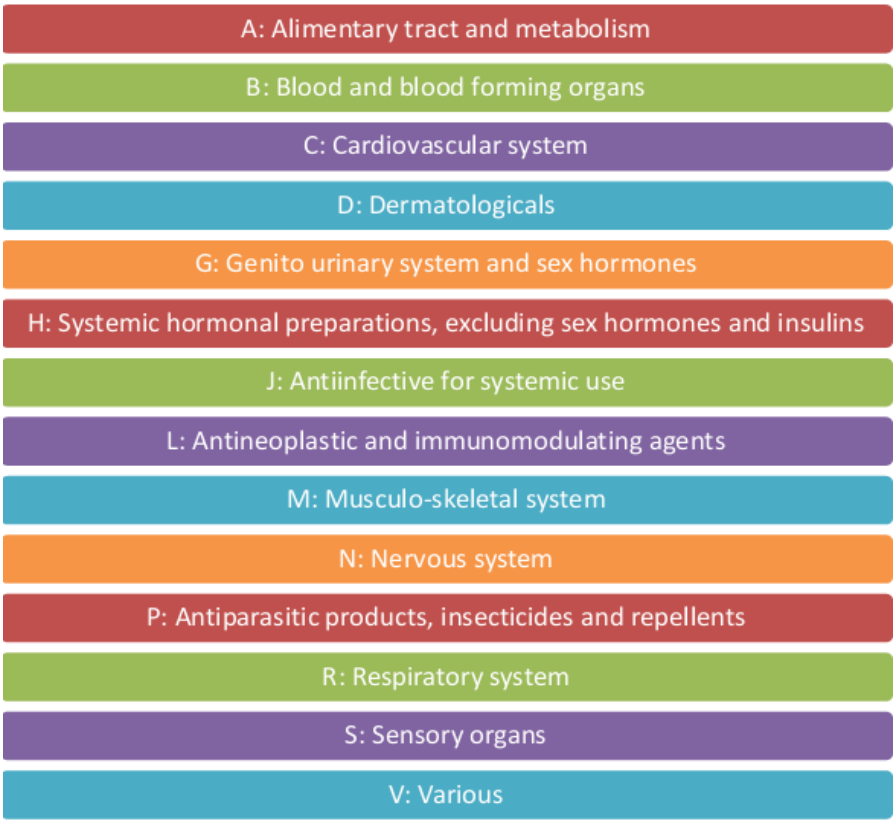


Figure : Coding of drugs based on their anatomical groups

Table : Coding of drugs based on their anatomical groups

Code	*Contents*
A	Alimentary tract and metabolism
B	Blood and blood forming organs
C	Cardiovascular system
D	Dermatologicals
G	Genito-urinary system and sex hormones
H	Systemic hormonal preparations, excluding sex hormones and insulins
J	Antiinfectives for systemic use
L	Antineoplastic and immunomodulating agents
M	Musculo-skeletal system
N	Nervous system
P	Antiparasitic products, insecticides and repellents
R	Respiratory system
S	Sensory organs
V	Various

The complete classification of metformin illustrates the structure of the code:

A	**Alimentary tract and metabolism (1st level, anatomical main group)**
A10	**Drugs used in diabetes (2nd level, therapeutic subgroup)**
A10B	**Blood glucose lowering drugs, excl. insulins (3rd level, pharmacological subgroup)**
A10BA	**Biguanides (4th level, chemical subgroup)**
A10BA02	**metformin (5th level, chemical substance)**

(ATC, https://www.who.int/medicines/regulation/medicines-safety/toolkit_atc/en/Accessed on 25/04/2020)

Thus, in the ATC system all plain metformin preparations are given the code A10BA02. For the chemical substance, the International Nonproprietary Name (INN) is preferred. If INN names are not assigned, USAN (United States Adopted Name) or BAN (British Approved Name) names are usually chosen. The coding is important for obtaining accurate information in epidemiological studies. The five different levels allow comparisons to be made at various levels according to the purpose of the study.

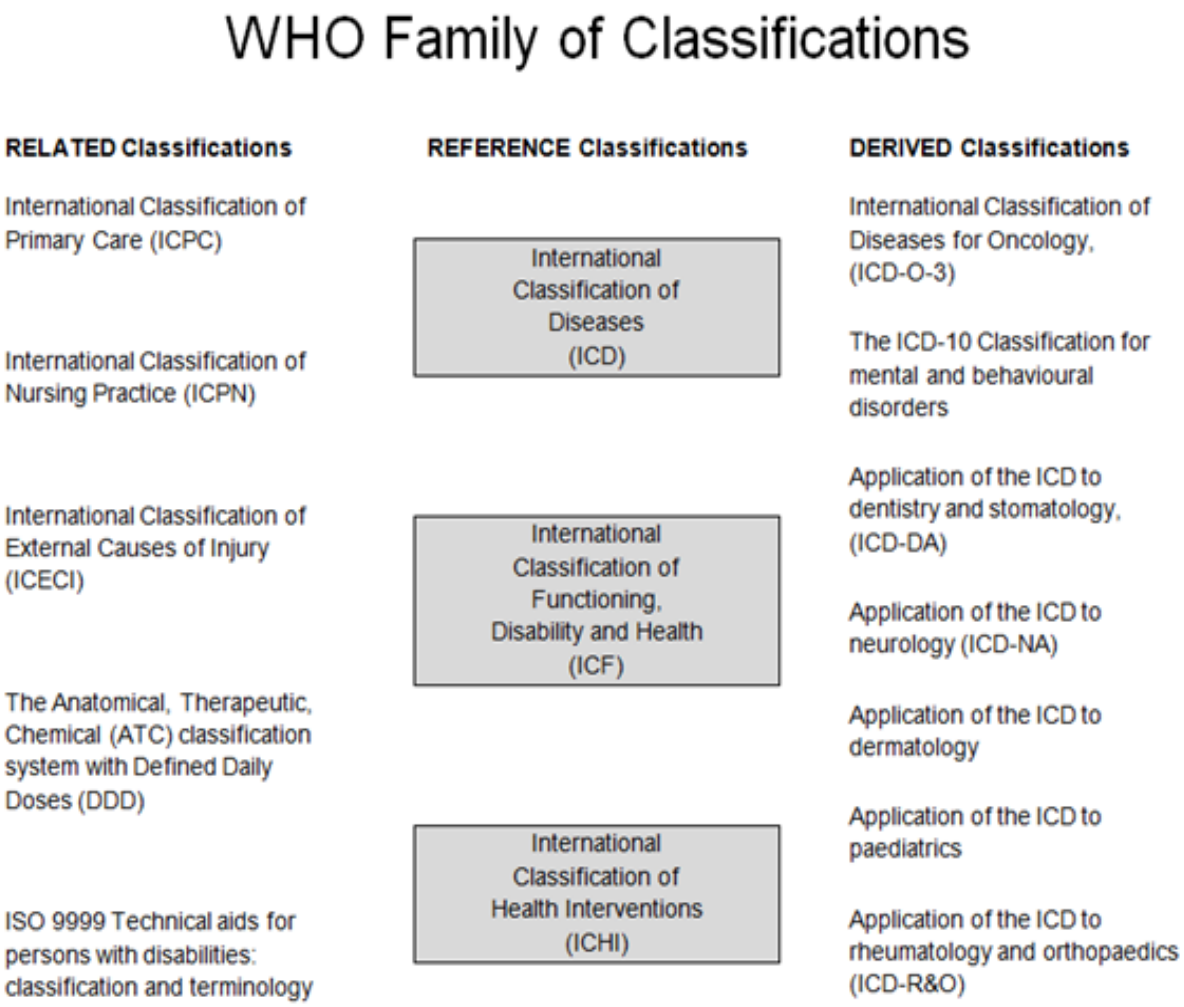
Applications of ATC/DDD

(https://www.who.int/medicines/regulation/medicines-safety/toolkit_atc/en/Accessed on 25/04/2020)

International Classification of Diseases

The **ICD** is originally designed as a health care **classification system**, providing a **system** of diagnostic codes for classifying diseases, including nuanced **classifications** of a wide variety of signs, symptoms, abnormal findings, complaints, social circumstances, and external causes of injury or disease.

Classification of Diseases



(https://www.dimdi.de/dynamic/en/classifications/icd/icd-10-who/history/family/accessed;25/04/2020

Importance of ICD

The ICD is **important** because it provides a common language for reporting and monitoring **diseases**. This allows the world to compare and share data in a consistent and standard way- between hospitals, regions and countries and over periods of time.

History of ICD

- In 1860, *Floresence Nightingale,* made 1st model of systemic collection of hospital data.
- In 1893, French Physician *Jacques Bertillon* introduced bertillon classification of cause of death.
- In 1898, American public health association recommended revision of ICD system every 10 years
- The revision followed minor changes untill 6th version of ICD, morbidity & mortality conditions and section on mental disorders
- WHO has responsibility of preparing & publishing the ICD revision every 10 years.

Who uses ICD ?

1. Users include physicians, nurses, other providers, researchers, health information managers and coders, health information technology workers, policy-makers, insurers and patient organizations.
2. ICD has been translated into 43 languages and it is being used by all member States. Most countries (117) use the system to report mortality data, a primary indicator of health status.
3. All Member States are expected to use the most current version of the ICD for reporting death and disease statistics (according to the WHO

Nomenclature Regulations adopted by the World Health Assembly in 1967).

International Non Proprietary Names for Drugs (INN)

INN facilitates the identification of pharmaceutical substances or active pharmaceutical ingredient. Each INN is a unique name that is globally recognized & is public property. **A nonproprietary name is also called generic name.**

It provides clear identification, safe prescription and dispensing of medicines to patients. It is also important for the communication and exchange of information among health professionals worldwide.

History of INN

- The system was established in 1950 by World Health Assembly and the first list of International Nonproprietary Names for pharmaceutical substances was published in 1953.
- The cumulative list of INN now stands at some 7000 names designated since that time, and thus number is growing every year by 120-150 new INN.

Uses of INN

Nonproprietary names are intended for use in pharmacopoeias, labeling, product information, advertising and other promotional material, drug regulation and scientific literature and as a basis for product names.

[B] Drug dictionaries and coding in pharmacovigilance

What is **MedDRA**?

Med=Medical

D=Dictionary

R=Regulatory

A=Activities

Definition:

- The MedDRA is a **medical terminology used to classify adverse event information associated with the use of biopharmaceuticals and other medical products (e.g. medical devices and vaccines).**
- It is used to classify the adverse drug events (ADEs) data from clinical trials, spontaneous adverse event reports by healthcare professionals, patients and others; and from other sources of the ADEs.

MedDRA has been developed by an ICH Working Group to provide:

- **An international, multi-lingual, medical terminology** ‰
  - Medical personnel can code ADR data in their native language
  - Safer – less likely to miscode data
- Standardized communication between regulators and industry/spponsors of clinical trials‰
  - Within regions and between regions

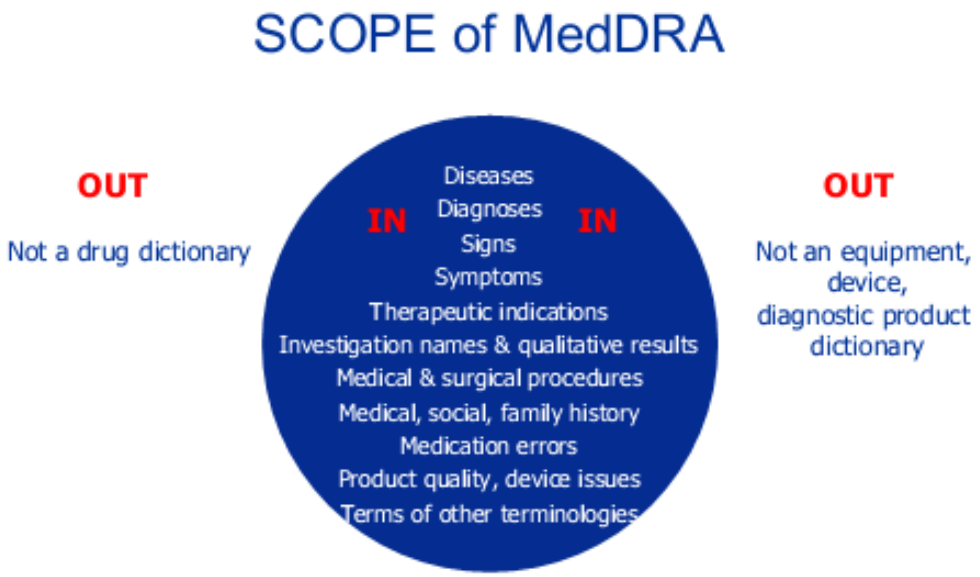
A single terminology for use through all phases of development cycle (both pre- and post-marketing)

- Clinical Trials (medical information, adverse events)
- Registration (study reports, analyses, summary of product characteristics/labeling – undesirable effects section)
- Post-authorization (adverse events)

Support for electronic submissions

- Each MedDRA term is assigned a unique **8-digit numeric code**

- Codes can fill certain data fields in e-submission types (**E2B*: ICSR-Individual Case Safety Reports, eCTD*: e-Common Technical Document**)
- Codes easier to transmit as no language boundaries



(https://www.meddra.org/sites/default/files/page/documents_insert/pharmacon_conference_meddra_belgrade_thouvay_2012.pdf/accessed on 24.04.2020)

Who develop MedDRA?

- It is developed by the International Council for Harmonization (ICH) of Technical Requirements for Pharmaceuticals for Human use.
- ICH has created a governance structure to nature and protects the integrity of MedDRA.
- ICH Med DRA committee oversees all the activities of the MedDRA maintenance and support services organization.

The Maintenance and Support Service Organization (MSSO)

- MSSO is the management Board appointed by ICH steering committee.
- Maintain and upgrades MedDRA.
- Releases updated MedDRA versions twice a year (in March and September).

MedDRA MSSO

- MedDRA is actively developed and maintained
  - **Two releases per year**
  - **Evolves to meet needs of regulators, industry, other users**
  - **Success depends on these activities**
- ICH contracted MSSO for this purpose
- MSSO activities are governed by ICH MedDRA Management Board

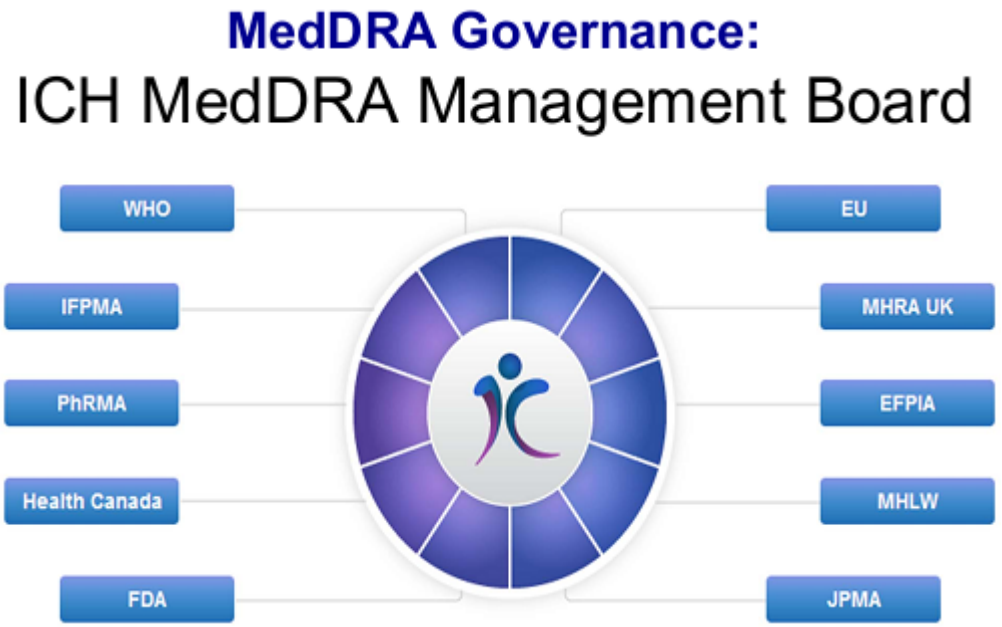
ICH MedDRA Management Board

Six Parties: EU, EFPIA, FDA, MHLW, JPMA, PhRMA,

Three Observers: WHO, EFTA, Canada European

1. **Commission - European Union (EU)**
2. **European Federation of Pharmaceutical Industries and Associations (EFPIA)**

3. **US Food and Drug Administration (FDA)**
4. **Pharmaceutical Research and Manufacturers of America (PhRMA)**
5. **Ministry of Health, Labor and Welfare, Japan (MHLW)**
6. **Japan Pharmaceutical Manufacturers Association (JPMA)**



(https://www.who.int/medicines/areas/quality_safety/regulation_legislation/WB_2.pdf?ua=1/accessed on 24.04.2020)

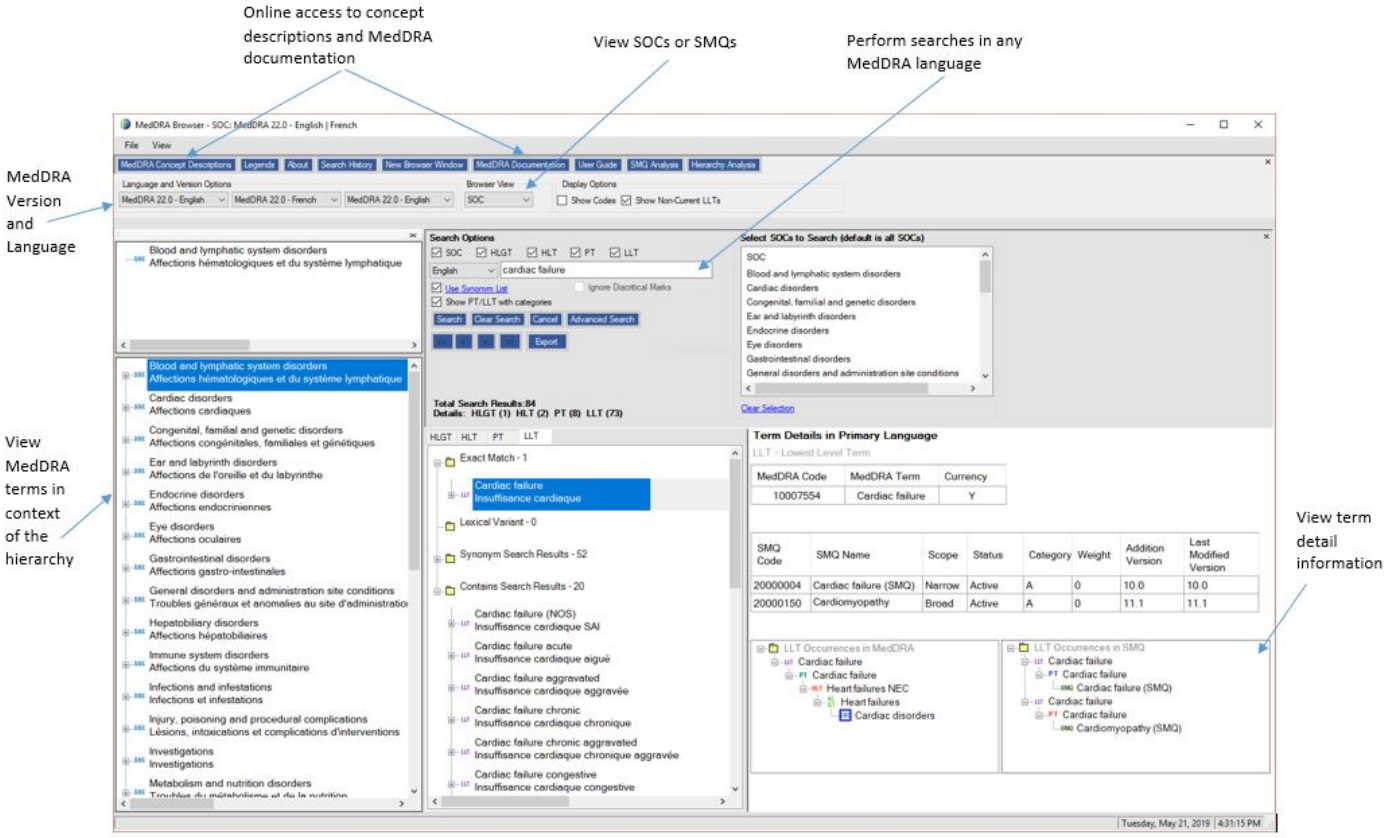
Objectives of MedDRA's Development

- International multi-lingual terminology
  - Used in 60 countries
  - Available in 11 languages
- Standardised communication between industry and regulators
- Application throughout all phases of development
- Classification of a wide range of clinical information
- Support multiple medical product areas
- Support electronic submissions

- Unique 8-digits codes for all terms
- For data fields in e- submission types (e.g. E2B)

MED-DRA CODE

- **Unique number assigned to each term in the dictionary**
- **8 digit number**
- **Starts with 10000001, initially started alphabetically**
- **As term added, codes assigned sequentially.**



(https://www.meddra.org/browsers/accessed on 02.05.2020)

WHO Drug Dictionary

The WHO Drug Dictionary is an international classification of the medicines created by the WHO Programme for International Drug Monitoring (IDM) and managed by Uppsala Monitoring Centre (UMC).

- A database with information about medical products from all over the world.
- It contains medicinal products and information related to the mina relational database system.
- Information is provided in a consistent and structured way
- It provides useful groupings of data useful for both data input and out put.
- It is continuously updated.

Eudravigilance medicinal product dictionary

Glossary

- EudraVigilance: European Union Drug Regulating Authority Pharmacovigilance
- ATC: Anatomical Therapeutic Chemical
- CIOMS: Council for International Organisations of Medical Sciences
- EEA: European Economic Area
- EMA: European Medicines Agency
- ESTRI: Elecronic Strandards for the Transfer of Regulatory Information
- EVDAS: Eudravigilance Data Analysis System
- EVCTM: Eudravigilance Eudravigilance Clinical Trial Module
- EVPM: Eudravigilance Post-Authorisation Modole
- ICH: International Conference of Harmonisation

Introduction

The history of pharmacovigilance is closely linked to the history of drug safety crises. With each crisis, the public and the media have demanded, and the legislators and regulators have provided, improved safety monitoring. The media and the public appear to expect zero-risk medicines. In the real world, zero risk medicines do not exist. For each new drug presented to the regulators for approval, the potential benefits for public health need to be balanced against known safety risks. Information on safety risks at the moment of approval comes from pre-clinical and more importantly, clinical data originating from clinical trials. As the time intervals and the number of patients involved in clinical trials are necessarily limited, the benefit risk balance must be continuously monitored after authorising a new medicinal product. The new medicines legislation also explicitly provides for risk management plans to be submitted by the applicants for marketing authorisation. It is therefore essential that we have in place systems which will allow us to collect, validate, store and process reports on adverse drug reactions for investigational and authorised medicinal products. The better the data quality and the larger the number of such reports received and processed the earlier will significant signals be detected. In view of the number of adverse drug reactions reported, this has to be carried out using modern tools of information and communications technology.

EUDRAVIGILANCE: (European Union Drug Regulating Authority Pharmacovigilance) is the European data processing network and management system for reporting and evaluation of suspected adverse reactions to medicines which have been authorized or being studied in clinical trials in the European Economic Area (EEA). The European Medicines Agency (EMA) operates the system on behalf of the European Union (EU) medicines regulatory network.

The European Eudravigilance system deals with the :

- Electronic exchange of individual case safety reports (ICSR, based on the ICH E2B specification):

- Eudravigilance Clinical Trials Module (EVCTM) for reporting Suspected Unexpected Serious Adverse Reactions (SUSARs).
- Eudravigilance Post-Authorisation Module (EVPM) for post-authorization ICSRs.

- Early detection of possible safety signals from marketed drug for human use.
- Continous monitoring and evaluation of potential safety issues in relation to reported adverse reactions.
- Decision-making process, based on broder knowledge of the adverse reaction profile of drugs.
- The first operating version was launched by EMA in December 2001

(http://eudravigilance.emea.europa.eu/human/index.asp/accessed on 2.05.2020)

Eudravigilance medicinal product dictionary (EVMPD):

The EudraVigilance Medicinal Product Dictionary (EVMPD) has been designed to support in a standardised and structured way the collection, reporting, coding and evaluation of data on authorised medicinal products and investigational medicinal products.

The EVMPD offers:

- A distributed and common approach for data collection through user-friendly and easy accessible software solutions available free of charge for pharmaceutical companies
- Integrated standard terminology to code e.g. active ingredients, excipients, pharmaceutical forms, routes of administrations, concentration ranges and units, country codes, marketing authorisation holders and sponsors.
- A hierarchical data structure accommodating coding requirements in pharmacovigilance to reliably capture product information in safety reports

taking into account the possible vagueness of the reported data by the primary source .

- A hierarchical, multi-axial data structure to support scientific data analysis of medicinal product data and grouping of data based on ingredients, strengths and pharmaceutical forms.
- Automated data import and systematic workflow with integrated quality control and audit checks.
- A standardised XML schema to support the collection and exchange of structured medicinal product information.
- Defined data ownership ensuring controlled data update through the respective product owner.
- A standardised approach to support updates, variations and withdrawals to medicinal product through the defined responsible product owner.
- Traceable and auditable regulatory changes to product information (recording of medicinal product history).

EudraVigilance contains other dictionaries:

MedDRA:

MedDRA is the Medical Dictionary for Regulatory Activities. It was developed in the frame of the ICH M1 activities as a clinically validated international medical terminology for regulatory authorities, and is maintained by the MedDRA's Maintenance and Support Services Organisation (MSSO). MedDRA is used by regulators and pharmaceutical industry for data entry, retrieval, evaluation and presentation during all phases of the drug regulatory process i.e. the pre- and post-authorisation phase. These processes include clinical studies, reports of spontaneous adverse reactions, events, regulatory submissions and regulated product information.

- VEDDRA

- Routes of Administration
- Dosage Units
- Pharmaceutical forms
- ATC

Purpose of Eudravigilance

- To support the public health of EU citizens by collecting safety information on medicines and making this available for scientific assessment.
- This assessment is carried out by regulatory authorities in the EU that supervise and monitor the correct use of the medicines in all EU countries on a continuous basis.
- Medicinal product authorization information.
- Pharmacovigilance information.

Eudravigilance support

- Electronic exchange of suspected adverse reaction reports (referred to as Individual Case Safety Reports) between European Medicines Agency (EMA), National Competent Authorities (NCA's), Marketing Authorization holders, and sponsors of clinical trials in the EEA.
- Early detection of possible safety signals from marketed drug for human use.
- Continuous monitoring and evaluation of potential safety issues in relation to reported adverse reactions.
- Decision-making process, based on brooder knowledge of the adverse reaction profile of medicinal products especially in the frame of risk Management.

Conclusion

- EudraVigilance is a powerful tool for monitoring the safety of medicinal products

- Once the complete feed of data has been established, it will be the largest database of its kind in the world.
- It will become an extremely useful resource for academic and commercial research once full access to data mining and statistical evaluation can be provided.

Information resources in pharmacovigilance

- DEFINTION:-The branch of science who`s activities relating to the detection, assessment, understanding, and prevention of adverse effects or any other drug related problem.

- ORIGIN OF PHARMACOVIGILANCE:-
  - The Thalidomide disaster in 1956 - Thalidomide launched in market and in 1956-61 report of foetal abnormalities (20000 cases) maximum in Germany.
  - In 1962 USA revised law requiring proving the safety and efficacy before issuing marketing authorization.
  - In 1963 British committee on safety of drug monitoring.
  - In 1964 UK starts the “YELLOW CARDS” system.
  - In 1964-65 National ADR reporting system UK, Australia, New Zealand, Canada, West Germany, Sweden .

- OBJECTIVE:

  1- To know what are the various sources of drug information.

  2- To select the appropriate source depending on the information.

➢ BASIC DRUG INFORMATION RESOURCES- Drug information is current, critically examined, relevant data about drugs and drug use in a given patient or situation.

- Current information uses the most recent, up-to-date sources possible.
- Critically examined information.
- Relevant information must be presented in a manner that applies directly to the circumstances under consideration (e.g. patient parameters, therapeutic objectives, alternative approaches).

➢ TYPES OF RESOURCES:-

(I) Primary resources

(II) Secondary resources

(III) Tertiary resources

(I) PRIMARY RESOURCES-

- Researcher`s and manufacturer`s information.
- Patents containing original information regarding the discovery of drug.

- Reports containing scientific data before product can be sold, supplied or represented.
- Scientific Journals
- Provide original studies or reports

➢ ADVANTAGES

- Most current evidences.
- Provide data on new drugs.
- Original document that was created at the time of the actual events.

➢ DISADVANTAGES

- Data can be controversial.
- Every study has limitation
- Complicated
- Time consuming.

(II) SECONDARY RESOURCES-

- Abstract or index which summarizes the information arising in primary resource.
- Indexing and abstracting services are valuable tools for quick and selective screening of the primary literature for specific information, data, citation, and article.
- Bibliographic database that provide abstract or full-text of studies.

➢ ADVANTAGES-

- Find specific information at high granularity.
- Pick out key point.
- Quick to read.

➢ DISADVANTAGES-

- Detail missing.
- Two different authors can interpret the same piece of original material in two widely different ways.
- May be inaccurate.

(III) TERTIARY RESOURCES-

- Compilation of knowledge in the field. e.g. Textbooks, handbook, online drug compendia.

➢ ADVANTAGES-

- Provide comprehensive information.
- Information reflects views of multiple experts in field.
- Fast, easy to use, and may be good for patients.

➢ DISADVANTAGES-

- Information may be dated due to gap between when resources is written and published.
- Chances of distorting a topic.

➢ OTHER SOURCES-

- Libraries
- Research association
- Government bodies
- Information center in industries

ADVERSE DRUG REACTION

Any noxious change which is suspected to be due to drug , occur at doses normally used in man,require treatment or decrease in dose or indicates caution in future use of the same drug.

CLASSIFICATION:-

1. **Type A effect:-** Augmented pharmacologic effects – dose dependent and predictable are those which are due to pharmacologic effects.
2. **Type B effect:-** Bizarre effects(idiosyncratic)- dose independent and unpredictable .
3. **Type C effect:-** Chronic effect refer to situation where the use of a medicine, often for unknown reasons, increase the frequency of a "spontaneous" disease.
4. **Type D effect:-** Delayed effects.
5. **Type E effect:-** End-of-treatment effect.
6. **Type F effect:-** Failure of therapy.

➢ SPECIALISED RESOURCE OF ADR

- Individual reporting
- Comprehensive Monitoring
- Population Monitoring
- Individual case safety report (ICSR)
- Spontaneous Reporting

➢ INDIVIDUAL REPORTING

- In individual reporting Doctor are the major source of report.
- The physician, during an outpatient or inpatient examination, may decide that the patient has a recognizable syndrome of signs, symptoms and/or

laboratory finding and that this syndrome may be associated with a previously administered drug.

- Since most severe reaction are seen in hospitals, physicians who are Hospital-based are often able to ascertain previous drug administration, link it to the reaction, and submit a report.

➢ COMPREHENSIVE MONITORING:-

- Comprehensive monitoring is typically performed in a hospital setting and the input of abstract of patient identification, drug administration, and patient reaction.
- Specialised method are used to ensure that this information is complete, and case report or tabulated summary data can be supplied to the national centre.

➢ POPULATION MONITORING:-

- In population monitoring the record of hospital or clinic patients, or of the entire population of a district, may be employed.
- Such monitoring could be effective when a large stable population is surveyed in an organized medical care system.

➢ INDIVIDUAL CASE SAFETY REPORT (ICSR):-

- Individual Case Safety Report is a report which contains information describing suspected adverse drug reaction related to administration of one or more medicinal product.
- A document providing the most complete information related to an individual case at a certain point of time.

➢ SPONTANEOUS REPORTING:-

- Spontaneous reporting is a system whereby case report of adverse drug event are volunteer submitted by healthy professionals, pharmaceuticals companies or consumers to the national pharmacovigilance centre.
- It is basically the reporting of a suspected adverse reaction on the initiative of the health professional who became aware of the problem, or the patient initiative. These report can be communicated by any means, but in countries with a well developed pharmacovigilance system they are most often reported on the country- specific reporting card.
- Such reporting is sometime referred to as intensified spontaneous reporting, or ideally, prospective

[D] Establishing pharmacovigilance programme

Established pharmacovigilanace program in a hospital and national programme

PV is a major post-marketing tool to ensure the safety of a medicinal product. Apart from the respective drug regulating authorities in each country, International Conference on Harmonization (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use, Pharmacovigilance Planning-ICH E2E and World Health Organization-Uppsala Monitoring Centre (WHO-UMC) also play key roles towards developing, enhancing and monitoring global PV system. A PV system is defined as a system used by an organization to fulfill its legal tasks and responsibilities in relation to PV that monitors authorised medicinal products' safety and detect if any change to risk benefit balance.

After the thalidomide disaster in the year 1961, WHO worked along with its Collaborating Centre to establish a programme for International Drug Monitoring and through this programme, WHO promoted PV at the country level. At the end of 2010, 134 countries were part of the WHO-PV Programme. To give

it a further impetus and fortify the drug regulatory framework in the country, the Drug Controller General of India (DCGI) has announced the CDSCO's "VISION 2020" which proposes to create a PV center in every medical college in the country which is an ambitious task keeping in view the fact that it is still at low ebb in many government medical colleges and the condition is the same or may be worse in the private institutes. Therefore, it is likely that the proposal may have to negotiate many bottlenecks to pay some dividends. In this backdrop, the article discusses the essentials of setting up a PV center and getting it operational

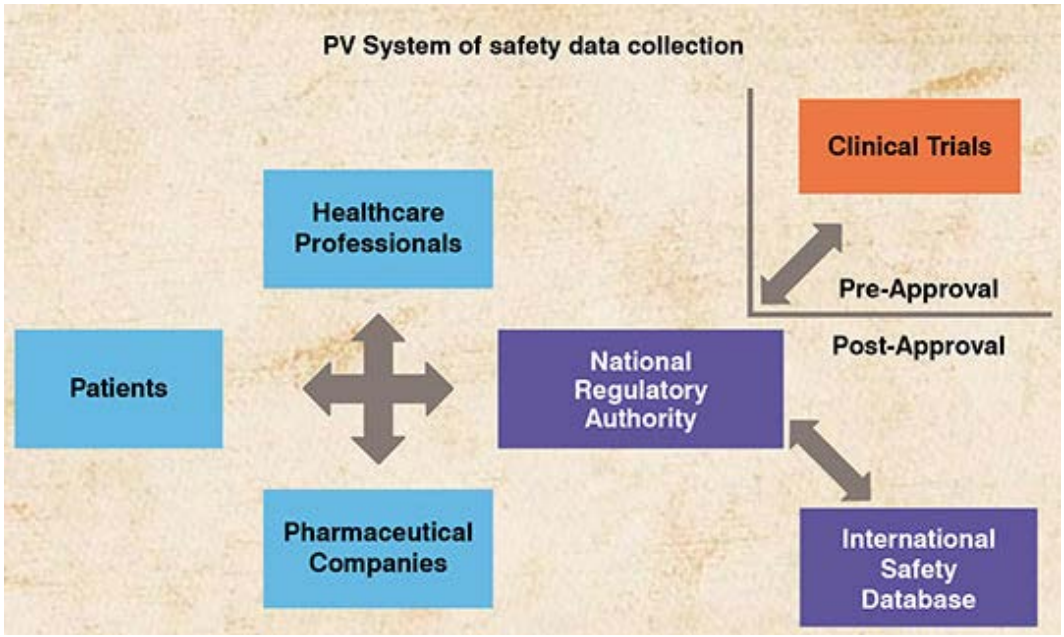
Essential for a Pharmacovigilance program:-

Pharmacovigilance is all about drug regulations and is based on thorough collaborative ties, coordination, communications, and public relations. The most suitable location for setting up a PV centre is dictated by the political governance and its healthcare priorities, including willingness to do, law enactment, its enforcement, funding, organisation, staffing, training, and development.

To Ensure a Good PV System, Certain Operational Requirements must be met, which include:-

- A properly structured drug safety management team to intensify the communication among the PV network. This will assure an organised structure and smooth functioning. Meetings among the PV physicians, managers, and technical agencies need to be held from time to time
- A countrywide database which provides provision for collating and managing ADR reports
- A national PV advisory committee
- A clear approach, to be communicated in detail, in regular situations as well as situations of crisis
- Funding to run different grounds of a system.

Basic Steps in Setting up a PV System Include:-



(https://www.pharmafocusasia.com/strategy/setting-pharmacovigilance-system/accessed on 02.05.2020)

Developing guidelines and communications with the health authorities-a general guideline is a standard strategy to confirm that the PV system at all levels meets the national and international standards and regulations. Getting into regular communications with the health authorities, local, regional and national bodies, and professionals involved in clinical medicine, pharmacology, toxicology, epidemiology, briefing them about the importance of the project and its applicability in modern therapeutics.

Minimum requirements for a functional national pharmacovigilance system

The following are the minimum requirements that WHO and partners agree should be met in any national pharmacovigilance system.

1. A national pharmacovigilance centre with designated staff (at least one fulltime), stable basic funding, clear mandates, well-defined structures and roles, and collaborating with the WHO Programme for International Drug Monitoring;
2. A national spontaneous reporting system with a national individual case safety report (ICSR) form, i.e. an ADR reporting form;
3. A national database or system for collating and managing ADR reports;
4. A national ADR or pharmacovigilance advisory committee able to provide technical assistance on causality assessment, risk assessment, risk management, case investigation and, where necessary, crisis management, including crisis communication;
5. A clear communication strategy for routine communication and communication during crises.

1. The Manpower and the machinery

a) Adequate qualified and experienced man power to run the system - PV staff should have complete knowledge regarding data collection and verification, coding of drugs and adverse events, causality assessment, signal detection, risk management, interpreting the data obtained etc.

***Staff**

The expertise desirable in the routines of a pharmacovigilance centreincludes: **Clinical medicine, pharmacology, toxicology, epidemiology**. However, a new pharmacovigilance centre often starts with only a part-time expert

- usually a physician or a pharmacist
- and some secretarial support.

It may soon become necessary to have one expert who is responsible for pharmacovigilance for most of his/her time and for secretarial assistance to be expanded. When the reporting of adverse reactions increases, staff resource requirements may be calculated by assuming that the average assessment time per case report is about one hour.

2. Planning the basics

A blueprint should be drawn up to establish and get a PV system to work. Care needs to be taken to establish the following:

a) Advisory Committees

A multi-disciplinary advisory committee is desirable, to support the pharmacovigilance centre with regard to the quality of the procedures in:

1. Data collection and assessment
2. Data Interpretation
3. Information publication

A network of experienced advisors in various specializations is helpful

b) Communication process

Getting in conversation with health authorities and local, regional, national bodies and groups engaged in clinical medicine, pharmacology, toxicology, epidemiology, briefing them about the importance of the project and its applicability in modern therapeutics. A bulletin or newsletter distributed to all healthcare professionals or a regular column in reputed (medical and pharmaceutical) journals are good means for the dissemination of information. Prompt data-sheet amendments are important, but data-sheets may be printed infrequently and their educational impact may not be large. In urgent cases of sufficient importance ‘Dear Doctor’ letters may alert the profession

c) Data acquisition

Designing a template for ADR reporting and making available ADR reporting forms at all times, to hospital departments and general practitioners, on which they can furnish relevant information to the data bank of the center.

d) Dissemination

Producing printed handouts as well as conducting meetings or workshops in hospitals and academia to acquaint health care professionals about the definitions, goals, scope, and methodology of the PV system to create awareness about its relevance in present times.

e) Establishment

Hiring the right qualified and interested staff, getting suitable place for accommodating them as well as the center, making arrangements for telephones, computers, printers, word processors, database management, bibliography support services and an internet.

f) Internal education

Ensuring proper education and frequent updating of the staff belonging to the PV centers by training them in data collection, filtration, mining, verification, interpretation and coding of ADRs, medicines coding, causality assessment, signal detection, risk management, and action in case of serious/fatal adverse drug events (ADE). Data mining is a relatively nascent interdisciplinary area which involves finding correlations and patterns among many fields in large databases with the aim of categorizing the data and summarizing identified relationships.

g) Database and information serivce

Creating a safely stored, classified database which is retrievable and guarded by required degrees of confidentiality. The provision of a high quality information service to healthcare professionals is a basic task of a pharmacovigilance centre and a major instrument in the stimulation of reporting. For this purpose and for the assessment of case reports the centre should have access to a comprehensive and up-to-date literature source and information database.

Location of the centre in a large hospital usually has the advantage of a library within reach. National pharmacovigilance centres can have online access to the database of the UMC and be on the mailing lists of adverse drug reaction and drug bulletins produced by the World Health Organization and many national or regional centers.

h) Promotion

To inculcate and promote the habit of reporting ADRs to the higher center, medical journals, health bulletins and other professional healthcare publications.

I) Networking

To encourage healthcare professionals to contact institutions working on a global scale in PV e.g. Uppsala Monitoring Centre (UMC) WHO department of Essential Medicines and Medicines Policy, Geneva, and net groups like International Network for the Rational Use of Drugs (INRUD), E-drug, and Network for Rational Use of Medicines (NetRUM)

3. Data

Pharmacovigilance at present thrives heavily on a regional/country wide reporting of suspected ADRs through spontaneous reporting system from motivated reporters. It usually picks up signals of rare, serious, unprecedented ADRs.

Reports of suspected ADRs are taken in case report forms (CRF) which in PV is defined as a notification relating to a patient with an ADE (or laboratory test abnormality) suspected to be induced by a medicine. The CRF should be distributed to health care professionals across the area covered by a particular PV center regularly, and a suitable system has to be developed to ensure that the filled forms are either collected or could be posted free, or sent by e mail/FAX to the center, so that there is an uninterrupted and free flow of data.

A CRF should contain minimum following information

- Patient: Age, gender, medical history in brief, ethnic origin (in some countries)
- ADE monitoring: Detailed description (nature, localization, severity, characteristics), reports of investigations and tests, date of appearance, course, outcome
- Suspected medicines: Name (brand, formulation, ingredient, concentration, manufacturer), dose, route of administration, date of initiation of therapy/date of withdrawal of therapy, indications for use, and rechallenge in case of non serious ADEs
- Other medicines: All other medicines used by the patient (including self medication) including their name, dose, route, date of initiation and withdrawal
- Risk factors: e.g. impaired renal function, past exposure to suspected medicines, history of allergy, and social drug use
- Reporter: Name and address of the reporter (confidential and to be used for data completion, verification, and follow up)

Health care professionals e.g. practicing physicians, pharmacists, nurses, dentists, and midwives are reliable sources of information. Pharmacists and nurses can illuminate on concomitant medication and history of medicine usage. It is imperative for pharmaceutical companies to report any ADRs of their products to regulatory authorities. In the event of patients directly reporting ADRs, it is

always better to communicate with their physicians for better understanding and verification of data.

The reporting can be done from peripheral to the regional PV centers, which sweep a particular region, which in turn pool into the zonal database, the analysis of which reflects a gross national overview. The entire national data should be reported to UMC.

4. Bringing a reporting culture

Reporting of ADR is a continuous process and important to cultivate and sustain the attention and interest of healthcare workers so that it gets incorporated as a routine procedure in healthcare. The following measures may be adopted to give a fillip to reporting:

- Easy and free availability of prepaid reporting forms and other modes of reporting
- Duly acknowledging the receipt of ADR reports telephonically or through personal communication
- Providing journal articles, ADR bulletins, newsletters to reporters
- Actively involving the PV center staff in scientific meetings, undergraduate and postgraduate education
- Collaborating with other PV committees, It is always ideal to look out for other organizations that may be able to collaborate with your PV Centre to reduce the financial and logistic burden. For example, poison control and drug information centres share similar PV interests. It may be useful to develop a PV system in conjunction with these centres.
- Collaborating with professional associations
- Utilizing PV data for development of clinical pharmacy and clinical pharmacology

5. Tasks for pharmacovigilance

a) Information service

One of the primary responsibilities of a center is to make high quality credible and latest medicine information available to health care professionals. For this, the center should have access to up-to-date and comprehensive literature database. The national centers should preferably have an online access to UMC database and be on the mailing list of ADR bulletins of WHO.

b) Reaching out

Newsletters, medicine bulletins, columns from reputed medical or pharmaceutical journals may be chosen as routes of effective propagation of latest developments in medicine research and therapy to the healthcare professionals.

c) Appraisal

The ADR case reports obtained are evaluated by the center staff, employing the collective know-how of clinical medicine, pharmacology, toxicology, and epidemiology.

d) Secondary prevention of ADRs

Secondary prevention of ADRs can be attempted by distribution of “patient alert cards” which are pocket size cards and could be carried around by patients. They provide relevant information about the medicines including ADRs and go a long way in preventing ADRs.

e) Data processing

Data is best managed electronically by computer, wherein, data is entered in a hierarchical format according to product name, medicine name or therapeutic category. This facilitates recording detailed case information and easy retrieval.

Internationally accepted terminologies regarding classification of medicines (Anatomical Therapeutic Chemical [ATC], International Nonproprietary Names [INN]) and ADRs e.g. WHO Adverse Reaction Terminology (WHO ART), Medical Dictionary for Regulatory Activity (MedDRA) should be used, so that the data can be globally shared.

f) Hypothesizing

This is one of the chief goals of PV center. Based on the case reports, the center should be able to generate hypothesis or detect a signal with regard to probable ADRs.

e) Medicine regulation

It is PV center's duty to keep a close eye on the new medicines launched in the market and follow them up to look for newer ADEs, issue warnings, unmask newer indications or changes or to advocate withdrawal of medicines in extreme cases. A center should actively take up activities towards furthering the role of PV with periodic safety update reports (PSURs), registries, risk management-minimization plans, and improved communication with changes in label of medicines.

The PV system needs to deal with large population and the rate of reporting governs the estimation of the money needed to run the complete system. Huge investment is required in terms of collection of data from the actual source to transforming it into a Regulatory reportable format. Funding can be obtained from various parties, such as drug Regulatory authority, university departments, health insurance companies, and professional associations.

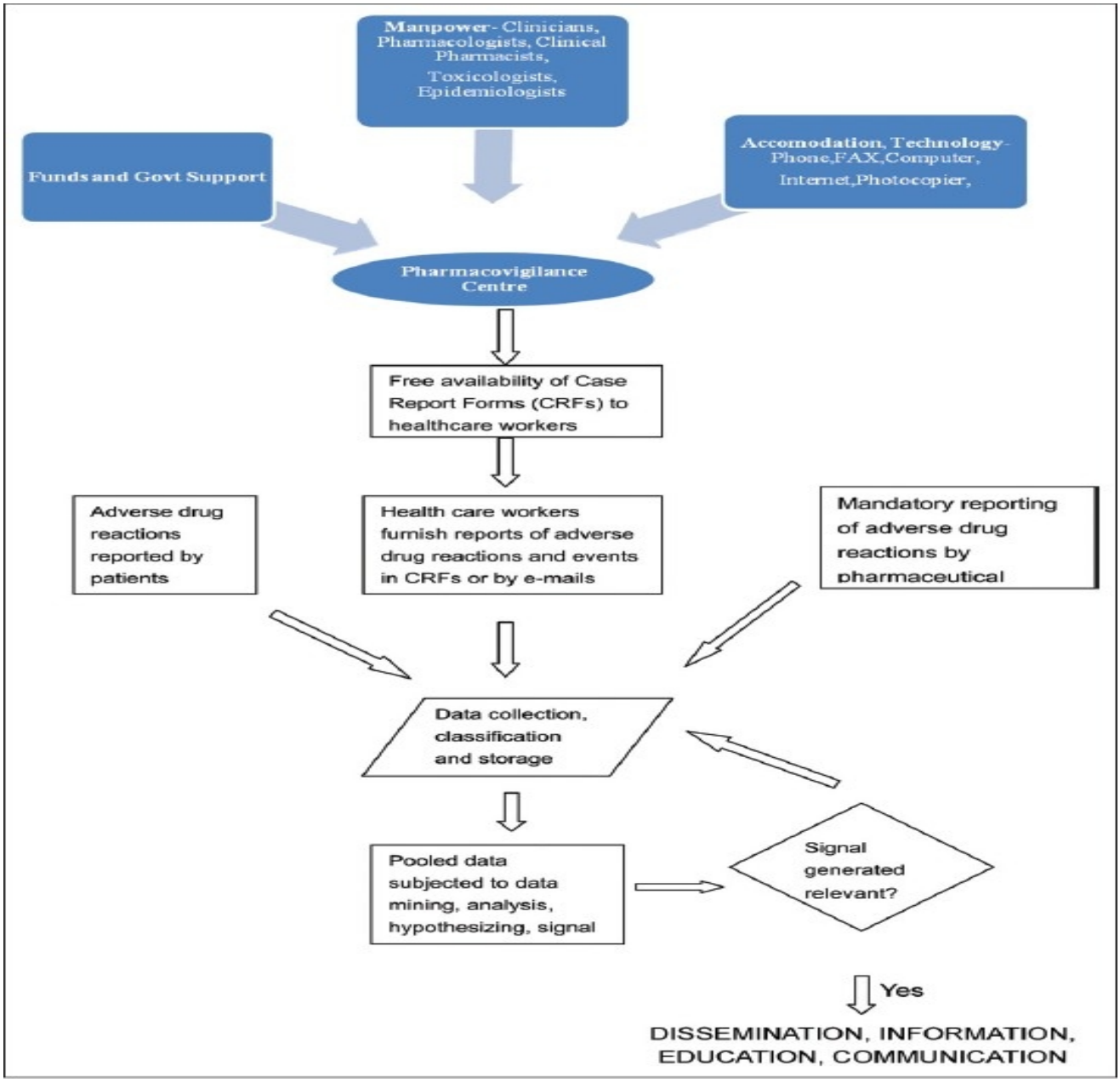


Fig :-Pharmacovigilance system: Constitution and functioning

Establishment & operation of drug safety department in industry

Introduction:-

- Pharmacovigilance has grown as a discipline over the past 10 to 15 year.
- An educational survey in 1994 revealed that more than 320 people currently worked in company pharmacovigilance function in the UK alone.
- Pharmaceutical companies are international, hence the number of staff working in this field within the industry,particularly in other European countries and USA.
- A major pharmaceutical company such as Astra has over 100 permanent, experienced staff in pharmacovigilance within its research and development organisation in Sweden and the UK and US similar number in local operating companies worldwide
- The number of individual reports of possible adverse drug reaction can be considerable, for key marketed products often more than 1000 case reports a year are received worldwide from healthcare professionals and other sources.

Aim of pharmacovigilance within the industry:-

- Protect patients from unnecessary harmby identifying previously unrecognised drug hazards.
- Refuting false safety signals and quantifying risk in relation to benefit.

Scientific characteristics:-

- Pharmacovigilance is related to a number of scientific disciplines
    i. Clinical medicine
    ii. Clinical and preclinical pharmacology

iii. Immunology
iv. Toxicology
v. Epidemiology ,

Identification and analysis of the safety characteristics of medicine .

- In two distinct stage:-

1. Before marketing:-

The main methodology is experimental with clinical trial comparing the new treatment to existing alternative treatment.

2. After marketing:-

Introduction of a new medicine into you generally use, the main safety methodology is observational i.e. uses data from observation of patients treated in clinical practice rather than from experimental situations.

Pre-marketing clinical trials:-

- Safety monitoring in clinical trials involves collecting adverse event, laboratory investigation and details of the clinical examination of patients.
- Pharmacovigilance may be involved to varying degrees all phases of clinical trials including planning, execution, data analysis, reporting of safety information.
- Safety issues from animal pharmacology and toxicology studies, finding in phase-1 studies, ADR with similar drugs, signals from other studies and special patient group (eg. elderly).
- The practice of collecting all adverse events rather than suspected ADR arose from the failure of clinical trials to detect serious reaction with protocol and after several years experience this is now the approach adopted by company in most studies.

- The involvement of pharmacovigilance staff in clinical trials also includes an important responsibility for the expedited reporting of individual cases and safety update required by the UK medicine control agency and other regulatory authorities.
- Safety analysis and clinical expert report in the marketing authorisation application submitted by the company and will be the basis of ADR, warning and precaution include in the prescribing informationi.e data sheet.

Methods of post marketing surveillance (PMS) used by the pharmaceutical industry:-

1. **First step in signal generation:-** Processes that can identify possible new ADR.

Signal generated through four different methods

- **Spontaneous reporting**
  - Recording and reporting clinical observation of a suspected ADR with a marketed drug is known as spontaneous reporting.
  - The National system in the UK is the yellow card.
  - Where doctors, dentists and recently hospital pharmacist are encouraged to report all suspected reactions to new medicines and serious suspected reactions to established medicines.
- **Published case reports**
  - Publishing case reports of suspected ADR in medical journals is an establish a way of alerting other to possible drug hazards.
  - A more recent development is report of possible ADR appearing on the internet and money companies are still determining how they should best handle them.

- **Cohort studies**
  - Companies may set up or sponsor prospective, non interventional cohort type studies to answer safety question rose after marketing or general hypothesis generating and testing tool to be used as need arises.
- **Post marketing clinical trials**
  - Large randomised clinical trials with wide entry criteria can be valuable in assessing the safety of marketed products as well as confirming efficacy.

Companies can use to set up or sponsor search studies to address particular safety issues.

2. Second step in signal generation:- Signals are subjected to hypothesis testing i.e. processes that determine whether the single-dose indeed indicate a new ADR or whether it is false.

- **The hypothesis testing process:-**A typical situation in company pharmacovigilance is that a small number of reports have been received, showing that the patients have developed a serious medical condition e.g.-liver function disturbance, convulsion.
- **Using spontaneous reporting data for hypothesis testing:-**It is common place in clinical practice to make decisions and take actions based on assessment of causality between an event and a certain drug in individual cases.
- **Epidemiological studies:-** during the last decade pharmacoepidemiology, the study of the use and effect of drugs in large populations e.g- NSAID treatment and gastrointestinal ulceration and bleeding.

- **National and international regulatory requirements:-**

  The reporting of safety information from clinical trials and with marketed product by pharmaceutical companies to regulatory authority has been mandatory for many years but with each National authority having different requirements.

  Pharmacovigilance is not just about reporting cases to the regulatory authority the result of post marketing surveillance and hypothesis testing should provide useful information.

- **Issue and crisis management:-** The signal generation and hypothesis testing processes are long-term and continuous throughout the lifetime of a product resulting in a gradual buildup of knowledge of safety properties.

- **The future:-** Pharmacovigilance in the industry will continue to grow and develop as a discipline. The strong development towards international harmonization will result in much more international requirement and the very rapid development in electronics communication will allowautomated distribution of case reports within companies and to regulatory authorities.