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A TEXT BOOK OF

PHARMACOVIGILANCE

FOR B.PHARMACY THIRD YEAR
(As per PCI Syllabus)

Writer's
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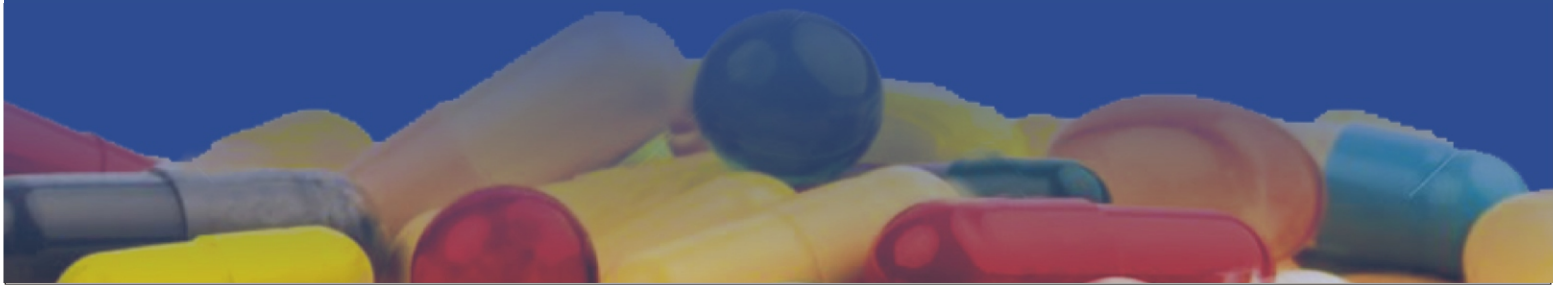
Mr. K. D. Khalode
Mr. M. N. Rangari
Mr. K. R. Bhendarkar
Mr. Sameer Shafi

Publisher

Aditi Publication



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PHARMACOVIGILANCE

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01. Introduction of Pharmacovigilance (PV)

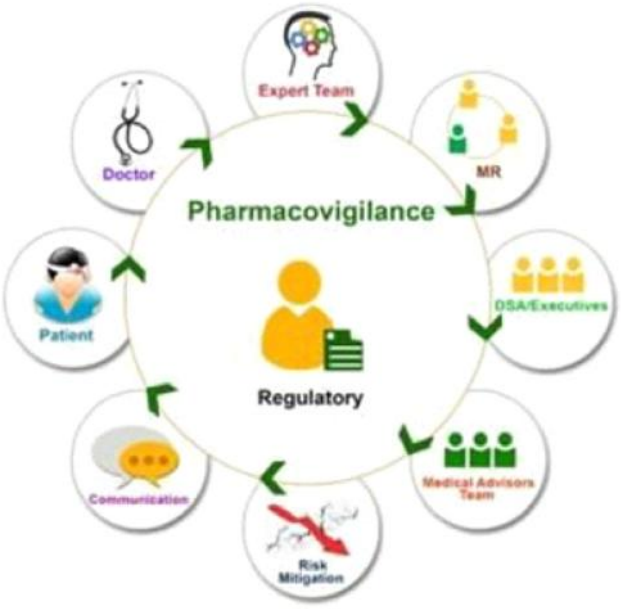
History and Development of Pharmacovigilance

Pharmacovigilance (PV) is defined by the European Commission (EU) as the "Process and science of monitoring the safety of medicines and taking action to reduce the risks and increase the benefits of medicines".

Aims of Pharmaacovigilance

- To improve patient care & safety
- To contribute to assessment of benefit, harm & effectiveness of medicine
- To Identify previously unrecognized adverse effects of the drugs
- To Promote rational & safe use of medicine
- To Promote education & clinical training
- To Identify patient related risk factors of ADR such as dose, age, gender
- Any response to a drug which is unintended , occurs at particular doses
- To diagnose or therapy of disease, or for the modification, of physiological function.

Pharmacovigilance is the way toward gathering, observing, exploring and assessing data from human services suppliers and patients for the reasons for comprehension and averting drug-related issues. Biotech Research Group pharmacovigilance framework gathers information all through the lifecycle of every item. At the point when critical security issues emerge, Biotech Research Group issues refreshed correspondences to specialists, patients and wellbeing controllers. At the inception of clinical preliminaries, the security profile of the item is produced from creature information and speculations from medications in the equivalent pharmacological class. This data is given to clinical preliminary examiners in the Investigator Brochure. From the main human portion and over the span of clinical preliminaries, wellbeing data is gathered and checked on by Biotech Research Group staff to give the most-breakthrough data conceivable about the security profile of Biotech Research Group items.



At the season of advertising endorsement, wellbeing information from the clinical preliminaries and non-clinical examinations are outlined in the affirmed marking (i.e., the bundle embed for the item). Post-advertising studies might be directed to keep on gathering data about advantages and dangers of the item. Also, medicinal services suppliers and patients unexpectedly report unfavorable occasions because of their encounters. Each is looked into and follow up contacts are started when extra data is required. Information from post-promoting contemplates and unconstrained reports are checked on intermittently, and when new data proposes that there might be an imperative new security issue developing, Biotech Research Group directs an assessment. On the off chance that investigations of the aggregate wellbeing data demonstrate an adjustment in the advantage/hazard profile of the item, at that point Biotech Research Group hazard administration programs are started. These hazard administration projects may incorporate correspondences to patients as updates to the bundle embed, letters to human services suppliers as well as patients, warning to controllers and further investigations to assess wellbeing concerns.

Pharmacovigilance Process

Often, people relate pharmacovigilance with safety reporting. Whereas this is a major aspect, it is actually only one of the components of the pharmacovigilance process, which also involves generating data, risk management, and input from regulatory authorities.

Pharmacovigilance Resources

Confirming drug safety during clinical product development alone is always a challenge due to data limitations. If labs had unlimited time to get their drugs to market, it would be less of a problem. Unfortunately, manufacturers need to start selling as soon as possible to maximize profits.

However, by dedicating more resources to pharmacovigilance, labs can maintain patient safety and public trust for a few reasons.

Importance of Safety Monitoring Of Medicine

Adverse Drug Reactions (ADRs) are among the top ten leading causes of death in most of the countries. An adverse drug reaction could be any unintended reaction in patient body which occurs as a result of administration of drug. Drug safety monitoring is a risk mitigation exercise in which the ADRs caused by therapeutic drugs, biologicals or devices can explored, prevented or minimized.

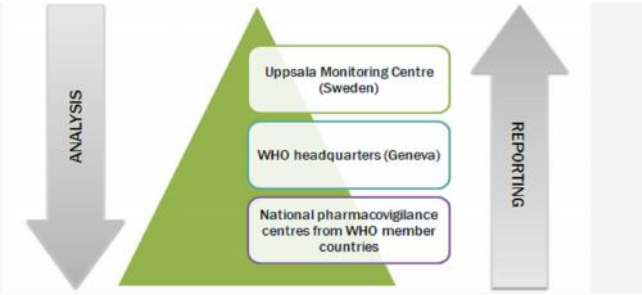
It is the process of identifying expected and unexpected adverse reactions resulting from the use of medicines in the post-marketing phase. Pharmacovigilance is an umbrella term used to describe the process of drug safety monitoring and can be defined as the branch of science that carries out activities related to detection, assessment, understanding and prevention of adverse drug reactions. It primarily aims at rational use of medicines to assure safety of patients. Thus pharmacovigilance has become a key aspect of effective clinical practice in many countries.

WHO International Drug Monitoring Programme

Established in 1968, The WHO Programme for International Drug Monitoring (PIDM) provides a forum for WHO Member States to collaborate in the monitoring of drug safety, and notably, the identification and analysis of new adverse reaction signals from data submitted to the WHO global individual case safety report (ICSR) database by member countries.

The programme consists of a three-part

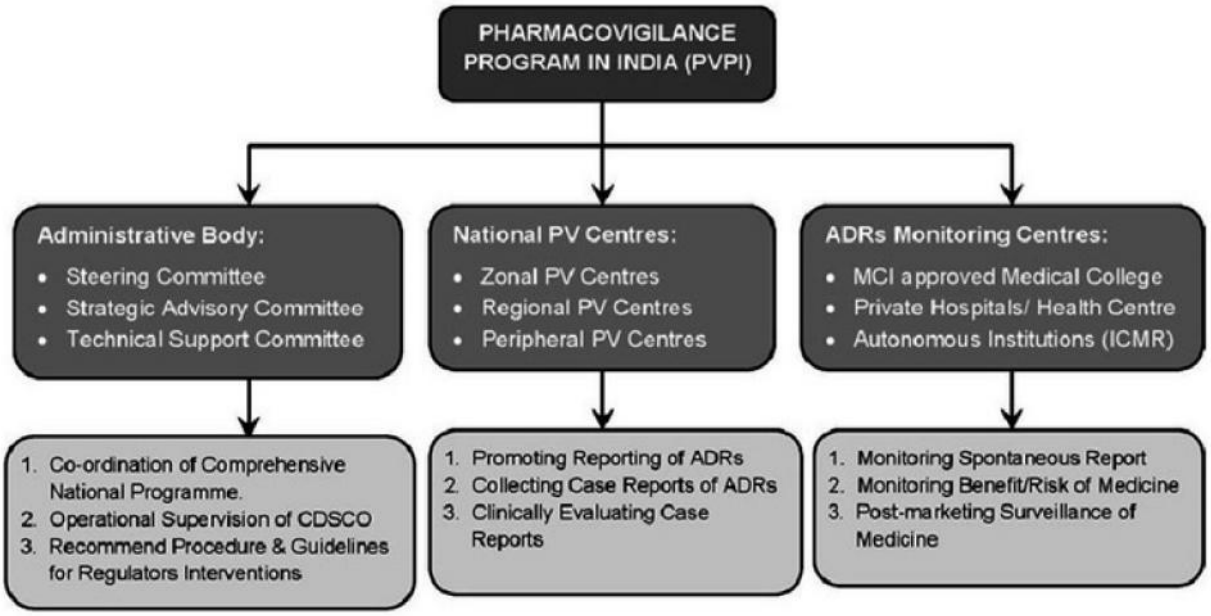
- National pharmacovigilance centres from WHO member countries are responsible for case reports sent to the WHO ICSR database (managed by the Uppsala Monitoring Centre (UMC) in Sweden),
- UMC oversees the WHO programme operations, including:
  - Collecting, assessing and communicating information from member countries about the benefits, harm, effectiveness and risks of drugs,
  - Collaborating with member countries in the development and practice of pharmacovigilance,
  - Alerting NRAs of member countries about potential drug safety problems via the WHO signal process.
- WHO headquarters in Geneva, Switzerland is responsible for policy issues.



Pharmacovigilance Program of India (PvPI)

The Pharmacovigilance Programme of India (PvPI) is the leading national authority for identifying and responding to drug safety problems in India. Its activities include receiving reports of adverse drug events and

taking necessary action to remedy problems. The Central Drugs Standard Control Organisation established the program in 2010. It is part of the Indian Pharmacopoeia Commission.



One of the challenges of the organization is training doctors and hospitals to report adverse drug reactions when patients have them. The Pharmacovigilance Program makes these reports itself, but ideally, such reports could originate from any clinic. The Pharmacovigilance Programme seeks to encourage a culture and social expectation of reporting drug problems.[3]

One of the successes of the program was detecting adverse effects of people in India using carbamazepine. While this drug is safer among people native to the Europe, people of South Asia have different genetics and are more likely to experience problems when using it. Other countries could not have been able to detect this problem, and the Pharmacovigilance Programme's detection of it was a success story.

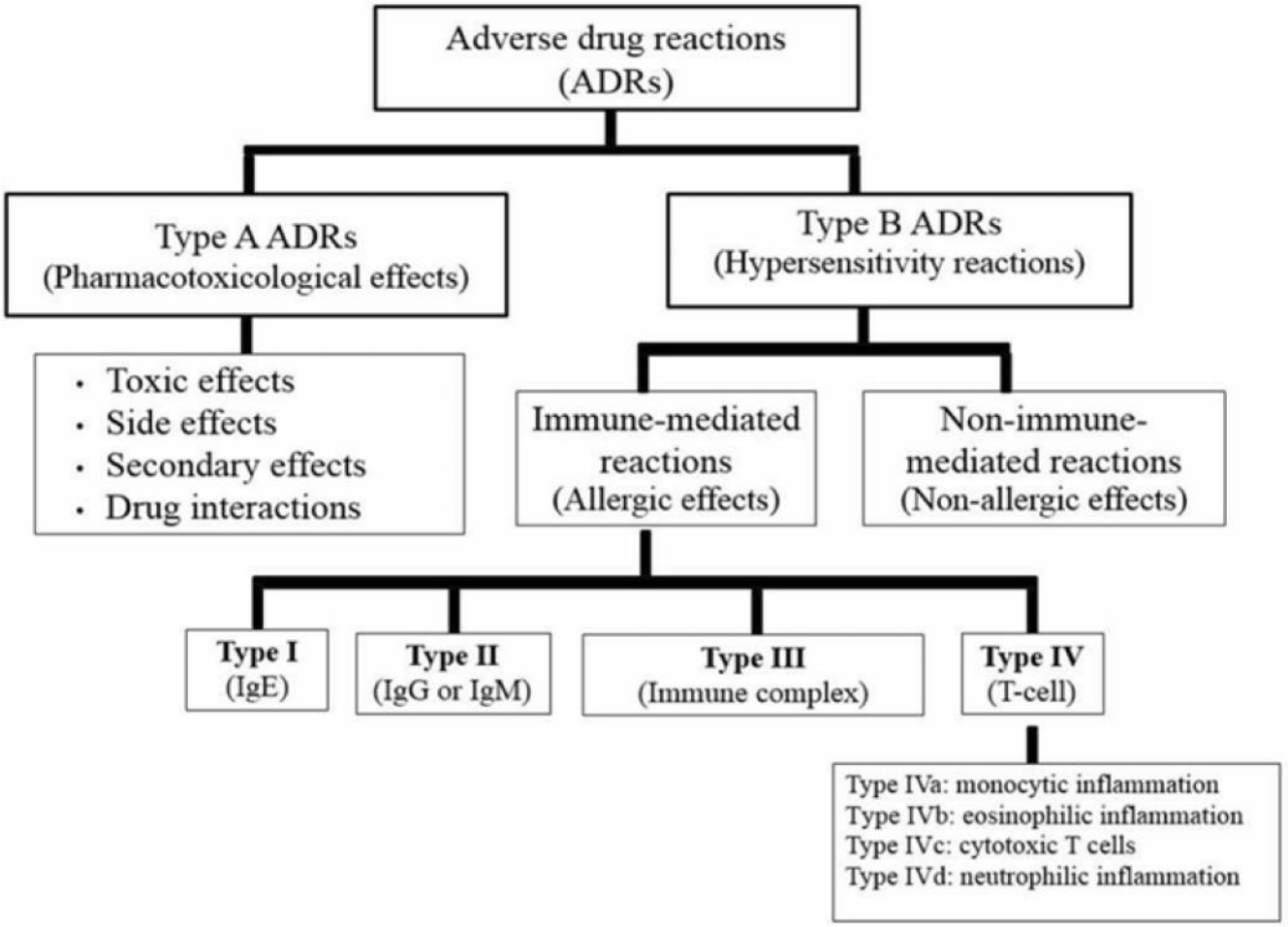
Iintroducation to Adverse Drug Reactions

Definitions and classification of ADRs Definitions ADRs

"An appreciably harmful or unpleasant reaction, resulting from an intervention related to the use of a medicinal product, which predicts hazard from future administration and warrants prevention or specific treatment, or alteration of the dosage regimen, or withdrawal of the product."

Adverse drug reactions (adverse effects) are any unwanted effects of a drug. There is no universal scale for describing or measuring the severity of an adverse drug reaction. Assessment is largely subjective. Reactions can be described as

1. Mild
2. Moderate
3. Severe
4. Lethal (deadly)



Mild or moderate adverse drug reactions do not necessarily mean that people must stop taking a drug, especially if no suitable alternative is available. However, doctors are likely to reevaluate the dose, frequency of use (number of doses a day), and timing of doses (for example, before or after meals; in the morning or at bedtime). Other drugs may be used to control the adverse drug reaction (for example, a stool softener to relieve constipation).

1. Mild adverse drug reactions

Mild reactions usually described as of minor significance include

- Digestive disturbances (such as nausea, constipation, diarrhea)
- Headaches
- Fatigue
- Vague muscle aches
- Malaise (a general feeling of illness or discomfort)
- Changes in sleep patterns

However, such reactions can be very distressing to people who experience them. As a result, people may be less willing to take their drug as instructed, and the goals of treatment may not be achieved.

2. Moderate adverse drug reactions

Moderate reactions include

- Rashes (especially if they are extensive and persistent)
- Visual disturbances (especially in people who wear corrective lenses)
- Muscle tremor
- Difficulty with urination (a common effect of many drugs in older men)
- Any perceptible change in mood or mental function
- Certain changes in blood components, such as a temporary, reversible decrease in the white blood cell count or in blood levels of some substances, such as glucose

Also, reactions that are usually described as mild are considered moderate if the person experiencing them considers them distinctly annoying, distressing, or intolerable.

3. Severe adverse drug reactions

Severe reactions include those that may be life threatening (such as liver failure, abnormal heart rhythms, certain types of allergic reactions), that result in persistent or significant disability or hospitalization, and that cause a birth defect. Severe reactions are relatively rare. People who develop a severe reaction usually must stop using the drug and must be treated. However, doctors must sometimes continue giving high-risk drugs (for example, chemotherapy to people with cancer or immunosuppressants to people undergoing organ transplantation). Doctors use every possible means to control a severe adverse drug reaction.

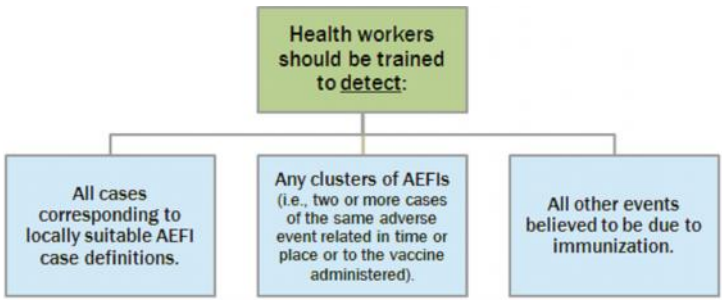
4. Lethal adverse drug reactions

Lethal reactions are those in which a drug reaction directly or indirectly caused death. These reactions are typically severe reactions that were not detected in time or did not respond to treatment. Lethal reactions can be the reasons that some drugs are withdrawn from the market.

Detection and Reporting OF Adverse Drug Reactions

Parents of immunized infants/children, health workers at immunization facilities and staff of accident and emergency rooms in hospitals are most likely to recognize or detect AEFIs (Adverse events following immunization when they first occur.

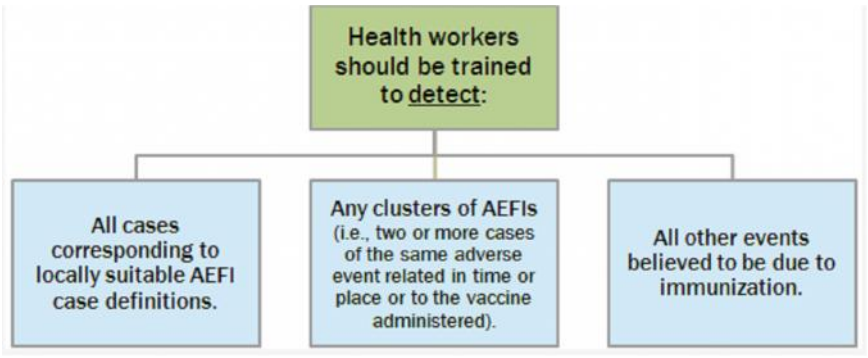
Health workers have the responsibility to detect AEFIs and report AEFIs when appropriate. They also have the responsibility to treat or refer patients for treatment. All immunization staff must be able to identify and report adverse events. Detection requires effective staff training and education to ensure accurate diagnosis of AEFIs based on clear case definitions, which can be included on the AEFI reporting form and in the national AEFI guidelines.



Immunization programme managers should establish appropriate criteria for detecting AEFIs by identifying adverse events of importance to the programme in their country.

Methods in Causality Assessment

Causality assessment outcomes help raise awareness of vaccine associated risks among healthcare workers. This, combined with knowledge of benefits of immunization, forms the basis of vaccine information for parents and/or vaccinees.



The quality of a causality assessment depends on the:

- quality of AEFI case report,
- effectiveness of AEFI reporting system,
- Quality of the causality review process.

Severity and Seriousness Assessment

The U.S Food and Drug Administration defines a serious adverse event as one when the patient outcome is one of the following:

- Death
- Life-threatening
- Hospitalization (initial or prolonged)
- Disability - significant, persistent, or permanent change, impairment, damage or disruption in the patient's body function/structure, physical activities or quality of life.
- Congenital abnormality
- Requires intervention to prevent permanent impairment or damage

Severity is a point on an arbitrary scale of intensity of the adverse event in question. The terms "severe" and "serious", when applied to adverse events, are technically very different. They are easily confused but cannot be used interchangeably, requiring care in usage.

A headache is severe if it causes intense pain. There are scales like "visual analog scale" that help clinicians assess the severity. On the other hand, a headache is not usually serious (but may be in case of subarachnoid haemorrhage, subdural bleed, even a migraine may temporally fit criteria), unless it also satisfies the criteria for seriousness listed above.

Predictability and Preventability Assessment

Predictability is the degree to which a correct prediction or forecast of a system's state can be made either qualitatively or quantitatively.

Causal determinism has a strong relationship with predictability. Perfect predictability implies strict determinism, but lack of predictability does not necessarily imply lack of determinism. Limitations on predictability could be caused by factors such as a lack of information or excessive complexity.

In experimental physics, there are always observational errors determining variables such as positions and velocities. So perfect prediction is *practically* impossible. Moreover, in modern quantum mechanics, Werner Heisenberg's indeterminacy principle puts limits on the accuracy with which such quantities can be known. So such perfect predictability is also *theoretically* impossible.

Management of Adverse Drug Reactions

Management of ADRs is integral to patient safety. Insufficient attention has been paid to identifying ADRs and no appropriate method has been universally adopted and applied to monitor and manage ADRs in clinical practice. Traditionally, doctors prescribe, pharmacists dispense and nurses administer medicines. Although the roles of some nurses and pharmacists have expanded, the task of monitoring patients for potential ADRs is not assigned to any one profession. Teamwork and involvement of all stakeholders in safety initiatives will facilitate development of more integrated and useable systems that will prevent errors, including preventable events relating to suboptimal monitoring, where potential known adverse effects do not receive due attentio, for example failure to check postural hypotension in patients prescribed diuretics or antihypertensives. Barriers to ADR monitoring and management include: patient non-adherence (accidental, deliberate, informed or uninformed); healthcare providers' workloads; unfamiliarity with/ ignorance of ADRs; uncoordinated care; lack of standardized monitoring systems; and communication failures. The negative effects on patients' health, and the burden ADRs place on healthcare systems, require effective policies and strategies to manage the challenge of ADRs. Nurses around the world have a crucial role in the provision of safe pharmacotheraphy, healthcare reform, and improving nursing practice through policymaking.

ADR Management: a policy vacuum this narrative review explores the contributions of nursing to monitoring and managing ADRs. English language work relating to "adverse drug reactions" nursing and "monitoring" was identified from PubMed and the Cochrane library, using these as keywords in titles and abstracts. Hand searches of journals and reference lists yielded additional material. Few relevant publications, and fewer clinical trials, were identified. Therefore, this narrative review also draws on qualitative and descriptive studies, experience and the wider literature. The international literature highlighted the need for: a commonly understood working definition of ADRs; agreed curricula for pre- and post- registration education; strategies to enhance nurses' involvement in managing ADRs; embedding structured medication monitoring systems into practice; application of information technologies; and central roles for nurse leaders in co-ordination and policy development. As with all narrative work, any inferences drawn by readers are logical or theoretical, rather than statistical. Towards an operational definition of ADRs A standardised definition of an ADR is needed before the impact of interventions on the reduction of ADRs can be assessed and common problems, such as incontinence, falls, xerostomia, or failure to breastfeed, are recognised as ADRs The U.S. Food and Drug Administration (FDA) promotes the reporting of serious adverse events that may be related to medicines, but there is less encouragement to report adverse events that are not life-threatening. The definitions from recognised experts are couched in general terms, and are not related to individual patients to help practitioners recognise ADRs and relate patients' signs and symptoms to medicines administered. Distinguishing subtle or ill-defined ADRs from symptoms of illness or ageing is not always easy, and common problems, such as incontinence, constipation, postural hypotension or confusion, may have multiple aetiologies, such as ageing, dehydration, diuretics, antihypertensives, or mental health medicines. Therefore, effective interventions to minimise ADRs need to take a person-centred, holistic approach, and measure outcomes on comprehensive lists of potential ADRs based on reviews, formularies and manufacturers' data sheets, since amelioration of problems is more important to patients than aetiology.

3. Basic Terminologies Used in Pharmacovigilance

Terminologies of adverse medication related events

Adherence: A patient's careful and willing observance of the guidelines for taking a medicine or managing a therapy. This term has largely replaced the term compliance.

Adverse drug reaction (ADR): A harmful effect suspected to be caused by a drug. This term has been used quite loosely to include all kinds of adverse events, many of which are not 'reactions' in the strict sense at all, and have not been subject to any assessment of causality. The term is properly reserved for late-stage analysis when the association between a medicine and an adverse effect has moved beyond 'unmeasurable' or 'uncertain'.

Adverse effect: A negative or harmful patient outcome that seems to be associated with treatment, including there being no effect at all.

Adverse event: Any negative or harmful occurrence that takes place during treatment, that may or may not be associated with a medicine. *Note*. A fall could be such an event that may – or may not – have any association with a medicine.

Attributable risk: Difference between the risk in an exposed population (absolute risk) and the risk in an unexposed population (reference risk); the difference from the absolute risk in the probability of an event happening, attributable to a drug or other variable

Benefit: (a) positive therapeutic effects of treatment in an individual; (b) positive health, social or psychological effects of treatment from the patient's perspective.

Benefit-harm: A description or assessment of both positive and negative effects of a medicine (not necessarily expressed in quantitative terms) as far as they are known, and as perceived by an individual. This is the critical information that health professionals and patients need to make wise therapeutic decisions. The perspectives of professionals and patients on the issues may differ.

Benefit-risk: 'Benefit-risk' is a logically mismatched pair, the more accurate, benefit-harm, is preferable. *See also effectiveness-risk*.

Conditional market authorisation: Approval with constraints, e.g. time limitation, of a medicine on the basis of less comprehensive data than normally required, allowing for more rapid access to novel medicines.

Consumer: The use of the term consumer can be misleading. A person may or may not be an actual consumer of health care or medicines at a given time, but all members of the general public are potential patients/consumers. For the latter group the term general public is preferred. The term patient is normally used when referring to actual consumers of medical or health care.

Control group: The comparison group in medicine-trials not being given the studied medicine.

Drug: See *medicinal product/medicine*: commonly used as a synonym for these terms, drug is falling out of favour in professional medical circles because of the prevalence of its use to describe illicit substances.

Effectiveness: A measure of the chances or odds (probability) of a medicine working positively as expected for patients.

Effectiveness-risk: A comparison of the statistical chances (probability) of a medicine working as expected and/or causing harm. This is the correct term for this comparison, not 'benefit-risk', which is a logically mismatched pair.

Efficacy: A measure of the extent to which a chemical substance or medicine works positively under laboratory conditions and in a selected group of patients.

Epidemiology: The study of disease in populations.

Event: A specific, identifiable happening or occurrence, e.g. the taking of a medicine; the experience of an adverse effect.

Excipients: Materials included to make a pharmaceutical formulation (e.g. a tablet) apart from the active drug substance, e.g. fillers, stabilisers, flavouring agents, colouring agents.

General public/the public: People collectively as members of the community.

Generics: Medicinal products containing the same, or near-identical, active ingredients as the originally approved branded (innovator) product. Dosage form, safety, strength, route of administration, quality, performance characteristics and intended use should be equivalent; but excipients may differ.

Harm: The damage or injury that is or might be caused by a medicine, including death. The concept extends to social and psychological damage or impairment, especially from the patient's perspective.

Hazard: The intrinsic chemical or biological characteristics of a medicine or its use that have the potential to cause harm.

Health professional/healthcare professional: Person who is trained and licensed to provide health care to humans. Includes: doctor, nurse, dentist, pharmacist, midwife; excludes: veterinarian.

Herbal medicine: The use of plants for medicinal purposes; also known as botanical medicine or phytomedicine. See also *Traditional medicine.*

Homeopathy: A treatment system based on the belief that disease symptoms can be cured by small doses of substances which produce similar symptoms in healthy people.

Incidence: Number of new cases of an outcome which develop over a defined time period in a defined population at risk. *Note.* Incidence is a frequency measurement of outcome development over time (compare *prevalence*).

Indication: Symptoms or disease for which a remedy or treatment is advisable or necessary. The concept 'reason for use' is broader and may include off-label use, misuse etc. In pharmacovigilance, the actual reason for use should ideally be recorded.

Individual case safety report (ICSR): Reports sent by health professionals or patients when an adverse effect has occurred in a patient taking one or more medicines. These have also been referred to as adverse drug reaction (ADR) reports or adverse event (AE) reports. See also *Pharmacovigilance reporting systems.*

Media: Means of communication. *Note.* This term includes any channel of communication, and may also refer to those engaged in them.

Mass media: Main channels of communication to the general public. Includes: newspapers, radio, television and internet. Includes journalists, editors, bloggers etc., engaged in such communication. See also *Social media.*

Medicinal product/medicine: Product intended to be administered to humans for treating or preventing disease; with the view to making a medical diagnosis; or to restore, correct or modify physiological functions.

Member countries: Countries that have joined the WHO Programme for International Drug Monitoring, fulfilling the membership criteria.

National centres: Organisations or entities recognised by government to represent their country in relation to pharmacovigilance in the WHO Programme for International Drug Monitoring.

Odds: Probability of an occurrence p divided by the probability of its non-occurrence (1-p).

Odds ratio: Ratio of the odds in a given population and the odds in another population. *Note*. In case-control studies the odds ratio is the odds of exposure (to a medicinal product) in cases (e.g. individuals with an adverse effect) divided by the odds of exposure in controls (e.g. individuals without the adverse effect). The odds ratio provides an estimate of the relative risk.

Over the counter (OTC): A medicine available for sale without a prescription

Patient: Person awaiting or under medical or health care treatment. This concept includes anyone taking medicines, also those who are self-medicating.

Pharmacoepidemiology: Branch of epidemiology (see above) dealing with the effects of medicines in populations.

Pharmacology: Study of the uses, effects and modes of action of drugs.

Pharmacovigilance: The science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other possible drug-related problems.

Pharmacovigilance reporting systems: The core data-generating system of pharmacovigilance, relying on healthcare professionals and patients to identify and report any suspected adverse effects from medicines to their local or national pharmacovigilance centre or to the manufacturer. Also referred to as postmarketing/ safety surveillance/spontaneous reporting systems.

Phocomelia: Characteristic deformity caused by exposure to thalidomide in the womb, also very rarely occurring spontaneously. Means: limbs like a seal.

Phytotherapy: Western-style, scientific treatment with plant extracts or materials.

Placebo: An inactive substance (often called a sugar pill) given to a group being studied to compare results with the effects of an active substance.

Pre-marketing: The developmental stage before a drug is approved and available for prescription or sale to the public.

Post-marketing: The stage when a drug is approved and generally available on the market. See also *Conditional market authorisation.*

Prescriber: Health professional licensed by law to prescribe. *Note.* A prescriber may have a limited licence, for instance allowing prescription of certain categories of medicinal products, e.g. in some countries midwives are licensed to prescribe only oral contraceptives.

Prescription only medicine (POM): A drug licensed for use only by prescription.

Prevalence: Number of existing cases of an outcome in a defined population at a given point in time. *Note.* Prevalence is calculated as a proportion (cases divided by total in population), often expressed as a percentage.

Prophylaxis: Prevention or protection.

Proportion: Number of cases of an outcome divided by the total number of individuals in the studied population. *Note.* A percentage is the proportion (cases divided by total in population) multiplied by 100.

Rare: In pharmacovigilance, an event with a probability between 1 in 10,000 and 1 in 1,000, or 0.01% and 0.1%.

Rate: Number of cases of an outcome divided by the total person-time of observation. *Note.* A rate figure normally has a large whole number as a multiplier, reflecting the actual, or a scaled-up, population

(e.g. 1,000, 10,000, 20,000).

Rational drug use: A visionary concept implying the achievement of optimal prescribing and use of drugs.

Reference risk: Risk in a population of unexposed persons. Synonyms: Baseline risk, background risk. *Note*. The unexposed population refers to a reference group, as closely comparable to the exposed population as possible, apart from the exposure.

Regulatory authority: The legal authority in any country with the responsibility for regulating all matters relating to drugs.

Relative risk: Ratio (comparison) of the risk in an exposed population (absolute risk) and the risk in an unexposed population (reference risk). *Note*. Relative risk is the result of a relative comparison between outcome frequency measurements, e.g. incidences.

Risk: The probability of harm being caused; the probability (chance, odds) of an occurrence. *Note 1*. The term risk normally, but not always, refers to a negative outcome. *Note 2*. Contrary to harm, the concept of risk does not involve any reference to the nature or severity of an outcome.

Serious: An adverse event or reaction that results in death; requires hospitalisation or extension of hospital stay; results in persistent or significant disability or incapacity; is life- threatening. *Note*. This contrasts with severe, which is used to indicate intensity (as in severe headache).

Side effect: Any unintended outcome that seems to be associated with treatment, including negative or positive effects. This term has come to be used exclusively in the sense of "adverse effect"; this loses the important dimension of potential reference to unintended positive effects as well as linguistically masking the adverse element of a negative side effect.

Signal: There are several definitions of signal, such as that by CIOMS and that by WHO (see What is a signal?). In essence, a signal is a hypothesis of a risk with a medicine, with various levels of evidence and arguments to support it. The complexity of the signal detection process cannot easily be captured in a single, precise definition. In addition to detecting previously unknown risks with medicines, signal detection should aim to find and communicate any important and relevant information that adds to previous safety knowledge about a medicine, including also risk factors/at risk groups, details of severity, time at risk, and duration of adverse effects.

SSFFCs: There is currently no universally agreed definition of what used to be widely known as "Counterfeit medicine". Since the 70th World Health Assembly in 2017, WHO is using the term "Substandard and Falsified (SF) medical products". For more information see the WHO website.

Stakeholder: Individual, or group of individuals, with a legitimate interest and responsibility in a human endeavour, e.g. pharmacovigilance. Their interest may be because they will have a role in implementing decisions, or because they will be affected by actions taken.

Thalidomide: Drug prescribed in the 1950s and early 1960s as a mild sleeping pill and remedy for morning sickness in pregnant women. Led to serious birth defects (see *Phocomelia*). The disaster was the catalyst for the formation of the WHO Programme for International Drug Monitoring. Thalidomide has returned as a treatment of certain cancers and a complication of leprosy.

Traditional medicine: The sum total of the knowledge, skills, and practices based on the theories, beliefs, and experiences indigenous to different cultures, whether explicable or not, used in the maintenance of health as well as in the prevention, diagnosis, improvement or treatment of physical and mental illness.

Regulatory Terminologies

Life Science: It is a very broad category including studies of living things on the molecular level up to ecosystems. These include pharma companies, Biotech companies and companies doing research in medical field.

Health Science: It is part of Life Science and concentrates on studying factors that affect the well being of creatures almost always animal kingdom and usually people(that's where the money is). These include hospitals, pharmacies, etc.

Pharmacovigilance: Pharmacovigilance is the science of collecting, monitoring, researching, assessing and evaluating information from healthcare providers and patients on the adverse effects of medications, biological products, herbalism and traditional medicines with a view to:

- identify new information about hazards associated with medicines
- Prevent harm to patients.

Pharmaceutical companies monitor the safety of their drugs during clinical studies and after their products are on the market. This process, called "pharmacovigilance," is also called "safety monitoring" during a clinical study. During a study, investigators submit "clinical safety reports" of serious adverse events (SAEs). Once a drug is on the market, patients, caregivers, physicians, pharmacists, other healthcare providers, and anyone else can submit "spontaneous reports" of adverse events that concern them

Argus Safety: Argus Safety is Oracle's complete pharmacovigilance software system designed to solve the pharmaceutical industry's toughest regulatory challenges. Argus Safety supports drug safety business processes from an easy-to-understand user interface.

Adverse Event: An adverse event (AE) is any unwanted medical occurrence in a patient who is consuming a medicinal product. This occurrence does not necessarily have to have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign (for example, an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to this medicinal product.

Adverse Drug Reaction: All noxious and unintended responses to a medicinal product related to any dose are considered adverse drug reactions. The phrase "responses to a medicinal product" means that a causal relationship between a medicinal product and an adverse event is at least a possibility. The difference between AE and ADR is that an ADR is characterized by the fact that a causal relationship between drug and the occurrence is suspected but it is not necessary in case of an AE.

Seriousness, Expectedness and Relatedness

ICH E2A guideline says that a "Serious" AE or ADR is any unfavourable medical occurrence that at any dose:

- results in Death
- is Life-Threatening
- requires Hospitalization (initial or prolonged)
- results in Disability — significant, persistent, or permanent change, impairment, damage or disruption in the patient's body function/structure, physical activities or quality of life.
- results in Congenital Anomaly
- is Medically significant

All AEs that are previously unobserved or undocumented are called "unexpected". Their nature or severity is not consistent with the applicable product information (e.g., Investigator's Brochure for an unapproved investigational medicinal product). Determination of expectedness is made by the sponsor on a case-by-case basis. Expected events typically do not require expedited reporting to the regulatory authorities.

"Relatedness" or "Causality Assessment" means that analysis is done to determine if the event has a reasonable possibility of being related to the consumption or exposure to product. Many terms and scales are used to describe the degree of causality, including terms such as certainly, definitely, probably, possibly, or likely related or not related, but there is no standard.

SUSAR: Suspected Unexpected Serious Adverse Reaction

Product: A product can be of 3 types: Drug, Vaccine or Device (e.g Syringe, Pacemaker). Following is product related information:

Product family
Product Group
Generic Name
Trade Name
Ingredients

e.g Product family can be Muti-Vitamins, Product group can be Nutritional Supplements, Generic Name can be B+Complex, Trade name can be Zevit, Ingredients can be Vitamin B1, B2, B3, B4, B6 and B12.

Every product should have a Licence. Trade name is governed by Licence. License is of 2 types: Investigational and Marketed.

Challenge-dechallenge-rechallenge (CDR): Challenge-dechallenge-rechallenge (CDR) is a medical testing protocol in which a medicine or drug is administered, withdrawn, then re- administered, while being monitored for adverse effects at each stage. The protocol is used when statistical testing is inappropriate due to an idiosyncratic reaction by a specific individual, or a lack of sufficient test subjects and unit of analysis is the individual. During the withdraw phase, the medication is allowed to wash out of the system in order to determine what effect the medication is having on an individual. CDR is one means of establishing the validity and benefits of medication in treating specific conditions as well as any adverse drug reactions. The Food and Drug Administration of the United States lists positive dechallenge reactions (an adverse event which disappears on withdrawal of the medication) as well as negative (an adverse event which continues after withdrawal), as well as positive rechallenge (symptoms re-occurring on re-administration) and negative rechallenge (failure of a symptom to re-occur after re-administration). It is one of the standard means of assessing adverse drug reactions in France.

ICSR (Individual Case Safety Report): ICSR is a report of information describing adverse event(s) / reaction(s) experienced by an individual patient. The event(s)/reaction(s) can be related to the administration of one or more medicinal products at a particular point in time. The ICSR can also be used for exchange of other information, such as medication error(s) that do not involve adverse events(s)/reaction(s). An ICSR may also be referred to as Safety Report.

E2B(Electronic to Business): E2B is the international standard for transmitting medicine adverse event reports specified by the ICH.

MedRA: Medical Dictionary for Drug Regulatory Affairs/Activities is a clinically validated international medical terminology used by regulatory authorities and the regulated biopharmaceutical industry throughout

the entire regulatory process, from pre-marketing to post-marketing activities, and for data entry, retrieval, evaluation, and presentation. MedDRA is used in the US, European Union and Japan. Its use is currently mandated in Europe and Japan for safety reporting.

The MedDRA dictionary is organized by System Organ Class (SOC), divided into High-Level Group Terms (HLGT), High-Level Terms (HLT), Preferred Terms (PT) and finally into Lower-Level Terms (LLT). In addition, the MedDRA dictionary includes Standardized MedDRA Queries (SMQs). SMQs are groupings of terms that relate to a defined medical condition or area of interest. WHO dictionary is used for products(drugs, vaccines or devices) while MedRA is used for events(e.g diagnosis, symptoms etc)

Sources of Individual Case Reports

1. Communication by healthcare professionals or consumers to a company, regulatory authority or other organization (e.g. WHO, Regional Centers, Poison Control Center) that describes one or more adverse drug reactions 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. These are called spontaneous reports
2. Cases of ADRs mentioned in scientific and medical literature. These are called Literature cases. Spontaneous and Literature cases' sources are also called "Unsolicited sources"
3. Cases received from organized data collection systems, which include clinical trials, post-approval named patient use programs, other patient support and disease management programs, surveys of patients or healthcare providers, or information gathering on efficacy or patient compliance. Such sources are also called "Solicited Sources"

Efficacy (of a medicine or treatment): The ability of a medicine or treatment to produce a result. A medicine passes efficacy trials if it is effective at the dose tested and against the illness for which it is prescribed.

Marketing Authorization Application (MAA): This is an EU term and is an application to the relevant health authority within the EU, for example the European Medicines Agency, for approval to market a medicinal product.

Marketing Authorization Holder (MAH): This is an EU term. The MAH is the company in whose name the marketing authorization has been granted. This party is responsible for all aspects of the product, including quality and compliance with the conditions of the marketing authorization.

New Drug Application (NDA): This is a US term. It is an application for a license to market a medicine for a specified indication, submitted to the US FDA after clinical trials have been completed.

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02. Drug And Disease Classification

1. Drug And Disease Classification

Anatomical, Therapeutic and Chemical Classification of Drugs Anatomical Classification of Drugs

The Anatomical Therapeutic Chemical (ATC) Classification System is a drug classification system that classifies the active ingredients of drugs according to the organ or system on which they act and their therapeutic, pharmacological and chemical properties.

Therapeutic Classification of Drugs

This type of categorisation of drugs is from a medical perspective and categorises them by the pathology they are used to treat. Drug classes that are defined by their therapeutic use (the pathology they are intended to treat) include:

- Analgesics
- Antibiotic
- Anticoagulant
- Antidepressant
- Anticancer
- Antiepileptic
- Antipsychotic
- Antiviral
- Sedative
- Antidiabetic
- Cardiovascular

Chemical Classifications of Drugs

- **Opioids:** Opioids are derived from the drug opium or synthetic versions that mimic the chemical structure of opium. This class of drugs interacts with neurotransmitters in the brain to block signals. Opioids are powerful. They cause both intense feelings of pleasure and can block pain. Opioid addiction is significant and is increasingly becoming the most serious addiction crisis facing America today.
- **Alcohol:** Alcohol is one of the most widely abused substances across the world. It's legal to consumer alcohol in the US, even though alcohol is a central nervous system (CNS) depressant. It causes severe long-term damage to the liver. Alcohol creates feelings of pleasure and lowers inhibitions.
- **Benzodiazepines and barbiturates:** These drugs function by interacting with a neurotransmitter called GABA (gamma-aminobutyric acid). These drugs impact the body and mind differently but generally create calming and sedative effects. Often prescribed to treat a variety of psychiatric and sleep conditions, they're highly addictive.
- **Cocaine and other stimulants:** These drugs accelerate the activity of the CNS making a person feel energized, focused, and alert for long periods of time. The converse reaction is that a person feels edgy, paranoid, and angry.
- **Inhalants:** Mostly consumed through breathing, these drugs can exist in vapor form at room temperature.

Most inhalants are found in household items so they're often used by adolescents and children. They tend to be less addictive than other substances but are incredibly dangerous.

- **Hallucinogens:** By interacting with the CNS, this class of drugs alters the perception of time, reality, and space. They might cause a user to hear things or imagine situations that don't exist.
- **Cannabis:** One of the most widely used drugs across the world. Cannabis affects the cannabinoid receptors in the brain. This drug comes in many different forms and affects each user differently.
- **New psychoactive substances:** This refers to anything that's been lab created to mimic naturally occurring drugs falls into this category. This includes synthetic cannabis, lab-created ketamine, and more.

International Classification of Diseases

- ICD (International Statistical Classification of Diseases and Related Health Problems), shortly known as International Classification of Diseases is the base/foundation for the identification of health trends and statistics.
- ICD is an international uniform standard for reporting diseases and health conditions.
- It is the diagnostic classification standard for all clinical and research purposes.
- ICD maps the human health condition from birth to death. No matter, however we die of, it will be recorded/ coded under ICD.
- ICD is a global base, where the global health movements are recorded by following the international standards, in company with the numerical analysis tools and techniques for broadcasting and recording the disease patterns along with the well-being of the people.
- ICD incorporates different factors influencing health, including external causes of morbidity and mortality.
- ICD defines the various patterns of infectious, communicable, and non-communicable diseases followed by disorders, injuries and numerous health disability in a systematic way, which helped in the uprising of following points:
  - √ Accessible health information that acts as a benchmark for planning health strategies.
  - √ Easy storing, retrieval and investigation of health statistics for evidenced based decision-making and accountability.
  - √ Exchange of health information between hospitals, institutions, nations, and different development regions.
- Relate data within the same areas across different periods.
- Developing international guideline and strategies to bring down the high prevalence and incidence rate, mortality rate, death rate of vulnerable diseases.
- Determining the risk factors that have negative impacts on health.
- Abundant use of monitoring and supervision skills in various field of health science in the identification of diseases in respect to their severity and detrimental to health.
- ICD also helps in resource allocation.

General Principles of Disease Classification

- A statistical classification of diseases must be confined to a limited number of mutually exclusive categories.
- The categories have to be chosen to facilitate the statistical study of disease phenomena.
- A specific disease entity that is of particular public health importance or that occurs frequently should have its own category.

- Every disease or morbid condition must have a well-defined place in the list of categories.
- A statistical classification of diseases should retain the ability both to identify specific disease entities and to allow statistical presentation of data for broader groups, to enable useful and understandable information to be obtained.

Principles of classification of ICD

The ICD is a variable-axis classification. The structure of ICD structure was developed of that proposed by William Farr during early days of international discussions. According to him, for all practical, epidemiological purposes, statistical data on diseases should be grouped in the following way:

- epidemic diseases
- constitutional or general diseases
- local diseases arranged by site
- developmental diseases
- injuries

Diseases Classified in ICD

The diseases are categorized On the basis of	Disease
Body system or region	Abdominal diseaseGastrointestinal disease
Anatomic	Lung diseaseLiver disease
Function	Metabolic disease
Pathological/ nature of the disease process	Inflammatory diseaseTumors formation
Etiologic/ cause	Bacterial infection
Epidemiology	Epidemic disease
Statistical	High prevalence and incidence rate disease.

Defined Daily Dose (DDD)

The basic definition of the defined daily dose (DDD) is:

The DDD is the assumed average maintenance dose per day for a drug used for its main indication in adults.

General principles for DDD assignment (to the top)

DDDs are only assigned to drugs with an ATC code and a DDD will normally not be assigned for a substance before a product is approved and marketed in at least one country.

The basic principle is to assign only one DDD per route of administration within an ATC code.

DDDs for single substances are normally based on monotherapy. Exceptions to this rule are given in the guidelines of the relevant ATC groups.

For substances indicated for rare disorders with highly individual dosing schedules, the Working Group could decide not to assign a DDD.

DDDs are not established for topical products, sera, vaccines, antineoplastic agents, allergen extracts, general and local anesthetics and contrast media.

When a new DDD is assigned, various sources are used to get the best overview of the actual or expected

use of a substance. The assigned DDD is based on the following principles:

- The average adult dose recommended for the main indication as reflected by the ATC code. When the recommended dose refers to body weight, an adult is considered to be a person of 70 kg. It should be emphasised that even special pharmaceutical forms mainly intended for children (e.g. mixtures, suppositories) are assigned the DDD used for adults. Exceptions are made for some products only used by children, e.g. growth hormones and fluoride tablets.
- The recommended maintenance dose (long term therapeutic dose) is usually preferred when establishing the DDD. The initial dose may differ from the maintenance dose but this is not reflected in the DDD. If the approved dose recommendation provides limited information about maintenance dose, the DDD will usually be the average of the maintenance dose range. Examples of interpretation of approved dose titration recommendations:
- "Titrate up to a high dose if it is tolerated": the high dose would normally be chosen as the DDD.
- "Consider to increase the dose only if efficacy is not satisfactory with initial dose": the DDD would normallybe based on the initial dose.
- For some groups of medicinal products specific principles for DDD assignment are established (e.g. the DDDs for the selective serotonin agonists in the treatment of migraine are based on the approved initial dose). These principles are given in the guidelines for the relevant ATC groups.
- The treatment dose is generally used. If, however, prophylaxis is the main indication, this dose is used, e.g. for fluoride tablets (A01AA01) and some antimalarials.
- A DDD is usually established according to the declared content (strength) of the product. Various salts of a substance are usually not given different DDDs. Exceptions are described in the guidelines for the relevant ATC groups. For example, the DDDs for antimalarials are expressed as the base.
- Different stereoisomeric forms are normally assigned separate DDDs and ATC codes. The DDDs for stereoisomeric forms are described in the respective ATC groups.
- Prodrugs, which have not been given a separate ATC code, are normally not given a separate DDD.
- The DDD is often identical for various dosage forms of the same drug. Different DDDs can be established when the bioavailability is substantially different for various routes of administration (e.g. oral and parenteral administration of morphine) or if the dosage forms are used for different indications. When the use of parenteral formulations represents only a minor fraction of the total use for a specific indication, these products have normally not received a separate DDD even if the bioavailability of the oral form is substantially different. This principle has not been strictly followed in recent years. Parenteral antibacterials are for example mainly used in hospitals and often for more severe infections than in primary care. The DDDs are frequently used as indicators for antibacterial use in hospitals, and it has been decided that assigning different DDDs for oral and parenteral formulations could be important in some cases to improve the usefulness of the methodology in drug utilization monitoring and research.
- Parenteral products with different routes of administration (e.g. i.v. and i.m.) have the same DDD.

International Non-proprietary Names for drugs

An international nonproprietary name (INN) is an official generic and non-proprietary name given to a pharmaceutical drug or an active ingredient. INNs are intended to make communication more precise by providing a unique standard name for each active ingredient, to avoid prescribing errors.[1] The INN system has been coordinated by the World Health Organization (WHO) since 1953.

Having unambiguous standard names for each drug (standardization of drug nomenclature) is important because a drug may be sold by many different brand names, or a branded medication may contain more than one drug. For example, the branded medications Celexa, Celapram and Citrol all contain the same active ingredient: citalopram; and the antibiotic widely known by the brand name Bactrim contains two active ingredients: trimethoprim and sulfamethoxazole. This combination of two antibiotic agents in one tablet has been available as a generic for decades, but the brand names Bactrim and Septra are still in common use.

Each drug's INN is unique but may contain a word stem that is shared with other drugs of the same class; for example, the beta blocker drugs propranolol and atenolol share the -*olol* suffix, and the benzodiazepine drugs lorazepam and diazepam share the -*azepam* suffix.

Drugs from the same therapeutic or chemical class are usually given names with the same *stem*. Stems are mostly placed word-finally, but in some cases word-initial stems are used. They are collected in a publication informally known as the *Stem Book*.

Examples are

- -*anib* for angiogenesis inhibitors (e.g. pazopanib)
- -*anserin* for serotonin receptor antagonists, especially 5-HT_2 antagonists (e.g. ritanserin and mianserin)
- -*ant* for various receptors antagonists (e.g. aticaprant and rimonabant)
- -*arit* for antiarthritic agents (e.g. lobenzarit)
- -*ase* for enzymes (e.g. alteplase)
- -*azepam* for benzodiazepines (e.g. diazepam and oxazepam)
- -*caine* for local anaesthetics (e.g. procaine or cocaine)
- -*cain*- for class I antiarrhythmics (e.g. procainamide)
- -*coxib* for COX-2 inhibitors, a type of anti-inflammatory drugs (e.g. celecoxib)
- -*mab* for monoclonal antibodies (e.g. infliximab); see Nomenclature of monoclonal antibodies
- -*navir* for antiretroviral protease inhibitors (e.g. darunavir)
- -*olol* for beta blockers (e.g. atenolol)
- -*pril* for ACE inhibitors (e.g. captopril)
- -*sartan* for angiotensin II receptor antagonists (e.g. losartan)
- -*tinib* for tyrosine kinase inhibitors (e.g. imatinib)
- -*vastatin* for HMG-CoA reductase inhibitors, a group of cholesterol lowering agents (e.g. simvastatin)
- -*vir* for antivirals (e.g. aciclovir or ritonavir)
- *arte*- for artemisinin antimalarials (e.g. artemether)
- *cef*- for cefalosporins (e.g. cefalexin)
- *io*- for iodine-containing radiopharmaceuticals (e.g. iobenguane)
- -*vec* for gene therapy vectors (e.g. alipogene tiparvovec)

2. Drug dictionaries and coding in pharmacovigilance

WHO adverse reaction

An international system for monitoring adverse reactions to drugs (ADRs) using information derived from Member States was established in 1971. WHO Headquarters is responsible for policy issues while the operational

responsibility for the programme rests with the WHO Collaborating Centre for International Drug Monitoring, Uppsala Monitoring Centre, (UMC), in Sweden. The system started with 10 countries that had already established national systems for spontaneous adverse reaction reporting and who agreed to contribute data. For an effective international system to become operative, a common reporting form was developed, agreed guidelines for entering information formulated, common terminologies and classifications prepared and compatible systems for transmitting, storing and retrieving and disseminating data were created. The ADRs database in Uppsala currently contains over three million reports of suspected ADRs.

WHO response WHO promotes global drug safety through its Programme for International Drug Monitoring (PIDM), which began in the 1960s. Through the cooperative effort, Member States and WHO work together to identify possible relationships between the use of a drug and adverse effects. Countries that are members in the WHO PIDM are supported by WHO to have national systems in place to report ADRs to the database managed by the WHO collaborating centre, the Uppsala Monitoring Centre. When signals of drug safety problems emerge, WHO shares the results with all Member States?

Facilitates regular information exchanges among Member States on the safety and effectiveness of medicines, involving a network of national pharmacovigilance officers:

- Informs promptly national health authorities about new information on serious adverse effects of pharmaceutical products;
- Provides guidelines to help countries set up national pharmacovigilance centres;\
- Trains health-care professionals on safety monitoring for new and complex medicines (e.g. antiretrovirals to treat HIV).
- Assists countries as they work to strengthen drug regulation and pharmacovigilance systems, to make informed regulatory decisions; and promotes best pharmacovigilance practices, worldwide.

MedDRA and Standardised MedDRA queries

Standardized MedDRA Query Analysis

A Standardized MedDRA Query Analysis (type SMQ in screening results) maps PTs to Standardized MedDRA Queries (SMQs), which are described below. Then a denominator- based disproportionality analysis compares the following:

- Proportion of subjects in the treatment group who experienced PTs meeting SMQ criteria
- Proportion of subjects in the comparator group who experienced PTs meeting SMQ criteria

For more information, see Scores for Disproportionality Analysis Types.

Note that an option is available to use days on drugs as the denominator for results generated for the absence of a time frame.

SMQ definitions

The following description of Standardized MedDRA Queries is based on materials provided by the MSSO (Maintenance and Support Services Organization).

Standardized MedDRA Queries (SMQs) are intended to aid in the identification and retrieval of potentially relevant individual case safety reports; they are groupings of MedDRA terms, ordinarily at the Preferred Term (PT) level, that relate to a defined medical condition or area of interest. Terms included in a given SMQ may relate to relevant signs, symptoms, diagnoses, syndromes, physical findings, laboratory and other physiologic test data,

etc. However, the methods used for SMQ development systematically exclude other parameters, such as timing of occurrence of an adverse event relative to drug administration, patient age, patient sex, disease severity, drug names, or case outcome. These other features may be essential elements of a given safety database search or an analysis of causality, but generally need to be considered separately from the adverse events of interest.

SMQs are not necessarily comprehensive, error-free, or universally applicable. However, results of performing a given SMQ search on a database should be reproducible and an identical search may be performed on any database utilizing the appropriate version of MedDRA. Thus, the overarching rationale for SMQs is to provide a framework for reproducible searches and to avoid expensive duplication of effort. SMQs are not intended to provide a final answer to a regulatory question(s), but rather provide a standardized frame of reference for application when appropriate.

Conceptually, SMQs as described by MSSO may have a mixture of very specific terms and less specific terms that are consistent with a description of the overall clinical syndrome associated with a particular adverse event and drug exposure. Some SMQs are a straightforward collection of terms; others must be designed to accommodate combinations of terms from more than one group. To address these varied aspects, SMQs may have certain specific design features:

- **Narrow and Broad:** This approach accommodates those instances in which a user may need to identify cases that are highly likely to represent the condition of interest (a "narrow" scope) and those instances in which a user seeks to identify all possible cases, including some that may prove to be of little or no interest on closer inspection (a "broad" scope).
- **Algorithm:** For some SMQs, it may aid in case identification if the user applies an algorithmic approach to the terms in the SMQ. In other words, better case identification may result if cases are selected based on a defined combination of selected terms. For algorithmic SMQs, all selected terms are assigned a Category (e.g., A, B, ..., I) by MSSO. Categories are used in algorithmic formulas (e.g., A or (B and C)) to identify "broad" scope term combinations. For algorithmic SMQs only, Category A is synonymous with "narrow" scope.
- **Hierarchy:** Some SMQs are a series of queries related to one another in a hierarchical relationship similar to the hierarchical structure of MedDRA itself. These consist of one or more subordinate SMQs that could be combined to create a superordinate, more inclusive SMQ. For example, in MedDRA 9.1 the two-level hierarchy Haemorrhages (SMQ) includes two subordinate SMQs:

  Haemorrhages

  Haemorrhage terms (excl laboratory terms)

  Haemorrhage laboratory terms

In the current implementation of the Standardized MedDRA Query Analysis, SMQs from all hierarchical levels may be generated for a study.

Implementation of the Standardized MedDRA Query Analysis is based on SMQs defined in the MSSO's *Introductory Guide for Standardized MedDRA Queries* for each MedDRA version beginning with MedDRA version 8.0. The SMQs generated by a Standardized MedDRA Query Analysis depend on the MedDRA version associated with the study.

Who Drug Dictionary

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

It is used by pharmaceutical companies, clinical trial organizations and drug regulatory authorities for identifying drug names in spontaneous ADR reporting (and pharmacovigilance) and in clinical trials. Created in 1968 and regularly updated, since 2005 there have been major developments in the form of a WHO Drug Dictionary Enhanced (with considerably more fields and data entries) and a WHO Herbal Dictionary, which covers traditional and herbal medicines. Since 2016 all of the WHODrug products have been available in a single subscription service called WHODrug Global.

WHO Drug drug code consist of 11 characters (alphanumeric code). It has 3 parts: Drug Record Number (DrugRecNo), Sequence number 1(Seq1) and Sequence number 2 (Seq2). DrgRecNo consists of 6 characters. It uniquely identifies active moieties, regardless of salt form or plant part and extract. Seq1 is used to uniquely identify different variations (e.g. salts and esters), plant parts and extraction methods, thereby defining active substances or a combination of active substances. WHODrug records sharing the same DrugRecNo and Seq1 contain the same variation/plant part/extract variation of the same active moiety. For single- ingredient records, Seq1=01 identifies a specific active moiety. If Seq1 is higher than 01 it refers to variations of that active moiety. For multi-ingredient records, Seq1=01 identifies a combination of active moieties. If Seq1 is higher than 01 it refers to variations of one or more of the active moieties in the combination. Finally, Seq2 uniquely identifies the name of the record in WHODrug.

Eudravigilance medicinal product dictionary

The submission of data on medicines by marketing-authorisation holders into the EVMPD is a legal requirement from the 2010 pharmacovigilance legislation.

Pharmaceutical companies can use in-house tools to initiate the electronic submission of information on medicinal products in full compliance with the agreed and mandatory format.. Electronic submissions of eXtended EudraVigilance Medicinal Product Report Messages (XEVPRMs) should be performed via the EudraVigilance Gateway to the Agency.

Pharmaceutical companies can use the XEVMPD data entry tool (EVWEB) provided by the Agency; this was specifically developed for Small and Medium Sized Enterprises (SMEs) but can be made available to any pharmaceutical company for the purpose of electronic submission of information on medicinal products to the Agency.

3. Information Resources In Pharmacovigilance

3.1. Basic Drug Information Resources

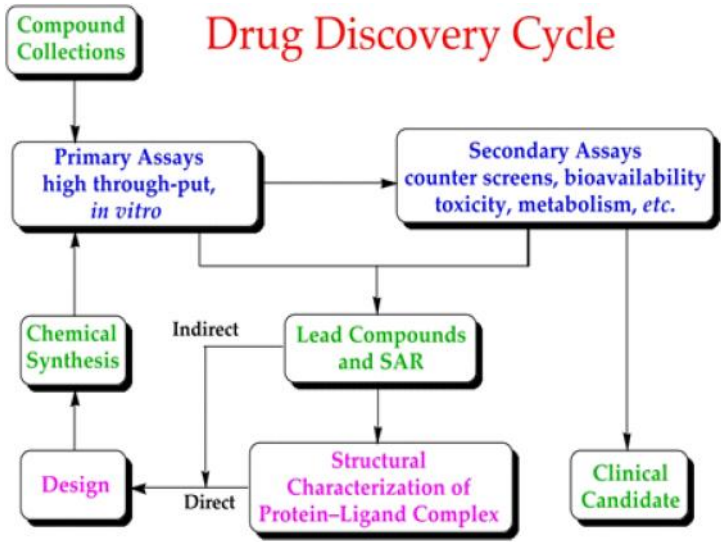
In the fields of medicine, biotechnology and pharmacology, drug discovery is the process by which new candidate medications are discovered.

Historically, drugs were discovered by identifying the active ingredient from traditional remedies or by serendipitous discovery, as with penicillin. More recently, chemical libraries of synthetic small molecules, natural products or extracts were screened in intact cells or whole organisms to identify substances that had a desirable therapeutic effect in a process known as classical pharmacology. After sequencing of the human genome allowed rapid cloning and synthesis of large quantities of purified proteins, it has become common practice to use high throughput screening of large compounds libraries against isolated biological targets which are hypothesized to be disease-modifying in a process known as reverse pharmacology. Hits from these screens are then tested in cells and then in animals for efficacy.

Modern drug discovery involves the identification of screening hits, medicinal chemistry and optimization of those hits to increase the affinity, selectivity (to reduce the potential of side effects), efficacy/potency, metabolic

stability (to increase the half-life), and oral bioavailability. Once a compound that fulfills all of these requirements has been identified, the process of drug development can continue. If successful, clinical trials are developed.

Modern drug discovery is thus usually a capital-intensive process that involves large investments by pharmaceutical industry corporations as well as national governments (who provide grants and loan guarantees). Despite advances in technology and understanding of biological systems, drug discovery is still a lengthy, "expensive, difficult, and inefficient process" with low rate of new therapeutic discovery. In the 21st century, basic discovery research is funded primarily by governments and by philanthropic organizations, while late - stage development is funded primarily by pharmaceutical companies or venture capitalists. To be allowed to come to market, drugs must undergo several successful phases of clinical trials, and pass through a new drug approval process, called the New Drug Application in the United States.



Discovering drugs that may be a commercial success, or a public health success, involves a complex interaction between investors, industry, academia, patent laws, regulatory exclusivity, marketing and the need to balance secrecy with communication. Meanwhile, for disorders whose rarity means that no large commercial success or public health effect can be expected, the orphan drug funding process ensures that people who experience those disorders can have some hope of pharmacotherapeutic advances.

3.2 Specialised Resources for ADRs

Maryland Mediation and Conflict Resolution Office: The Maryland Mediation and Conflict Resolution office, commonly known as MACRO, is a nationally recognized leader in the dispute resolution community. MACRO is a small statewide office which has pioneered the use of collaborative processes in government agencies, private business and the juvenile and criminal justice systems in Maryland.

American Bar Association Section of Dispute Resolution: The American Bar Association's Section on Dispute Resolution promotes the use of multiple dispute resolution options in all areas of legal practice. The site contains information and technical assistance for legislators, government departments and the general public on all aspects of dispute resolution.

International Ombudsman Association: This is the largest association of professional Ombuds practitioners in the world. It supports organizational ombudsman with professional development, training and strategic partnerships.

Program on Negotiation at Harvard Law School: This link is a search engine for alternative dispute resolution books, articles, training tapes and working papers.

National Arbitration Forum: NAF provides dispute resolution services through a roster of attorneys with specialized expertise.

The Journal of Dispute Resolution: The University of Missouri Law School publishes this journal which is recognized as the leading legal publication in the area of alternative dispute resolution.

The Conflict Resolution Information Service: This site is a goldmine of information on ADR processes, conflict and peacemaking and includes education and training resources.

4. Establising Pharmacovigilance Programme Establishing In a Hospital

The hospital based practice of acupuncture and integrative medicine not only offers unique insights and challenges; it also requires several ingredients either de-emphasized or wholly absent from private practice.

Hospitals can primarily be of two types- government or private. Further, they can be general, speciality or multispecialty hospitals. Following are the pointers one needs to keep in mind and set in place for setting up a private hospital

1. **Location of the Hospital:** This has to be chosen well, because if there are already some hospitals in the locality, then it will be difficult to pool in patients. Also, the hospital needs to be set up in an area which has good transportation facility or is close to a railway station. Considering the cost of real estate, a huge financial investment is required.
2. **Facilities Your Hospital Offers:** One has to be sure what set-up is planned and what infrastructure is required. A pediatric, orthopedic, gynecologic, oncology, pathology, imaging, etc facility in the hospital all require different facilities.
3. **Permits for Your Hospital:**
   A. **Land and construction:** Land allotted for agriculture cannot be used. To start building the hospital wing, several permissions from local authorities need to be taken. Numerous documents need to be approved, like land deed, architect's plan, etc.

   An occupation certificate is obtained after clearing all formalities.

   B. **Electricity and water:** As per the requirements of the hospital, permission has to be taken from the local governing body to obtain electric meters and water supply. Water requirement has to be calculated, which for any setup is approx 100 litres per day.

   C. **Sewage:** Proper disposal of waste requires a well planned sewage and drainage system, which is done after permission is sought from the local board.

   D. **Biomedical waste:** This is very vital aspect and permission of Municipal Corporation is required for installing incinerators required to dispose of medical waste and body parts.

   E. **Fire and Health Licence:** A Fire licence is necessary to prove that the hospital will not cause any damage or loss of life and needs to be procured from the local municipal council. Procuring a health licence is vital to provide health care to the patients.

4. Planning your hospital infrastructure

Take care of all these:

1. Doctors, their qualifications and registration numbers recorded
2. Nurses and working shifts discussed and set
3. Medical equipment and instruments purchased
4. Computers and other hardware devices set up
5. Engineers and staff required for maintenance, plumbing, medical gas pipelines, air conditioning, etc. set

Multiple medical laws and ethics must be followed at every step. A set of guide lines and eligibility criteria have been put forth by our government for hospitals, which provide services to central government health scheme beneficiaries.

A tremendous amount of planning, large finances, approvals, certifications, licences and guide lines need to be followed while setting up a hospital in India. It might be well worth it at the end, but needs ample time and mammoth effort to pool together the resources in place.

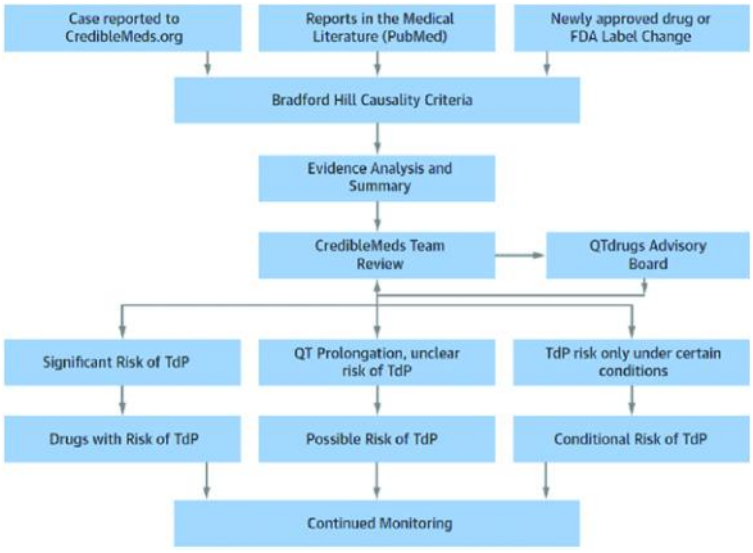
Establishment & Operation of Drug Safety Department in Industry

Drug safety (also known as pharmacovigilance), is the science of detection, assessment, understanding and prevention of side effects which allows us to understand more about the risks and benefits of a medicine.

Preclinical Safety

Drugs carry a number of risks and understanding the science behind adverse drug reactions can help increase the safety of new medicines. ABPI member companies work together to share knowledge and experiences in a 'pre-competitive space' in order to help maximise drug safety from the earliest point of developing a new medicine.

A vital part of medicines development, particularly preclinical safety research, involves the use of animals. Indeed, UK and European regulations currently require that all new medicines are tested on animals before being used in humans, to ensure patient safety.



Schematic for the ADECA process for causality analysis of drug safety. Drugs from one or more of the three primary sources (cases, the medical literature, or new or revised drug labeling for marketed drugs) are evaluated for their risk of QT prolongation, TdP, or both. The Bradford Hill criteria [7] are used to analyze all available evidence and construct a summary report that is reviewed by the CredibleMeds.org team and, in some cases, referred to the Advisory Board for consideration. On the basis of this analysis, an iterative process is used to decide whether the drug should be placed on one of the three lists: drugs with Known Risk of TdP; drugs with Possible Risk of TdP; or drugs with Conditional Risk of TdP. All drugs on these lists are monitored continuously for new evidence that could result in a change in their TdP risk classification. FDA ¼ Food and Drug Administration; TdP ¼ torsades de pointes.

Contract Research Organisations (CROs)

A contract research organization (CRO) is a company that provides support to the pharmaceutical, biotechnology, and medical device industries in the form of research services outsourced on a contract basis. A CRO may provide such services as biopharmaceutical development, biologic assay development, commercialization, preclinical research, clinical research, clinical trials management, and pharmacovigilance.

CROs are designed to reduce costs for companies developing new medicines and drugs in niche markets. They aim to simplify entry into drug markets, and simplify development, as the need for large pharmaceutical companies to do everything 'in house' is now redundant CROs also support foundations, research institutions, and universities, in addition to governmental organizations (such as the NIH, EMA, etc.)

Many CROs specifically provide clinical-study and clinical-trial support for drugs and/or medical devices. CROs range from large, international full-service organizations to small, niche specialty groups.

CROs that specialize in clinical-trials services can offer their clients the expertise of moving a new drug or device from its conception to FDA/EMA marketing approval, without the drug sponsor having to maintain a staff for these services.

Types of Services at Contract Research Organizations Services vary by the CRO, but typically include:

- Biological and chemistry expertise
- Formulation assistance
- Project management
- Database design and build
- Data entry and validation
- Clinical trial patient recruitment
- Clinical trial data management
- Medicine and disease coding
- Quality and metric reporting
- Statistical analysis plans and reports
- Validation programming
- Safety and efficacy summaries
- Study report evaluation and submission
- Marketing assistance

Some CROs provide comprehensive services in most or all of the above areas, and that too, for a wide variety of clients in the medical industry. In contrast, niche CROs specialize in specific areas or for certain types of clients. For example, a biometric CRO might choose to specialize in statistical analysis and data management for medical device companies.

Establishing a national programme

The National Pharmacovigilance Program was officially inaugurated by the honorable Health Minister Dr. Anbumani Ramadoss on 23 November, 2004 at New Delhi. Central Drugs Standard Control Organization (CDSCO) initiated a well-structured and highly participative National Pharmacovigilance Program which is build on the structure recommended by WHO in a document titled as "Safety Monitoring of Medicinal Products – Guidelines for Setting up and Running a Pharmacovigilance Centre". The Main focus of National Pharmacovigilance Program was to collate, analyze and archive adverse drug reaction data for creating healthy environment for the Regulatory Authorities to analyse the drugs to be marketed in India.

National Pharmacovigilance Program is a three layered structure consisting of peripheral, regional and zonal centres. These are monitored by an apex body i.e. National Pharmacovigilance Advisory Committee and the National Pharmacovigilance Centre which are based at the Central Drugs Standard Control Organization, New Delhi. The 3 tier structure report the serious, unexpected Adverse Drug Reactions to the National Pharmacovigilance Centre directly so as the regulators to act on it promptly.

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03. Vaccine Safety Surveillance

1. Vaccine Safety Surveillanc

Vaccine Pharmacovigilance

- ❖ Ensure the minimization of negative effects to individuals: Vaccine pharmacovigilance aims to detect adverse events early to trigger accurate risk assessment and appropriate response (risk-management) to the problem.
- ❖ Lessen the potential negative impact on immunization programs: This lowers tolerance for risks from vaccines translates into a greater need to detect and investigate any adverse event following immunization (AEFI) than is generally expected for other pharmaceutical products.
- ❖ Vaccines are regulated right from development, to licensure and, to final use. National regulatory authorities play an important role in the entire process. Therefore, implementation of proven safety measures is required:
- ❖ Capacity to handle a large number of adverse event reports in a short period of time and collection of adverse events following immunization (AEFI).
- ❖ Early assessment of the potential connection between an event and the vaccine administered.
- ❖ Assessment of vaccine failures or reversal of virulence for live attenuated vaccines.
- ❖ Accuracy and efficiency to identify, assess and analyze signals.
- ❖ Understanding complex global regulatory requirements for vaccine licensurefor

An approach to Vaccine Pharmacovigilance

APCER Life Sciences, as your partner, understands the nuances of planning and execution in addressing vaccine safety needs.

We partner with companies by:

- Leveraging cumulative experience of over 12 years in complex therapeutic areas including vaccines (Outbreak, Travel, Infectious diseases)
  - ✓ Travel vaccines (Typhoid, Cholera, Measles, Diptheria)
  - ✓ Outbreak vaccines (Anthrax, Botulism, Small poax)
  - ✓ Developmental Products (Chikunguya, Zika, Anthrax, Covid-19)
- Setting up a robust Medical Information & Pharmacovigilance integrated system
- Quality-driven integrated advanced software solutions for management & collation of large number of serious & non-serious adverse events in a short period of time.
- Combining strong medical assessment and expertise with efficient operational processes for handling complexities in case processing, follow-ups and aggregate reporting.
- Developing Standard Operating Procedures, managing study configuration specifically to therapeutic products like vaccines under aggressive timelines
- Bringing together experienced teams across all phases including global multicentric trials for multiple therapeutic areas
- Supporting regulatory submissions of reports via accepted pathways to FDA and other Regulatory Authorities.
- Scaling up quickly to manage unique situations such as pandemics/epidemics and product recalls.
- Robust Vaccine Adverse Event Reporting System (VAERS) setup for collecting vaccine related information

to maintain vaccine safety and to monitor potential rare vaccine associated side effects.

Vaccine	Category
Smallpox vaccine	Anti-viral
Anthrax vaccine	Anti-bacterial
Japanese encephalitis vaccine	Anti-viral
Typhoid vaccine	Anti-bacterial
Cholera vaccine	Anti-bacterial
Influenza A (H1N1, H5N1 & H3N2)	Anti-viral

Vaccination Failure

Vaccines are used to prevent or reduce problems that can occur when a poultry flock is exposed to field disease organisms. Vaccinations should be thought of as insurance. Like insurance, there is a price to be paid for protection against a potential threat. Costs include price of the vaccine, time spent designing the vaccination schedule and administering the vaccines, and losses due to vaccine reactions from the live-type vaccines and localized tissue damage from killed-type vaccine injections.

(1) Vaccine-related (host-related)

(a) immunodeficiency (leading to suboptimal or even absent immune response after vaccination);

(b) age-related maturation and senescence of immune responsiveness;

(c) insufficient or suboptimal immune response (other than a defined immunodeficiency) to one or more antigenic vaccine components or vaccine strains or serotypes; this may or may not be measurable by standard laboratory tests such as serum antibody tests;

(d) interference due to other infectious agents (e.g. wild type enter virus infection causing interference with the immune response to oral poliomyelitis vaccine (OPV));

(e) waning immunity;

(f) suboptimal health status (e.g. underlying disease, nutrition);

(g) immunological interference (e.g. maternal antibodies, administration of immunoglobulin's);

(h) pre-existing infection with pathogen targeted by the vaccine (e.g. with specific HPV genotypes) or immunization during incubation period (after exposure to pathogen);

(i) Immunosuppressive therapy.

(2) Vaccine-related

(a) vaccine is not 100% efficacious against included antigens;

(b) incomplete coverage of strains, serotypes, genotypes, antigenic variants or escape mutants that can cause a vaccine-preventable disease;

(c) antigenic interference or other vaccine-vaccine interactions in case of co-administered vaccines;

(d) manufacturing-related (e.g. batch variations, quality defect).

B. Failure to vaccinate

(3) Usage issues

(a) administration error (wrong or suboptimal route, inadequate dose, incorrect diluent);

(b) vaccination series incomplete, non-compliance with recommended schedule, including lack of recommended booster vaccination(s) ("failure to vaccinate" rather than "vaccination failure");

(c) storage-related (e.g. cold chain);

(d) Vaccine beyond expiry date when used.

(4) Immunization programme-related issues

(a) suboptimal recommendations regarding number and time points of primary and/or booster vaccinations;

(b) Shortage of vaccine leading to no or incomplete vaccination.

Confirmed clinical vaccine failure

The occurrence of the specific vaccine-preventable disease in a person who is appropriately and fully vaccinated taking into account the incubation period and the normal delay for the protection to be acquired as a result of immunization.

Suspected clinical vaccine failure

Suspected vaccine failure is defined as the occurrence of disease in an appropriately and fully vaccinated person, but the disease is not confirmed to be the specific vaccine-preventable disease, e.g. invasive pneumococcal disease of unknown serotype in a fully vaccinated person.

Confirmed immunological vaccine failure

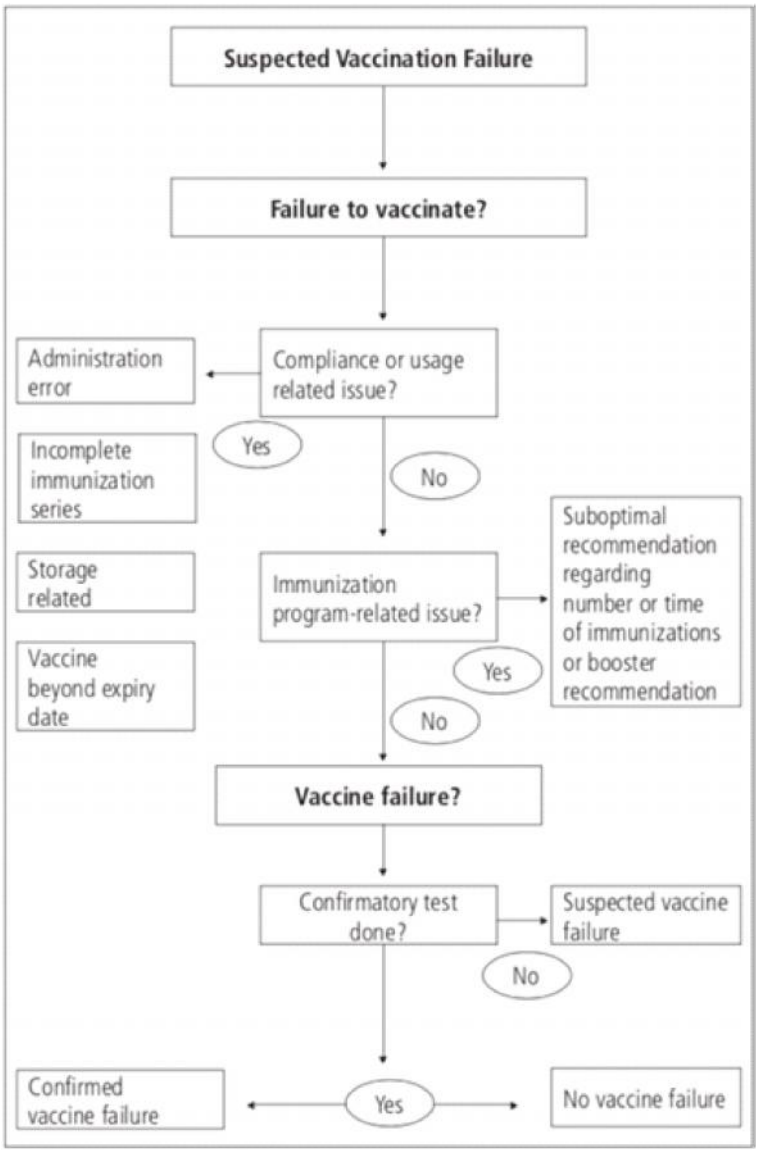
In addition to clinical vaccine failure, there is the possibility of immunological vaccine failure, not necessarily associated with a clinical manifestation of the vaccine-preventable disease. Immunological failure is defined as failure of the vaccine to develop the accepted marker of protective immune response after being fully and appropriately vaccinated.

Adverse Events Following Immunization

As vaccine-preventable infectious diseases continue to decline, people have become increasingly concerned about the risks associated with vaccines. Furthermore, technological advances and continuously increased knowledge about vaccines have led to investigations focused on the safety of existing vaccines which have sometimes created a climate of concern.

Adverse event following immunization is any untoward medical occurrence which follows immunization and which does not necessarily have a causal relationship with the usage of the vaccine. If not rapidly and effectively dealt with, can undermine confidence in a vaccine and ultimately have dramatic consequences for immunization coverage and disease incidence.

Alternatively, vaccine-associated adverse events may affect healthy individuals and should be promptly identified to allow additional research and appropriate action to take place. In order to respond promptly, efficiently, and with scientific rigour to vaccine safety issues, WHO has established a Global Advisory Committee on Vaccine Safety.



2. Pharmacovigilance methods

Steps in carrying out surveillance

surveillance involves carrying out many integrated steps by many people:

Reporting: Someone has to record the data. This is usually health care providers who provide clinical care, such as doctors, nurses, clinical officers, etc. They complete a form recording various bits of information about patients seen in their practice.

Data accumulation: Someone has to be responsible for collecting the data from all the reporters and putting it all together. This is often someone in the Ministry of Health, the local health authorities, or the organization coordinating surveillance.

Data analysis: Someone has to look at the data to calculate rates of disease, changes in disease rates, etc. This is often an epidemiologist with specific data analysis and computer skills.

Judgment and action: Someone has to decide, based on the results of analysis, what needs to be done. This is often the public health authorities at the local, provincial, or national level. In emergencies, it is often a joint opinion of local and national health authorities, the organization coordinating health, and all the organizations providing health services.

If any of these steps break down or is unavailable, you will not have usable information with which to take the appropriate (and sometimes necessary) public health action.

Pharmacovigilance Methods Objective

- ✓ To establish a functional reporting system to monitor the safety of all medicines
- ✓ To learn more about the safety profile of new medicines in the early post-marketing phase
- ✓ To learn more about the ADR profile of a specific medicine(s) in your population
- ✓ To estimate the incidence of a known ADR to a specific medicine in your population
- ✓ To gather more information on the safety profile of a new chemical entity in early post-marketing phase
- ✓ To make use of existing electronic health records and registries to support pharmacovigilance activities

Methods

- Passive surveillance
  - Spontaneous reports
  - Case series
- Stimulated reporting
- Active surveillance
  - Sentinel sites
  - Drug event monitoring Registries
- Targeted clinical investigations
- Comparative observational studies Cross sectional study
  - Case control study Cohort study
- Descriptive studies
  - Natural history of disease, Drug utilization study

Spontaneous Reports

- A communication by consumers or healthcare professionals to a company or Regulatory Authority, that describes one or more ADR in a patient, who has given the drug.
- It plays a major role in the, identification of safety signals once the drug is marketed.
- Gives alerts on rare AEs that were not detected in earlier clinical trials or pre marketing studies.
- Provides important information on at risk groups, risk factors and clinical features of known serious ADRs.

Case series

- Series of case reports can provide evidence of an association of a drug and AEs.
- Generally more useful for generating hypothesis than for verifying an association between drug exposure and outcome.
- Certain distinct adverse events occur more frequently with drug therapy, such as anaphylaxis, aplastic anemia and Stevens-Johnson syndrome events such as these are spontaneously reported for detailed and rapid follow-up.

Stimulated Reporting

- A method used to encourage and facilitate reporting by health professionals for new products, or for limited period.
- Online reporting of AE, systematic stimulation of reporting of AEs.
- Drawbacks- data are often incomplete.

  Not useful to generate accurate incidence rates.

Active surveillance

- To ascertain completely the no. of AEs via a continuous pre-organized process.

  E.g. follow up of patient treated with a particular drug.
- More feasible to get comprehensive data on individual AE reports.

Sentinel Sites: Active surveillance carried out at Institutions, Nursing Homes and Hospitals etc. provides information such as data from specific patient subgroups, drug abuse etc.

Drug Event Monitoring: Patients are identified by electronic prescription data or automated health insurance claims. A follow up questionnaire can be sent to each physician or patient at specified intervals. Information on patient demographics, indication for treatment, duration of therapy, dosage, clinical events, and reasons for discontinuation can be included in the questionnaire.

Registries: A registry is a list of patients presenting with same characteristics. E.g. Disease registry, drug registry, pregnancy registry etc. Differs from each other depending on type of patient.

Comparative Observational Studies

- Traditional epidemiologic methods are a key component in the evaluation of AEs.
- Observational study designs are useful in validating signals from spontaneous reports or case series.

Cross Sectional Studies

- Data collected from a population of patients at a single point in time regardless of exposure or disease status.

- Primarily used to gather data for surveys or for ecological analysis. Best used to examine the prevalence of a disease at one time point or to examine trends over time, when data for serial time points can be captured.

Case Control Study: In this case of disease are identified. Controls or patients without the disease or event of interest, are selected from the source population. Exposure status of the two groups is compared using the odds ratio.

Cohort Study: A population at risk for the disease is followed over a time for the occurrence of the disease or events. Information on exposure status is known throughout the follow up and hence incident rates can be calculated.

Comparison cohorts of interest are selected on the basis of drug use and followed over time. Multiple AEs can also be investigated using the same data source in a cohort study.

Targeted Clinical Investigations

- When significant risks are identified from pre-approval clinical trials, further clinical studies might be called, to evaluate the mechanism of action for ADRs.
- PK and PD studies might be conducted.
- Specific studies to investigate potential drug-drug interactions and food-drug interactions might be called.

Descriptive Studies

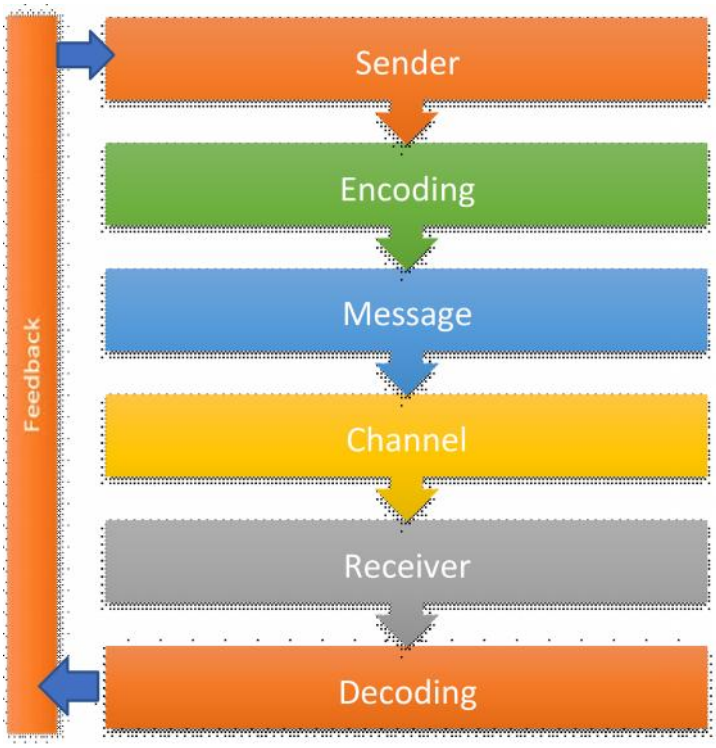
- Primarily used to obtain the background rate of outcome events and/or to establish the prevalence of the use of drugs in specified populations.
- Natural History of Disease- Focused on the natural history of disease, including the characteristics of diseased patient and the distribution of disease in selected populations, as well as estimating the incidence and prevalence of potential outcomes of interest.

Drug Utilization Study: These studies provide data on specific populations, such as the elderly, children, or patients with hepatic or renal dysfunction, often stratified by age, gender, concomitant medication, and other characteristics.

3. Communication

The act of sharing or exchanging information, ideas or feelings.

Communication Process



Principles of Good Pharmacovigilance Communication

- ✓ Relate the messages to the audience's perspective
- ✓ Avoid comparisons which trivialize the concern
- ✓ Ensure completeness of the message
- ✓ Be balanced, honest and sympathetic
- ✓ Focus on the specific issue that needs to be handled
- ✓ Pay attention to what the audience already knows
- ✓ Be respectful of people's right to be concerned
- ✓ Be honest about the limits to scientific knowledge
- ✓ Acknowledge uncertainty
- ✓ Evaluate the impact of your message

Effective Communication in Pharmacovigilance

One can achieve effective way of communication just by following the principles of good pharmacovigilance communication.

Why do we need to improve our communication?

- ✓ Improve patient care and understanding
- ✓ Eradicate disease / improve disease control
- ✓ Promote transparency and accountability

Why do Communications matter in Drug Safety?

- ✓ For Welfare of millions of people worldwide
- ✓ To overcome Extreme dangers of failure
- ✓ Communications are commonly poorly executed, second-rate and ineffective, so to improve the quality.

Communication Challenges:

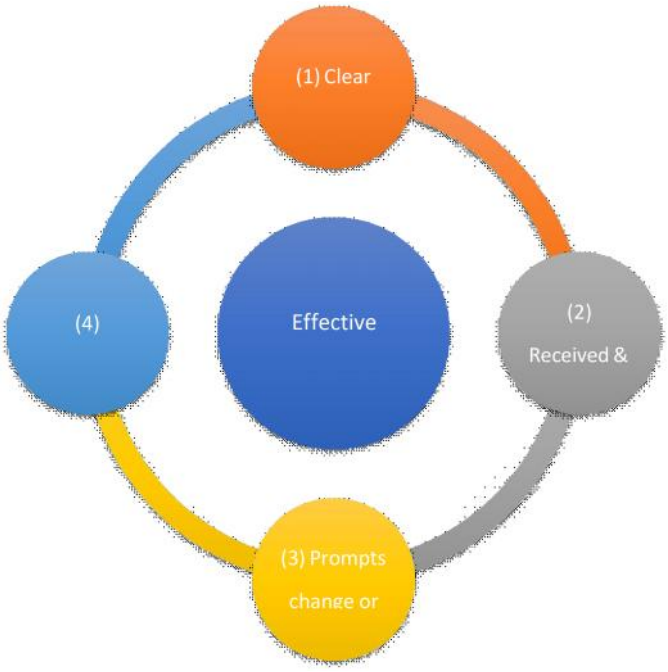
- ✓ The importance of ADRs and reporting them
- ✓ Information about benefit – harm and effectiveness – risk
- ✓ Encouraging rational drug use/adherence
- ✓ Communicating uncertainty
- ✓ Dealing with traditional beliefs and practices
- ✓ Involving patients; reaching informed consent
- ✓ Preventing or resolving crises

Problematic issue in Drug Safety

all reliant on communications for safety

- ✓ Adverse effects: 'no drug 100% safe'
- ✓ Risk as a concept in medicine
- ✓ Safety and medicines (prescribing, dispensing)
- ✓ Benefit-harm
- ✓ Effectiveness-risk
- ✓ Public health and commercial goals
- ✓ Public health and individual welfare
- ✓ Access to medicines
- ✓ Uncertainty

What is an Effective Communication?



Principles of Effective Communications

- ✓ Be clear about your message and purpose
- ✓ Know your audience(s): empathy; tailor the message
- ✓ Choose appropriate methods/media
- ✓ Present message with impact
- ✓ Make benefits clear
- ✓ Pre-test and revise message
- ✓ Repeat message
- ✓ Seek feedback, monitor effects, start again

Qualities of Modern Communications

- ✓ Intimacy
- ✓ Immediacy and high impact
- ✓ Peer-to-peer
- ✓ Addressing competition and low attention levels
- ✓ Benefits

Planning Communications

- ✓ Today's modern standards and methods
- ✓ Simple, clear message
- ✓ Stimulating motivation and offering benefits (including rewards and feedback)
- ✓ The use of specialist skills and creative imagination

Summary

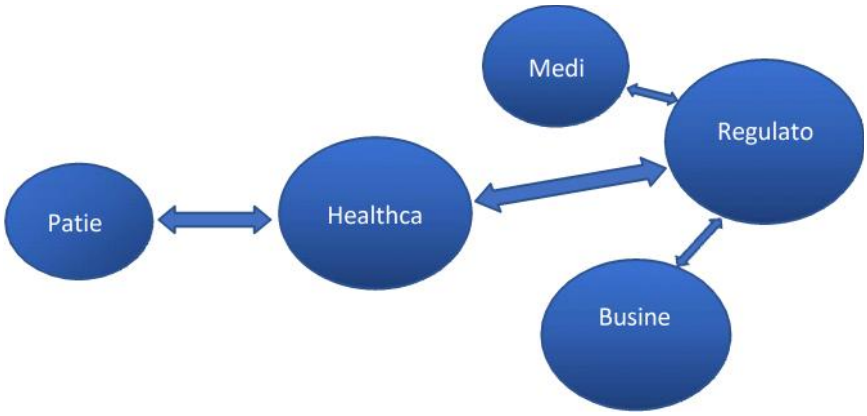
- – Our communications must:
- – Be strong and visible
- – Be precisely targeted and tested
- – Change attitudes, values, behaviour
- – Be followed up and revised
- – Embrace modern standards and skills

1. Communication in Drug Safety Crisis Management

- Crisis will happen (fire, death, ADRs…)
- Assess risks
- Anticipate and plan for all likely and unlikely events
- Create, rehearse and revise crisis plans
- In crisis, communicate
  - – Quickly
  - – Openly and honestly
  - – Express regret, apologise

- Explain what is being done to solve the crisis and prevent repetition

2. Communicating with Regulatory Agencies, Business partners, Healthcare facilities & Media



3. Communication with Media

Who are the media?

- ✓ Print -magazines, newspapers, community newspapers
- ✓ Electronic -radio, TV, internet
- ✓ Local and national levels

Some basic questions a reporter will ask you….

- ✓ WHO-is affected, responsible
- ✓ WHAT-has happened and what is being done about it
- ✓ WHERE-has it happened
- ✓ WHEN-did it happen
- ✓ WHY-did it happen
- ✓ WILL-it happen again

Communications practices to avoid

- ✓ "Spinning"! (distortion or decoration of facts for beneficial effects)
- ✓ All communications are subjective, but do not be manipulative or dishonest
- ✓ Avoid "No comment"–rather say why there's nothing to say and what is beingdone
- ✓ Avoid confusing statistics
- ✓ Do not avoid taking responsibility
- ✓ Don't attack the messenger/accuser
- ✓ Don't deny, justify or excuse your mistakes

Partners & Audiences in Drug Safety

Partners	Audiences
• Manufacturers	• The public
• Regulators	• Patients
• Politicians	• Consumer groups
• Employees	• Lawyers
• Health professionals	• The media
• Academics	• International community
• Bosses/managers	

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1. Drug Development Safety

Modern drug safety and pharmacovigilance dates back to the thalidomide disaster. The growing cost of drug development is driving pharmaceutical companies to identify potential safety issues earlier in the process. Valuable safety data are available in public databases and internal sources, but much of this is unstructured text. Linguamatics NLP transforms this text into actionable data that can be visualized and analyzed at every stage of the drug development process.

Modern drug safety and pharmacovigilance began in the early 1960s following the thalidomide disaster. Thalidomide, a drug designed to prevent morning sickness, was released in 1959 and resulted in over 10,000 children in 46 countries being born with birth defects.

In the wake of thalidomide, the World Health Organization (WHO) set up the Programme for International Drug Monitoring (PIDM). Today, PIDM has more than 150 participating countries, with over 16 million Adverse Event Reports (ADRs) collected.

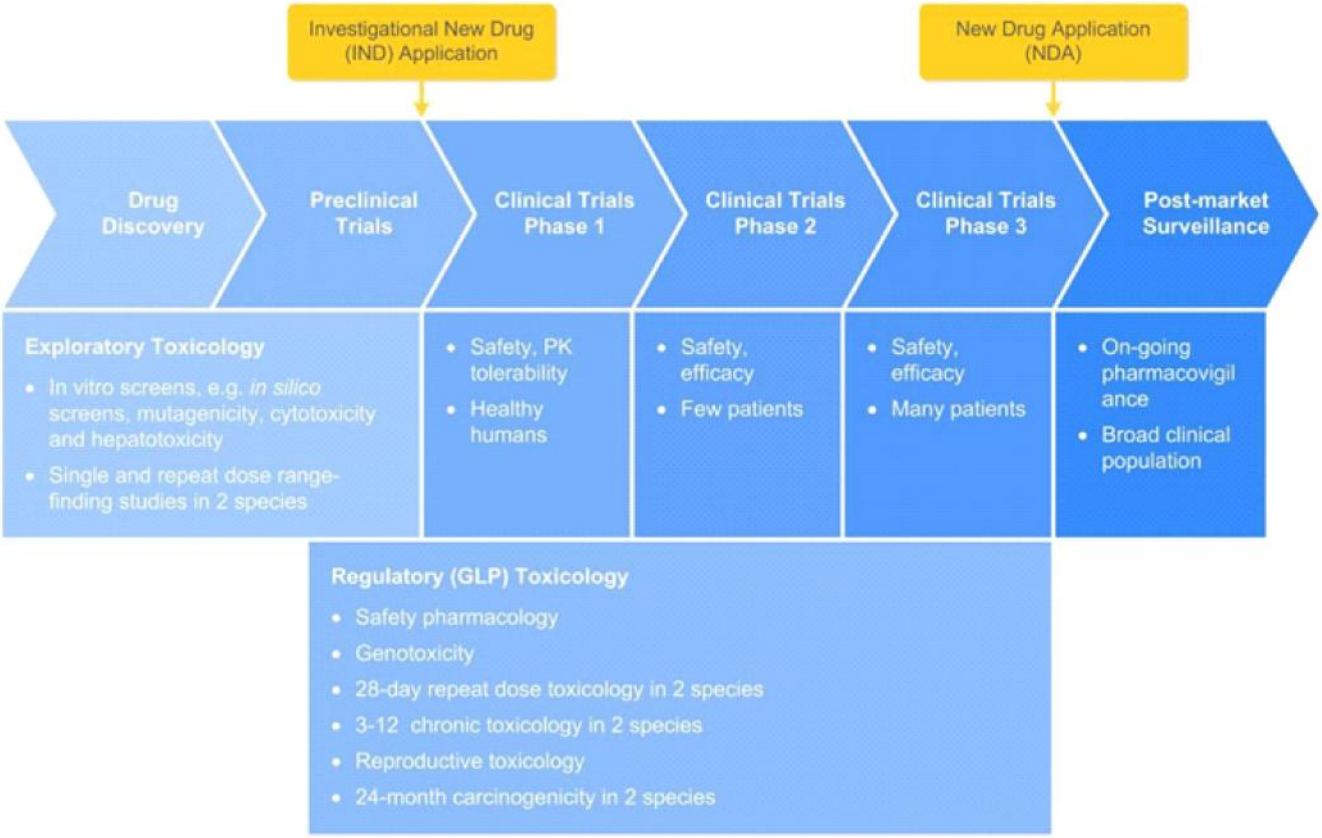
In parallel, the United States Congress passed the Kefauver-Harris Drug Amendments (1962). For the first time, these laws required drug makers to prove their drugs worked safely before the Food and Drug Administration (FDA) would approve them for sale.

These changes were the start of a wave of regulatory changes designed to ensure reliable evidence of drug safety, efficacy and chemical purity prior to market release.

While a lack of clinical efficacy is the major cause of drug attrition, a poor safety profile is also a significant factor in the failure of drugs during development. This may occur at any stage in the development process, from initial drug discovery to preclinical trials, clinical trials and post-marketing surveillance (pharmacovigilance).

Drug Development Pipeline

The diagram below shows the timing of the main safety assessment studies conducted during the drug development process.



Drug Discovery

Typically this involved highly parallelized processes for making new compounds and testing them in high-throughput screens. From this, a certain number of hits will be obtained and these will be whittled down by further analysis into a set of leads.

Preclinical Trials

This includes *in vitro* and *in silico* testing of the compounds to identify the best members of a series to take into Clinical Trials. This is also where the first stages of safety assessment are undertaken via toxicity testing in animals. If a drug shows promise in preclinical trials, a pharmaceutical company can request permission from the FDA to begin testing in humans (known as First-in-Man or FIM trials). This is called an Investigational New Drug (IND) application. In Europe, the European Medicines Agency (EMA) equivalent is an Investigational Medicinal Product Dossier (IMPD).

Phase 1 Clinical Trials

Phase 1 clinical trials are concerned primarily with establishing how a drug is absorbed, distributed, metabolized and excreted by the human body - a study known as pharmacokinetics (PK).

The dosage range of a new drug is determined by administering increasingly larger doses to one or more groups of subjects, who are closely monitored for harmful side effects. The goal is to learn the maximum tolerated dose that does not produce unacceptable side effects.

Phase 2 Clinical Trials

Phase 2 clinical trials are designed to answer the question: *does drug X improve disease Y?*

Subjects in a phase 2 clinical trial may benefit from their participation if they receive an active treatment. Most phase 2 clinical studies are randomized, with subjects assigned randomly (by chance and not by choice) to receive the experimental drug, a standard treatment or placebo (harmless, inactive substance). Since larger numbers of patients receive a treatment in Phase 2 clinical trials, there is a greater chance to observe and compile information on potential side effects.

Phase 3 Clinical Trials

Phase 3 clinical trials are conducted at multiple centers with hundreds or thousands of patients for whom the drug is intended. Testing on large patient populations allows continuous generation of data on a drug's safety and efficacy. As in phase 2, most phase 3 clinical trials are randomized and blinded. A drug in this phase can be studied for several years.

New Drug Application (NDA)

Once the Phase 3 clinical trials are complete, a pharmaceutical company can request FDA approval to market the drug within the USA. This is called a New Drug Application (NDA). The NDA contains all the scientific data that the company has gathered during clinical trials. Within the EU, pharmaceutical companies submit a Marketing Authorization Application (MAA).

Regulatory (GLP) Toxicology

These studies are performed to Good Laboratory Practice (GLP) standards and comprise those required by local regulatory authorities or ethics committees before a drug can be given to human subjects for the first time. Regulatory toxicology also covers the studies required to support a New Drug Application (NDA).

Post-market Surveillance (Pharmacovigilance)

Overseen by the FDA or EMA, post-market surveillance is designed to ensure the safety of a drug once it released onto the market. Pharmacovigilance is designed to ensure that regulators monitor any adverse events reported by the public who may be suffering from a wide range of medical conditions (far wider than those to which the drug would have been exposed during clinical trials).

Shortcomings of the Drug Development Process

There are a number of problems associated with the drug development process as it stands, but they can be distilled into three factors: cost, time and effectiveness.

Drug Development Costs

For years, the pharmaceutical industry has relied on development cost estimates from the Tufts Center for the Study of Drug Development (TCSDD), the most recent of which (2015) puts the cost of bringing a drug from discovery to market launch at $2.9 billion. This includes actual out-of-pocket costs averaging $1.4 billion, opportunity costs of nearly $1.2 billion and the cost of post-market studies amounting to $312 million.

Time to Market

On average, it takes 12 years to bring a new drug to market. This is one reason why the process is so expensive, as capital costs are magnified by the amount of time that money is tied-up in a single project.

Effectiveness

Almost 90% of drugs that start testing in patients don't reach the market because they are unsafe or ineffective, and there is a pressing need to improve the understanding of safety issues during drug discovery, development and after launch. A successful drug development process demands that potential safety issues are recognized as early as possible.

At all stages of drug development, critical data is being generated and retrieved from unstructured text. Project teams need the most comprehensive view of all relevant data, and text mining plays a key role in access to actionable insights for drug safety.

1.1 Pre Clinical Phase

Deciding whether a drug is ready for clinical trials (the so-called move from bench to bedside) involves extensive preclinical studies that yield preliminary efficacy, toxicity, pharmacokinetic and safety information. Wide doses of the drug are tested using in vitro (test tube or cell culture) and in vivo (animal) experiments, and it is also possible to perform in silico profiling using computer models of the drug–target interactions.

Much like for clinical trials, there are certain types of trials that have to be done, such as toxicology studies in most cases, and other trials that are specific to the particular study compound or question. Understanding that the goal of preclinical trials is to move into the clinical stage is key and the studies should be designed around that goal. Watch our online seminar on moving from preclinical to clinical trials.

Don't get too worked up on too many preclinical trials that may not be necessary but make sure to consult with experts who can help you decide, which trials you should do and if you are ready to move into clinical stage. At Profil we have a team of experts who can advice you on such questions and who will help you with the transition into clinical trials.

The following table outlines the typical duration for various types of preclinical studies and the preferred timing relative to clinical trials they support.

Pre/Nonclinical Study	Duration	Time	Clinical Study Supported
Safety pharmacology Toxicokinetic, pharmacokinetic studies Single dose acute toxicityor dose escalation study in two species Local tolerance studies using relevant route of administration	1-3 weeks, depending on kinetic data 14 days A few hours to several weeks depending on sample and test type	Prior to Phase I. Information should be available by the time early Phase I trials are completed.	Phase I/II
Repeated dose toxicity studies in one rodent and one non-rodent model	Should equal or exceed the duration of Phase I/II studies: (minimum 2 weeks,	Prior to Phase I Prior to Phase III	Phase I/II: 2 weeks to 12 months

	maximum 12 months; generally 1-3 months for biotech-derived products) To support Phase III: 1 month 3 months 6 months		Phase III: < 2 weeks < 1 month > 1 month
Genotoxicity studies	Variable	Complete prior to start of Phase II and all pediatric clinical trials	Phase I/II Pediatric clinical trials
Reproductive toxicity studies	(> 1 month-long repeated dose toxicity studies required prior to tests). Pre-mating treatment interval of 4 weeks for males and 2 weeks for females. Continue treatment throughout mating for males and at least through implantation	Not required if repeated dose toxicity studies including evaluation of male and female reproductive organs have been done. Complete all female reproductive toxicity and genotoxicity studies prior to Phase I/II	Phase I/II (males, and females not of child-bearing potential) Phase I/II (pregnant females and females of childbearing

	for females. Collect and evaluate data through two or more generations.	studies. Pre- and postnatal development study prior to marketing approval. Complete prior to pediatric studies	potential) Pediatric clinical trials
Carcinogenicity studies	Variable	Prior to long-term pediatric trials. Not usually needed unless there is cause for concern.	Pediatric clinical trials
Juvenile animal safety studies	Variable	When previous safety data are insufficient	Pediatric clinical trials
Supplementary toxicity studies	Variable; dependent on previous toxicity studies	Required if previous findings indicate special concerns	

Clinical trials are done only after pre-clinical findings suggest that the new drug or treatment is likely to be safe and will work in people.

Pre-clinical studies, also called laboratory studies, include:

- **Cell studies:** These are often the first tests done on a new treatment. To see if it might work, researchers look for effects of the new treatment on cancer cells that are grown in a lab dish or a test tube. These studies may be done on human cancer cells or animal cancer cells.
- **Animal studies:** Treatments that look promising in cell studies are tested next on cancers in live animals. This gives researchers an idea of how safe the new treatment is in a living creature.

Pre-clinical studies give a lot of useful information, but not all that is needed. Humans and mice can be very different in the way they absorb, process, and get rid of drugs or treatments. A treatment that works against cancer in a mouse might or might not work in people. There could also be side effects and other problems that didn't show up when the treatment was used in mice but could show up in people.

If the pre-clinical studies are completed and the treatment still seems promising, the US Food and Drug Administration (FDA) must give permission before the treatment can be tested people.

1.2 Clinical Phase

Once clinical trials are approved to start, each one must follow certain steps in order. The steps are called "phases." They are designed to keep volunteers safe. Making sure all the steps are done helps protect patients and give accurate results about what the clinical trial is testing.

You may join any phase of a clinical trial. The clinical trial just needs to be appropriate for you, your health, and your cancer. Here is a **chart about the different phases of clinical trials**.

Phase I clinical trials

Doctors do a phase I clinical trial to learn if a new drug, treatment, or treatment combination is safe for people. They may have already tested it in laboratory animals.

In a phase I clinical trial, doctors collect information on:

- The dose or treatment
- When you take it, and how often
- Any side effects or problems
- How the treatment affects you, such as how it affects the cancer or side effects

In a phase I clinical trial, you could be one of the first people to get the new drug or treatment.

Phase I clinical trials each last several months to a year. They usually have 10 to 30 volunteers. The treatment might help the cancer. Also, information from the clinical trial may help other people in the future.

Phase II clinical trials

A phase II clinical trial tells doctors more about how safe the treatment is and how well it works. Doctors also test whether a new treatment works for a specific cancer. They might measure the tumor, take blood samples, or check how well you can do certain activities. Or you might keep a log of your daily activities and symptoms. These are all ways to learn how well the treatment works.

A Phase II clinical trial lasts about 2 years. Volunteers sometimes receive different treatments. For example, a phase II trial could have 2 groups.

- **Group 1:** People who receive the usual treatment for the condition. This is also called the standard treatment. It is the best treatment known.
- **Group 2:** People who receive the usual treatment plus the new treatment doctors are studying.

Or a phase II clinical trial could have 3 groups. Volunteers in each group get a different dose of the treatment doctors are studying.

If the phase II clinical trial shows the treatment works and is as safe as the regular treatment, doctors can do a phase III trial.

Doctors use a computer program to put volunteers into different groups. The computer does this at random, which means by chance. Each volunteer has an equal chance of going in any of the groups. The name for this process is "randomization."

Using a computer to put volunteers in groups keeps the research staff from possibly changing the clinical trial results. They might do this if they chose who went in which group. For example, they might think a certain volunteer would benefit from the new treatment. So they might put that person in the new-treatment group. But this could change the clinical trial results. Randomization helps avoid this. It is very important to use randomization when a clinical trial compares 2 treatments or more.

Phase III clinical trials

A phase III clinical trial tests a treatment that worked well for volunteers in a phase II clinical trial. Doctors use phase III to compare the new treatment with the standard treatment. They want to know if the new treatment is better, has fewer side effects, or both. So they put volunteers in different groups. The volunteers in each group get a different treatment.

Phase III clinical trials can take many years. They may have several thousand volunteers. These must include men, women, and people of different ages and ethnic groups, if possible. This helps doctors learn how the treatment works in different people.

If a phase III clinical trial shows the treatment works well, doctors might begin using it with people outside the clinical trial. For example, if they learn that a certain amount of exercise lowers your cancer risk, they publish a report. This shares the information with other doctors. If the researchers or sponsor learn a new medicine is safe and effective, they can ask the government to approve it for people to use. In the United States, they ask the Food and Drug Administration (FDA). The FDA looks at the results of the clinical trial's phases. They approve the treatment if the results meet their standards.

Phase IV clinical trials

Doctors can prescribe a drug for their patients after the FDA approves it. But the FDA may require the sponsor to keep studying that approved treatment. In these clinical trials, doctors may check if the treatment benefits people as much as it did earlier. They also look for more possible side effects. These clinical trials are called phase IV clinical trials.

In a Phase IV clinical trial, doctors might study the drug or treatment in different doses, or with other drugs or treatments. Or they might study how it works if people take it at different times. They might study it in different people than earlier clinical trials did. For example, they might study how well it works for children or older adults. Doctors can also study how well a drug or treatment works over time.

Drug makers may do phase IV clinical trials even if the FDA does not ask them to. They might do this to get FDA approval to use the drug in a new way. For example, they might want to use it for another type of cancer.

Phase IV clinical trials can also check the safety of drugs or treatments being used now. They do this to make sure drug makers report any new or serious side effects. The FDA may take away a drug's approval if new research shows it is not as safe or effective as earlier testing showed. Doctors cannot prescribe it any longer if this happens.

The different clinical trial phases are described in further detail below and summarised in the table at the end of this blog.

Phase	Objectives	Dose	Approximate Size/Population
Phase 0*	PK, particularly oral bioavailability and half-life of the drug	Subtherapeutic	10 healthy subjects
Phase 1	Testing of drug on healthy volunteers to confirm safety and likely therapeutic dose	Often subtherapeutic, but with ascending doses	15-30 healthy subjects
Phase 2	Testing of drug on patients to assess efficacy and safety	Therapeutic dose	Up to 300 patients
Phase 3	Testing of drug on patients to assess efficacy, effectiveness and safety	Therapeutic dose	Over 300 patients
Phase 4	Postmarketing surveillance – monitoring the use of the drug after approval	Therapeutic dose	Anyone seeking treatment from their doctor

1.3 Post Approval Phase (PMS)

Surveillance for Clinical Trials

CMIC supports a wide scope of services from monitoring (collection of site contracts, re- investigation or query, and fixed case report forms) to the post-authorization safety study (PASS). We can assist whether a study needs a plan implemented in the early phases, or our clients need continuing safety surveillance with a non-interventional study to evaluate real- world practice. Our support covers risk management development, pharmacovigilance, epidemiology studies, clinical usage analysis reporting, and more. We create and operate risk management plans (RMP), as well as support early phase post-marketing pharmacovigilance either via contract medical representatives (MR) or good pharmacovigilance (GVP) outsourcing.

Our Edge in Post-Marketing Surveillance

Extensive experience and leading track record

Our unique business model is built on expertise from working on a multi-drug, multi-Sponsor joint survey (ongoing since 1997) that covers 38 products from a total of 15 companies

Integrated Capabilities

Providing post-marketing surveillance monitoring and data management outsourcing services, leveraging one-stop solutions to support the entire process from drafting of Risk Management Plan (RMP) for pharmaceuticals to re-examination.

Marketing Authorization Holder (MAH)

With regard to the obligation of submitting Risk Management Plan (RMP) for pharmaceutical products since April 2013, we do not limit ourselves to preparation of submission materials, but leverage our know-how in clinical development, approval application and PMS as Marketing Authorization Holder (MAH) at CMIC Holdings Co., Ltd. to support implementation.

Services

- Database entry
- Patient registration plans
- Safety evaluation meeting materials
- Epidemiology studies
- Monitoring (Adverse Events, submissions to IRB, surveillance reports)
- Health economic outcomes research and technology assessment
- Project leader coordination (monitor training, records retention, self-inspection)
- Clinical usage and analysis

2. ICH Guidelines for Pharmacovigilance

2.1 Organization and Objectives of ICH Objective of ICH:

The main objective of ICH is to

* Promote international harmonization of technical requirements to develop safe, effective, and high quality medicines.
* Reduce the registration cost.
* Promote public health.
* Prevent the duplication of clinical trialsin Humans
* Minimize the animal use without compromising in the safety, qualitut compromising in the safety, quality.

2.2 Expedited Reporting

Julphar will transmit all Individual Case Safety Reports (ICSRs) requiring expedited reporting promptly and no later than 15 calendar days from receipt. This applies to initial and follow-up information.

The clock for expedited reporting starts as soon as one or more of the following has received the minimum information (an identifiable patient, an identifiable reporter, a suspected reaction, and a suspected drug) required for the submission of an adverse reaction report:

- Any personnel of Julphar – including sales representatives.
- The Qualified Person responsible for Pharmacovigilance (QPPV) or persons working for or with this person.
- Where Julphar has entered into relationships with a second company for the marketing of, or research on, the suspected product, the clock starts as soon as any personnel of Julphar receives the minimum information. However, wherever possible, the time frame for regulatory submission should be no longer than 15 calendar days from first receipt by the second company and explicit procedures and detailed agreements will exist between Julphar and the second company to facilitate achievement of this objective.

- In the case of relevant world-wide scientific literature, the clock starts with awareness of the publication by any personnel of Julphar; Julphar will maintain awareness of possible publications by accessing a widely used systematic literature review and reference database, no less frequently than once a week, or by making formal contractual arrangements with a second party to perform this task; Julphar will also ensure that relevant publications are appropriately reviewed.
- Expedited reporting of serious adverse reaction will be reported as soon as possible, but in no case later than 24 hours of initial receipt of information by the healthcare provider.

2.3 Individual Case Safety Report

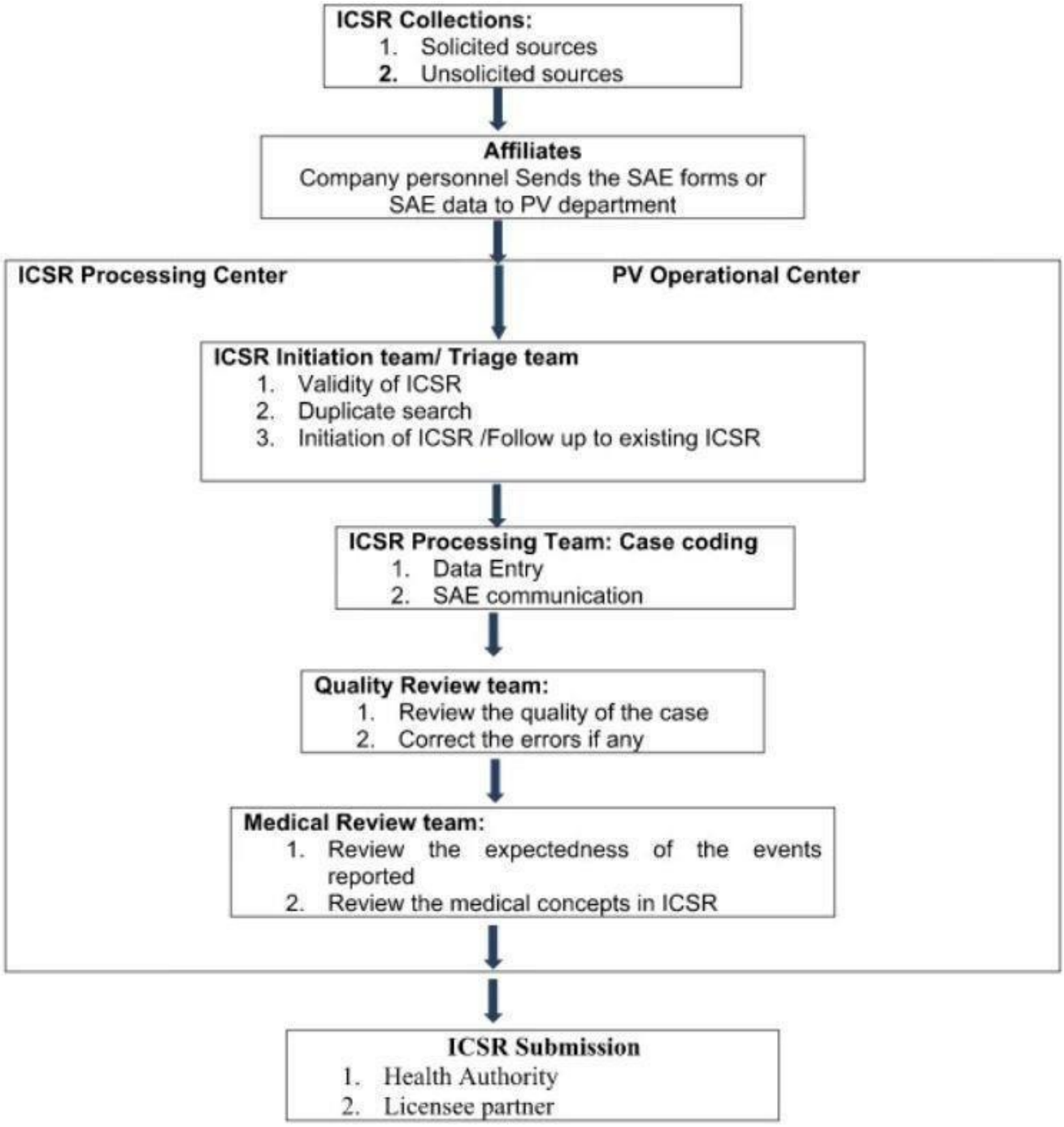
An Individual Case Study Report (ICSR) is a safety service document which includes information required for reporting the adverse events and problems related to products and complaints filed by consumers with respect to any product. It is an important facet of adverse event reporting which is a source of data in PV (pharmacovigilance). The ICSR is most commonly associated with PV. To build a compliant ICSR, there are four elements which must be mentioned:

- A diagnosed patient
- A reporter
- A suspect drug
- An adverse event

Adverse event reporting is a Regulatory requirement in most of the countries for pharmaceutical companies. It also provides data to the companies and drug Regulatory authorities that play a key role in assessing the risk-benefit profile of a given drug. The source of adverse event reports may include reports from:

- Healthcare professionals or patients
- Patient support programs
- Clinical or post-marketing studies
- Literature sources
- Media including websites
- Or, reported to drug Regulatory authorities themselves

The implementation of ICSR varies from drug to drug. The applicant must reach out to the Regulatory agency before submitting the reports to clarify the content of ICSR. More details about the content and guidance document of ICSR are available on the websites of the agencies.



2.4 Periodic Safety Update Report (PSUR)

- PSURs are important pharmacovigilance documents applying to drugs already approved for marketing – regularly updating regulatory authorities on the worldwide safety experience of approved drugs.
- A new format for PSURs, the PBRER (Periodic Benefit Risk Evaluation Report: ICH E2C (R2)), came into force in the European Union and European Economic Area on 2nd July 2012 – as the result of the European Medicines Agency (EMA) guidance on Good Pharmacovigilance Practices (GVP) issued in June 2012. The same PBRER format has also been adopted to replace PADERs in the United States.

- Trilogy's experience extends to more than 100 PSURs across an extensive range of indications.
- Trilogy helps our clients' pharmacovigilance departments identify new safety signals (if present), giving advice on the Marketing Authorisation Holder (MAH) response and communicating the key messages to reviewers in a clear and easy-to-understand manner.
- PSURs must be submitted every 6 months after product authorisation until 2 years after the initial placing on the EU market, yearly for the following 2 years, and at 3- year intervals thereafter.
- Trilogy can also arrange full clinical review and sign-off, produce Summary Bridging Reports as well as published literature summary and analysis, and provide suggestions for company comments.

format and Content of a PSUR

A PSUR should contain all the present available information of the product in addition to emerging information. The report must present all the relevant data of the risk and benefits associated with the product along with its impact on the market authorization. The following information can be a part of the PSUR:

- Non-clinical studies
- Spontaneous reports
- Active surveillance systems
- Product quality investigations
- Product usage data along with information related to drug utilization
- Clinical trials
- Observational studies
- Patient support programs
- Systematic reviews and meta-analysis
- MAH sponsored websites
- Scientific literature which has already been published or reports compiled from abstracts
- Manuscripts which have not been published before
- Licensing partners, other sponsors or academic institutions and research networks
- Competent authorities

2.5 Periodic Safety Update Reports (Psurs)

A Periodic Safety Update Report (PSUR) is a pharmacovigilance document intended to provide an evaluation of the risk-benefit balance of a medicinal product at defined time points post-authorisation. The objective of the PSUR is to present a comprehensive and critical analysis of the risk-benefit balance of the product taking into account new or emerging safety information in the context of cumulative information on risk and benefits.

The legal requirements for submission of PSURs are established in Regulation (EU) No 1235/2010, Directive 2010/84/EU and in Commission Implementing Regulation (EU) No 520/2012. The format of PSURs follows the structure described in the Implementing Regulation Article 35 and Module VII of the Guidelines on Good Pharmacovigilance Practices (GVP) provides guidance on the preparation, submission and assessment of PSURs. This format is a legal requirement for both Nationally Authorised Products (NAPs) and Centrally Authorised Products (CAPs).

Who should submit PSURs?

The 2010 legislation introduces the principle of EU single assessment where a substance is authorised in more than one Member State. The European Medicines Agency maintains a list of EU reference dates and

frequency of submission of PSURs (EURD list) for active substances contained in medicines in the EU and is updated on an ongoing basis.

Marketing Authorisation Holders (MAHs) are required to submit PSURs according to the data lock points published in the EURD list. The legislation introduces derogation for routine PSUR reporting for certain products. Unless there is a specific condition in the authorisation, or it is indicated otherwise in the EURD list, routine PSUR reporting is not required for medicinal products authorised under the following articles of Directive 2001/83/EC:

- Article 10.1 generics
- Article 10.a well-established use
- Article 14 homeopathic medicines
- Article 16a traditional herbal medicines

Further information on GVP and the EURD list may be found on the European Medicines Agency website. Please note that the EURD list is a living document, which will be amended whenever considered necessary by the PRAC, the CHMP or CMDh in response to the emergence of relevant new safety information, newly authorised substances and requests received from MAHs. Substances can be added or removed as appropriate. MAHs should therefore maintain an awareness of the current status of the list, which is reviewed on a monthly basis.

Guidance on PSUR Submission

Mandatory submission of PSURs via the EU PSUR Repository

It is mandatory for all MAHs to submit PSURs for human medicines authorised in the EU directly to the PSUR repository. The repository acts as the single point for all submissions (including responses and supplementary information). This is mandatory for both centrally authorised and nationally authorised medicinal products whether they follow the EU single assessment or a purely national assessment procedure. All PSURs should be submitted to the PSUR repository using the eSubmission Gateway/Web Client.

Information on the repository, guidance on how to register and multimedia tutorials for MAHs on how to submit a PSUR, as well as on the correct structured electronic formats, can be found on the EMA's PSUR repository web pages.

Further information for MAHs on changes to submission of PSURs for human medicines is available here: PSUR repository mandatory use: Q&A

Users of the repository should direct any questions on use of the EMA PSUR repository and/or the eSubmission Gateway/Web Client to the EMA Service Desk portal.

For further information on submission dates, PSUSA procedure number and requirements for submission of products referred to in articles 10(1), 10a, 14, 16a of Directive 2001/83/EC as amended please refer to the EURD list.

Detailed guidance on procedural aspects of the EU single assessment is available on the EMA website: PSURs: questions and answers

2.6 Pharmacovigilance Planning

Pharmacovigilance Planning Guidance

This Pharmacovigilance planning guidance is intended to aid in planning pharmacovigilance activities, especially in preparation for the early post marketing period of a new drug. The main focus of this Guideline is on a Safety Specification and Pharmacovigilance Plan that might be submitted at the time of licence application.

The guidance is divided into the following sections:

- Safety specification
- Pharmacovigilance plan
- Annex — Pharmacovigilance Methods

Safety Specification

The focus of the safety specification should be on the identified risks, important potential risks, and important missing information. The following elements should be considered:

1. **Nonclinical:** This section should present nonclinical safety findings that have not been adequately addressed by clinical data, for example:
   - Toxicity (including repeat-dose toxicity, reproductive/developmental toxicity, nephrotoxicity, hepatotoxicity, genotoxicity, carcinogenicity, etc.)
   - General pharmacology (cardiovascular, including QT interval prolongation; nervous system; etc.)
   - Drug interactions
   - Other toxicity-related information or data
2. **Clinical:** This section should include the following elements:
   - Limitations of the human safety database
   - Populations not studied in the preapproval phase
   - Adverse events (AEs)/adverse drug reactions (ADRs)
   - Identified and potential interactions, including food-drug and drug-drug interactions
   - Epidemiology
   - Pharmacological class effects

Pharmacovigilance Plan

The pharmacovigilance plan should be based on the safety specification. The structure can be varied depending on the product in question and the issues identified in the safety specification. The pharmacovigilance plan should include:

- Summary of Ongoing Safety Issues
- Routine Pharmacovigilance Practices
- Action Plan for Safety Issues
- Summary of Actions To Be Completed, Including Milestones

Definition

Good Clinical Practice (GCP) is an international ethical and scientific quality standard for the design, conduct, performance, monitoring, auditing, recording, analyses and reporting of clinical trials. GCP provides assurance that the data and reported results are credible and accurate, and that the rights, integrity and confidentiality of trial subjects are respected and protected. It was finalised in 1996 and became effective in 1997, but was not enforced by law at that time. The Medicines for Human Use (Clinical Trials) Regulations 2004 and the European Union (EU) Directive on Good Clinical Practice changed the world perspective , and compliance with GCP is now a legal obligation in the UK/Europe for all trials involving the investigation of medicinal products.

Historical Background

It is very important to understand the background of the formation of the ICH-GCP guidelines as

this, in itself, explains the reasons and the need for doing so ((Table 1)). The concept of the 'good physician' dates back to the ancient world and it is evidenced by the Hippocratic Oath (460 BC). In the United States, the first landmark in the regulation of drugs was the Food and Drugs Act of 1906. This was a result of harmful and lethal drugs that could be bought across the counter just like any other consumer product. Some examples are: 'Grandma's Secret' and 'Kopp's Baby's Friend' which contained large doses of morphine, as well as 'Dr King's Consumption Cure' and 'Dr Bull's Cough Syrup' which contained morphine and chloroform [3]. In 1938, the Federal Food, Drug and Cosmetic Act was enacted by the Food and Drug Administration (FDA) and for the first time, manufacturers were required to test drugs for safety and present the evidence of safety testing to the FDA prior to marketing.

Table 1: Historical background of GCP

460BC	Oath of Hippocrates
1930's	U.S. Food, Drugs and Cosmetic Act
1947	Nuremberg Code
Dec. 10th 1948	Declaration of Human Rights
1962	Kefauver-Harris Amendment
1964, revised 2000	Declaration of Helsinki
1979	The Belmont Report
1982	International Guidelines for Biomedical Research Involving Human Subjects
1996	ICH-GCP guidelines issued
1997	ICH-GCP guidelines becomes law in some countries

In 1947, the Nuremberg Code was created as a result of the unethical and horrific experiments carried out during World War II at Nazi war camps by German physicians, who were subsequently tried and charged at the Nuremberg Military Tribunal. This code states the need for a scientific basis in research on human subjects and voluntary consent and protection of participants. The Universal Declaration of Human Rights (December 10th 1948) was also adopted and proclaimed by the United Nations after the atrocities of World War II and it further reiterated the human factor involved in medical experiments.

In 1964, the Declaration of Helsinki was developed by the World Medical Assoc iation, forming the basis for the ethical principles that underlie the ICH-GCP guidelines we have today. The focus of this declaration is the protection of the rights of human subjects and this is clear in its introduction.

"The World Medical Association has developed the Declaration of Helsinki as a statement of ethical principles to provide guidance to physicians and other participants in medical research involving human subjects. It is the duty of the physician to promote and safeguard the health of the people. The physician's knowledge and conscience are dedicated to the fulfilment of this duty"

In 1962 the world was once again shocked by the severe foetal limb deformities linked to the use of maternal thalidomide. In fact this drug reaction was only discovered after 10,000 infants were born in over 20 countries worldwide. In response to this, the Kefauver-Harris Amendments were passed which required the FDA to evaluate all new drugs for safety and efficacy.

Another important milestone in the formation of the ICH-GCP guidelines was The Belmont Report which was issued in April 1979 by the National Commission for Protection of Human Subjects of Biomedical and Behavioural Research. The principles of this report are as follows:

1. ***Respect for Persons*:** This principle acknowledges the dignity and freedom of every person. It requires obtaining informed consent from research subjects (or their legally authorised representatives)
2. ***Beneficence*:** This principle requires that researchers maximise benefits and minimise harms associated with research. Research-related risks must be reasonable in light of the expected benefits.
3. ***Justice*:** This principle requires equitable selection and recruitment and fair treatment of research subjects.

In 1982, the World Health Organization (WHO) and the Council for International Organizations of Medical Sciences (CIOMS) issued a document entitled 'International Guidelines for Biomedical Research Involving Human Subjects'. This document was released to help developing countries apply the principles of the Declaration of Helsinki and the Nuremberg Code. Worldwide, many organisations and committees issued various documents and guidelines on the same issue, and a decision was taken to consolidate all these guidelines into one universal guideline to be used globally.

In an effort to overcome international GCP inconsistencies throughout the countries, the International Conference for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) issued the ICH Guidelines: Topic E6 Guideline for GCP. This guideline was approved on 17 July 1996 and implemented for clinical trials from 17 January 1997. The participants of these guidelines were representatives of authorities and pharmaceutical companies from the EU, Japan and the United States as well as those of Australia, Canada, the Nordic countries and WHO [8].

ICH-GCP

The ICH-GCP is a harmonised standard that protects the rights, safety and welfare of human subjects, minimises human exposure to investigational products, improves quality of data, speeds up marketing of new drugs and decreases the cost to sponsors and to the public. Compliance with this standard provides public assurance that the rights, safety and well- being of trial subjects are protected and consistent with the principles of the Declaration of Helsinki, and that the clinical trial data is credible [8]. A historical background of the reasons and the importance of GCP is summarised in (Table 2).

Table 2: Reasons for GCP

Increased Ethical Awareness
Improved Trial Methods
Clinical Trial Concept Better Understood
Public/Political Concern over Safety Aspects
Frauds and Accidents during Trials
Growing Research and Development Costs
Increasing Competition
Mutual Recognition of Data
New Market Structure

There are 13 core principles of ICH-GCP and they are as follows:

1. Clinical trials should be conducted in accordance with ethical principles that have their origin in the Declaration of Helsinki, and that are consistent with GCP and the applicable regulatory requirement(s).
2. Before a trial is initiated, foreseeable risks and inconveniences should be weighed against anticipated benefit for the individual trial subject and society. A trial should be initiated and continued only if the anticipated benefits justify the risks.

3. The rights, safety and well-being of the trial subjects are the most important considerations and should prevail over interest of science and society.
4. The available non-clinical and clinical information on an investigational product should be adequate to support the proposed clinical trial.
5. Clinical trials should be scientifically sound, and described in clear, detailed protocol.
6. A trial should be conducted in compliance with the protocol that has received prior institutional review board (IRB)/ independent ethics committee (IEC) approval/favourable opinion.
7. The medical care given to, and medical decisions made on behalf of subjects should always be the responsibility of a qualified physician or, when appropriate, of a qualified dentist.
8. Each individual involved in conducting a trial should be qualified by education, training, and experience to perform his or her respective task(s).
9. Freely given informed consent should be obtained from every subject prior to clinical trial participation.
10. All clinical trial information should be recorded, handled, and stored in a way that allows its accurate reporting, interpretation and verification.
11. The confidentiality of records that could identify subjects should be protected, respecting the privacy and confidentiality rules in accordance with the applicable regulatory requirement(s).
12. Investigational products should be manufactured, handled and stored in accordance with applicable Good Manufacturing Practice (GMP). They should be used in accordance with the approved protocol.
13. Systems with procedures that assure the quality of every aspect of the trial should be implemented.

These principles are self-explanatory and, when summarised, simply mean:

All clinical trials should be conducted in accordance with ethical principles, sound scientific evidence and clear detailed protocols. The benefits of conducting trials should outweigh the risks. The rights, safety and well-being of trial participants are of paramount importance and these should be preserved by obtaining informed consent and maintaining confidentiality. The care must be given by appropriately qualified personnel with adequate experience. Records should be easily accessible and retrievable for accurate reporting, verification and interpretation. Investigational products should be manufactured according to Good Manufacturing Practice (8).

It is also important to mention the participants of GCP in clinical trials and their respective responsibilities. These are summarised in (Table 3).

Table 3: GCP participants

Regulatory Authorities	Review submitted clinical data and conduct inspections
The sponsor	Company or institution/organization which takes responsibility for initiation, management and financing of clinical trial
The project monitor	Usually appointed by sponsor
The investigator Team leader.	Responsible for conduct of clinical trial at the trial site.
The pharmacist at trial location	Responsible for maintenance, storage and dispensing of investigational products eg. Drugs in clinical trials
Patients	Human subjects
Ethical review board or	Appointed by Institution or if not available then the
Committee for protection of subjects	Authoritative Health Body in that Country will be responsible
Committee to monitor large trials	Overseas Sponsors eg. Drug Companies

GCP In the Asia Pacific Region

Since the conception of the ICH-GCP guidelines, many countries in the Asia-Pacific region realised the need to formulate guidelines of their own based on the framework of the original guidelines [7]. This is clearly seen in (Table 4) that tabulates the adoption of GCP in our country and its neighbours.

Table 4: Table 4 GCP Adoption in the Asia Pacific Region

Original ICH-GCP Guidelines	1996
Singapore GCP	1998
Chinese GCP	1999
Malaysian GCP	1999, revised 2004
Thailand	2000
Indonesia	2001

In Malaysia, similar guidelines were formulated in the wake of greater demand by the pharmaceutical industry to conduct clinical trials in the country. The Malaysian Guidelines for GCP was first published in October 1999 and the second edition was released in January 2004. The guideline adopts the basic principle outlined by the International Committee on Harmonization of Good Clinical Practice (ICH-GCP) with some modifications to suit local requirements [1,7].

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05. Pharmacogenomics of Adverse Durg Reactons

1. Pharmacogenomics of Adverse Durg Reactons

Background On Pharmacogenetics

At its most basic, the term pharmacogenetics describes any influence that genetics can have on drug therapy. The newer term pharmacogenomics is often used interchangeably with pharmacogenetics, but there are some subtle differences. Pharmacogenetics mainly deals with single drug-gene interactions. In contrast, pharmacogenomics incorporates genomics and epigenetics to look at the effect of multiple genes on drug responses. Pharmacogenomics is considered the future of drug therapy and is a rapidly growing field in the area of precision (personalized) medicine. illustrates how pharmacogenomic approaches have been used in drug hypersensitivity. Many factors can determine whether differences in genetic polymorphisms will be clinically relevant.8 The therapeutic index of a drug is one important factor. A polymorphism affecting the concentration of a drug that is safe over a wide range of concentrations is unlikely to have a clinically relevant effect. However, if a drug has a narrow therapeutic window (eg, warfarin), minor variations in concentrations from polymorphisms could be important. If the metabolite of a drug has a similar effect as the parent drug, polymorphisms in the enzyme creating the metabolite are unlikely to be important. If multiple metabolic or elimination pathways are present for a drug, the effect of a polymorphism affecting one pathway might also be negligible. Regarding drug hypersensitivity, polymorphisms must not only be associated with a significant risk but also have a degree of specificity that would not eliminate a large proportion of patients who would unlikely be harmed by taking the drug.

History of Pharmacogentics

One of the earliest examples of pharmacogenetic observations is from Pythagoras, who noted in 510 BC that some subjects would have an acute illness and even die after ingestion of fava beans.9 It was not until 1956 that we discovered that a deficiency in the enzyme glucose-6- phosphate dehydrogenase (G6PD) was the cause of hemolytic anemia from ingestion of fava beans or drugs such as primaquine.10 Shortly after this, pseudocholinesterase deficiency was discovered as a genetic cause for prolonged apnea from anesthesia with succinylcholine.11 Fig 2 shows a timeline of some important discoveries of pharmacogenetics regarding ADRs. One of the most well-known early examples of the genetics of drug metabolism is the acetylation polymorphism. Studies from the early 1950s observed that isoniazid, which was at the time a recently introduced treatment for tuberculosis, had marked differences in excretion among patients. These differences were discovered to be related to differences in a subject's ability to convert isoniazid to acetylisoniazid, and ''slow acetylators'' were more likely to have peripheral neuropathy. These studies triggered many further epidemiologic, pharmacologic, and clinical studies in numerous countries, providing a model of how pharmacogenetic traits could be analyzed. This acetylation polymorphism also influenced the metabolism of other drugs, including sulfonamides, dapsone, hydralazine, procainamide, and many others. Many decades later, the molecular causes of these traits were discovered.

Adverse drug reactions

An adverse drug reaction is a harmful reaction to a medicine given at the correct dose. The reaction can start soon after you take the medicine, or up to 2 weeks after you stop. An adverse drug reaction can cause serious conditions such toxic epidermal necrolysis (TEN) and anaphylaxis. TEN can cause severe skin damage. Anaphylaxis is a sudden, life-threatening reaction that needs immediate treatment. Ask your healthcare provider for more information on TEN, anaphylaxis, and other serious reactions.

There are several terms commonly used to describe adverse effects of drug therapy:

- An adverse drug reaction (ADR) is an unwanted or harmful reaction experienced following the administration of a drug or combination of drugs under normal conditions of use and is suspected to be related to the drug. An ADR will usually require the drug to be discontinued or the dose reduced.
- An adverse event is harm that occurs while a patient is taking a drug, irrespective of whether the drug is suspected to be the cause.
- A side-effect is any effect caused by a drug other than the intended therapeutic effect, whether beneficial, neutral or harmful. The term 'side-effect' is often used interchangeably with 'ADR' although the former usually implies an effect that is less harmful, predictable and may not even require discontinuation of therapy (e.g. ankle oedema with vasodilators).
- Drug toxicity describes adverse effects of a drug that occur because the dose or plasma concentration has risen above the therapeutic range, either unintentionally or intentionally (drug overdose).
- Drug abuse is the misuse of recreational or therapeutic drugs that may lead to addiction or dependence, serious physiological injury (such as damage to kidneys, liver, heart), psychological harm (abnormal behavior patterns, hallucinations, memory loss), or death.

Types of Adverse Drug Reactions

Adverse drug reactions (adverse effects) are any unwanted effects of a drug. There are several different types:

1. Dose-related
2. Allergic
3. Idiosyncratic

1. **Dose-related adverse drug reactions** represent an exaggeration of the drug's therapeutic effects. For example, a person taking a drug to reduce high blood pressure may feel dizzy or light-headed if the drug reduces blood pressure too much. A person with diabetes may develop weakness, sweating, nausea, and palpitations if insulin or another antidiabetic drug reduces the blood sugar level too much. This type of adverse drug reaction is usually predictable but sometimes unavoidable. It may occur if a drug dose is too high (overdose reaction), if the person is unusually sensitive to the drug, or if another drug slows the metabolism of the first drug and thus increases its level in the blood (see Drug Interactions). Dose-related reactions may or may not be serious, but they are relatively common.
2. **Allergic drug reactions** are not dose-related but require prior exposure to a drug. Allergic reactions develop when the body's immune system develops an inappropriate reaction to a drug (sometimes referred to as sensitization). After a person is sensitized, later exposures to the drug produce one of several different types of allergic reaction. Sometimes doctors do skin tests to help predict allergic drug reactions.
3. **Idiosyncratic adverse drug reactions** result from mechanisms that are not currently understood. This type of adverse drug reaction is largely unpredictable. Examples of such adverse drug reactions include rashes, jaundice, anemia, a decrease in the white blood cell count, kidney damage, and nerve injury that may impair vision or hearing. These reactions tend to be more serious but typically occur in a very small number of people. Affected people may have genetic differences in the way their body metabolizes or responds to drugs.

Some adverse drug reactions are not related to the drug's therapeutic effect but are usually predictable,

because the mechanisms involved are largely understood. For example, stomach irritation and bleeding often occur in people who regularly use aspirin or other nonsteroidal anti- inflammatory drugs (NSAIDs). The reason is that these drugs reduce the production of prostaglandins, which help protect the digestive tract from stomach acid.

Signs And Symptoms Of An Adverse Drug Reaction

- **Mild symptoms** include red, itchy, flaky, or swollen skin. You may have a flat, red area on your skin that is covered with small bumps. You may also have hives.
- **Severe symptoms** include skin that blisters or peels, vision problems, and severe swelling or itching. Severe reactions include conditions such as toxic epidermal necrolysis (TEN). Ask your healthcare provider for more information on TEN and other serious conditions.
- **Anaphylaxis symptoms** include throat tightness, trouble breathing, tingling, dizziness, and wheezing. Anaphylaxis is a sudden, life-threatening reaction that needs immediate treatment. Anaphylaxis may occur if you exercise after exposure to another trigger, such as after you take an antibiotic.

Adverse Drug Reaction Diagnosed

Your healthcare provider will ask about your medical history and allergies. You may need additional testing if you developed anaphylaxis after you were exposed to a trigger and then exercised. This is called exercise-induced anaphylaxis. Medicines can be a trigger. You may also need any of the following:

- **A patch test** means a small amount of the drug is put on your skin. The area is covered with a patch that stays on for 2 days. Then your healthcare provider will check your skin for a reaction.
- **A skin prick test** means a small drop of the drug is put on your forearm and your skin is pricked with a needle. Your healthcare provider will watch for a reaction.
- **An intradermal test** means a small amount of liquid containing the drug is put under the surface of your skin. Your healthcare provider will watch for a reaction.
- **A drug provocation test** is also known as a challenge test. Your healthcare provider gives you increasing doses of the drug and watches for a reaction.

Adverse Drug Reaction Treated

- **Antihistamines** decrease mild symptoms such as itching or a rash.
- **Epinephrine** is medicine used to treat severe allergic reactions such as anaphylaxis.
- **Steroids** reduce inflammation.
- **Desensitization** may be done after you have a reaction, if you need to be treated with the drug again. Your healthcare provider will give you small doses of the drug over a few hours. He will treat any allergic reaction that you have. The dose is increased a little at a time until the full dose is reached and the drug stops causing an allergic reaction.

Pharmacokinetic Parameters

- Pharmacodynamics.
- Half Life Time.
- Drug Concentration.
- Bioavailability.
- Toxicity.

Pharmacodynamics

In drug discovery trials, the potential for a molecule to do harm to an organism must be known accurately. Understanding how a substance under investigation behaves once in the body informs the design of clinical trials and provides invaluable data for the release of new drugs onto the market. One field of study which can help to inform drug discovery and design is pharmacodynamics.

But what is pharmacodynamics? This article will provide a brief overview of the subject and how it is used in drug discovery preclinical trials. A brief discussion on current research into increasing the scalability of PK/PD (pharmacokinetic/pharmacodynamic) models, which are commonly used in preclinical studies, will also be presented.

Pharmacodynamics – an overview

Pharmacodynamics (PD and pharmacokinetics (PK) constitute the two main branches of pharmacology. Pharmacodynamics studies the biological and physiological effects of drugs on an organism, whereas pharmacokinetics studies how the organism affects the drug. Pharmacodynamics and pharmacokinetics are often combined in PK/PD models. These models are used extensively in preclinical trials.

Both pharmacodynamics and pharmacokinetics together influence factors such as dosing, drug benefits, and adverse effects. Pharmacodynamics places particular emphasis on dose-response relationships, which are the relationships between the concentration of a drug and its effect, whether negative or positive, upon the organism.

Negative/undesirable effects include the increased probability of cell mutation (otherwise known as carcinogenic activity), induced physiological damage, abnormal chronic conditions, adverse reproductive effects, and lethality. Therefore, knowledge of a drug's behavior is absolutely vital in drug development studies.

Multicellular Pharmacodynamics

Recently, pharmacodynamic concepts have been expanded to include multicellular pharmacodynamics (MCPD). MCPD concepts help researchers to understand the dynamic and static relationships between drugs and multicellular four-dimensional organization in organisms. In this way, a drug's action upon a minimal multicellular system can be studied both *in vivo* and *in silico*.

Pharmacodynamics Studies

Successful drug candidates for clinical development require a safe and effective dosing regimen. Drug candidates must be able to distribute to the site of action and have sufficient duration of pharmacological response plus an acceptable safety profile. Pharmacology studies have been performed worldwide for decades as part of the nonclinical evaluation of pharmaceuticals for human use. Since pharmacologic response is a function of both drug affinity for a molecular target as well as the determinants of drug distribution to the target, pharmacodynamics characterizations are important considerations when defining a dosing regimen. *In vivo* safety pharmacology studies should be designed to precisely define the dose-response relationship of the adverse effect observed.

Pharmacodynamics Services at Creative Biolabs

Many PD and PK factors affect the clinical evaluation of respiratory disease drugs. The route of administration and duration of treatment are variables that have impacts on the study outcome. Due to metabolic differences and PD factors, varying results may be obtained relying on whether drugs are orally or intravenously administered. Creative Biolabs has strong abilities to provide various pharmacological assessments to determine the PD characteristics and metabolic profiles of a drug, enabling the most efficient testing protocols for this potential agent.

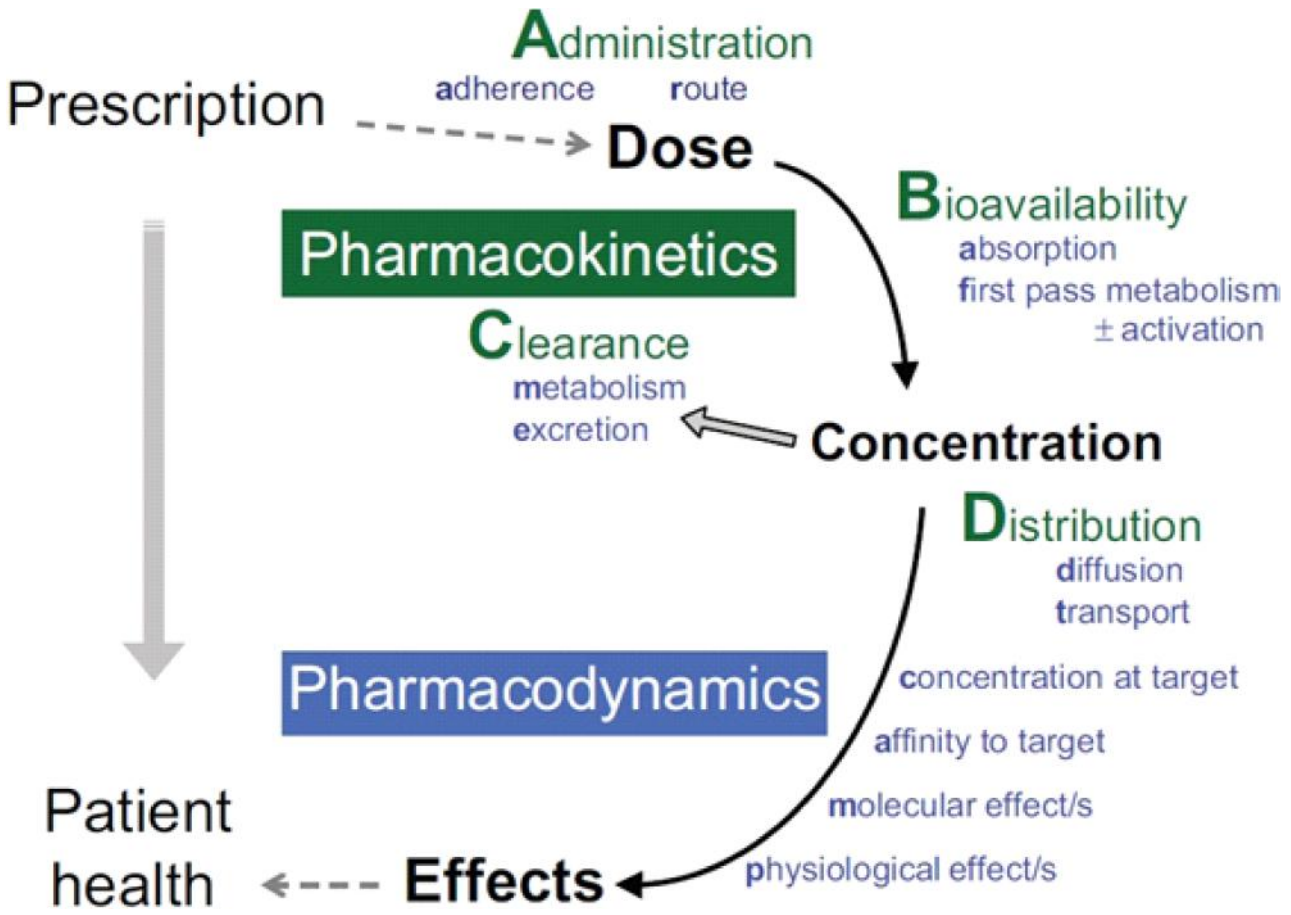


Fig.1 From prescription to patient health - mapping the medicine to the patient.

- **Cell-based *in vitro* pharmacodynamics**
- **Tissue/Organ bath assays**

We can provide mature biological models that are independent of the systemic influence on *in vivo* preparations. Tissue or organ models have been established for studies on respiratory disease drugs (tracheal rings; phrenic diaphragm; pulmonary arterial smooth muscle; lung parenchyma; bronchi).

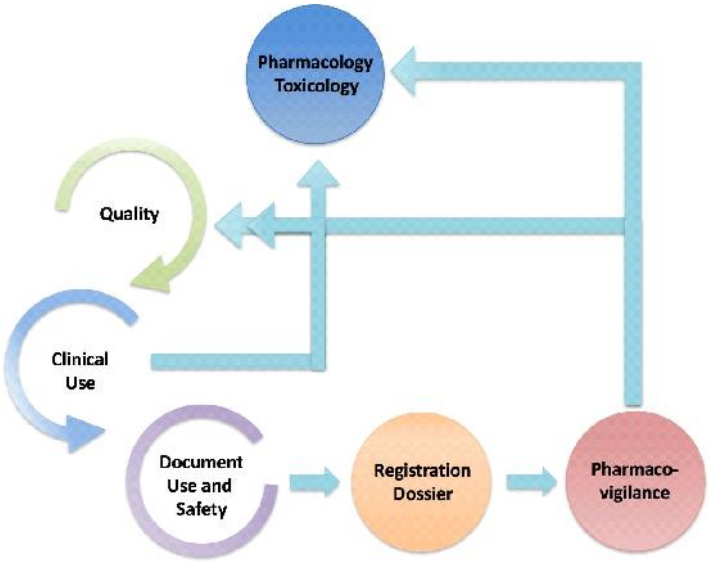
- **Dosing simulations**
- **Preclinical profiling**

We can perform varieties of data analysis as required, including PK, drug-drug interaction (DDI), multiple ascending dose (MAD), single ascending dose (SAD), thorough QT (TQT), food effect, *etc*.

- **Risk analysis**

By integrating PD models with pre-clinical data, we can offer probabilistic risk analysis to weed out weak candidates before clinical trials and make the development of respiratory disease drug more efficient.

Pharmacodynamics (PD) is the study of the physiologic and biochemical effects of drugs (especially pharmaceutical drugs) and to discover how the drug affects the organism. Pharmacodynamics particularly emphasizes on dose-response relationships, in other words, the relationships between drug concentration and its effect. It dedicates to determining the dose, duration of the effect in clinical use. Usually, animal models are built to conduct research on the drug discovery and development program. Currently, animal models that mimic various human diseases provide an opportunity to better investigate pharmacology and pharmacodynamics, and to anticipate the clinical and adverse responses to drugs in humans. Animal models in the pharmacodynamics evaluation play a significantly important role in preclinical assessments of new agents, dosing optimization for those that are clinically approved, and setting or confirming susceptibility breakpoints.



Creative Biolabs offers a broad variety of standard disease models for our worldwide clients. With years of experience in the field of pharmacology and pharmacodynamics studies as well as excellent professional skills, our scientists are proud to help you identify the most appropriate disease models for your research of interest. And you can also explore our extensive and bro ad- based library of animal models to find the one you need.

Following is the list of available disease models in **Creative Biolabs,** which are used in different ways to explore human disease.

Half-Life

Why use a term like half-life rather than lifetime? The answer can be found by examining Figure 1, which shows how the number of radioactive nuclei in a sample decreases with time. The *time in which half of the original number of nuclei decay* is defined as the *half-life*, *t*1/2. Half of the remaining nuclei decay in the next half-life. Further, half of that amount decays in the following half-life. Therefore, the number of radioactive nuclei decreases from *N* to N2N2 in one half-life, then to N4N4 in the next, and to N8N8 in the next, and so on. If *N* is a large number, then *many* half-lives (not just two) pass before all of the nuclei decay. Nuclear decay is an example of a purely statistical process. A more precise definition of half-life is that *each nucleus has a 50% chance of living for a time equal to one half-life t1/2*. Thus, if *N* is reasonably large, half of the original nuclei decay in a time of one half-life. If an individual nucleus makes it through that time, it still has a 50% chance of surviving through another half-life. Even if it happens to make it through hundreds of half-lives, it still has a 50% chance of surviving through one more. The probability of decay is the same no matter when you start counting. This is like random coin flipping. The chance of heads is 50%, no matter what has happened before.

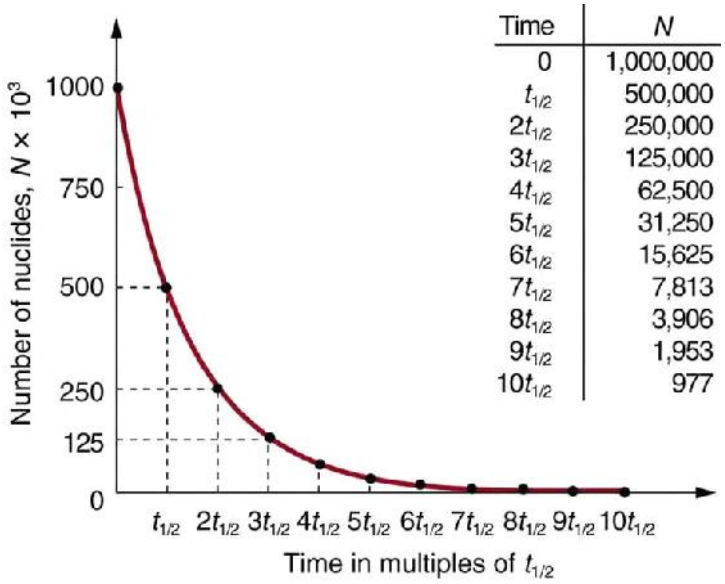


Figure 1: Radioactive decay reduces the number of radioactive nuclei over time. In one half- life *t*1/2, the number decreases to half of its original value. Half of what remains decay in the next half-life, and half of those in the next, and so on. This is an exponential decay, as seen in the graph of the number of nuclei present as a function of time.

There is a tremendous range in the half-lives of various nuclides, from as short as 10"23 s for the most unstable, to more than 1016 y for the least unstable, or about 46 orders of magnitude. Nuclides with the shortest half-lives are those for which the nuclear forces are least attractive, an indication of the extent to which the nuclear force can depend on the particular combination of neutrons and protons. The concept of half-life is applicable to other subatomic particles, as will be discussed in Particle Physics. It is also applicable to the decay of excited states in atoms and nuclei. The following equation gives the quantitative relationship between the original number of nuclei present at time zero (*N*0) and the number (*N*) at a later time *t*: $N = N0e^{-\lambda t}$, where *e*=2.71828… is the base of the natural logarithm, and λ is the *decay constant* for the nuclide. The shorter the half-life, the larger is the value of λ, and the faster the exponential $e^{-\lambda t}$ decreases with time. The relationship between the decay constant λ and the half- life *t*1/2 is

λ=ln(2)t1/2H”0.693t1/2λ=lna (2)t1/2H”0.693t1/2.

To see how the number of nuclei declines to half its original value in one half-life, let $t = t1/2$ in the exponential in the equation $N = N0e^{-\lambda t}$. This gives $N = N0e^{-\lambda t} = N0e$”0.693 = 0.500*N*0. For integral numbers of half-lives, you can just divide the original number by 2 over and over again, rather than using the exponential relationship. For example, if ten half-lives have passed, we divide *N* by 2 ten times. This reduces it to N1024N1024. For an arbitrary time, not just a multiple of the half-life, the exponential relationship must be used.

Radioactive dating is a clever use of naturally occurring radioactivity. Its most famous application is *carbon-14 dating*. Carbon-14 has a half-life of 5730 years and is produced in a nuclear reaction induced when solar neutrinos strike 14N in the atmosphere. Radioactive carbon has the same chemistry as stable carbon, and so it mixes into the ecosphere, where it is consumed and becomes part of every living organism. Carbon-14 has an abundance of 1.3 parts per trillion of normal carbon. Thus, if you know the number of carbon nuclei in an object (perhaps determined by mass and Avogadro's number), you multiply that number by 1.3 × 10"12 to find the number of 14C nuclei in the object. When an organism dies, carbon exchange with the environment

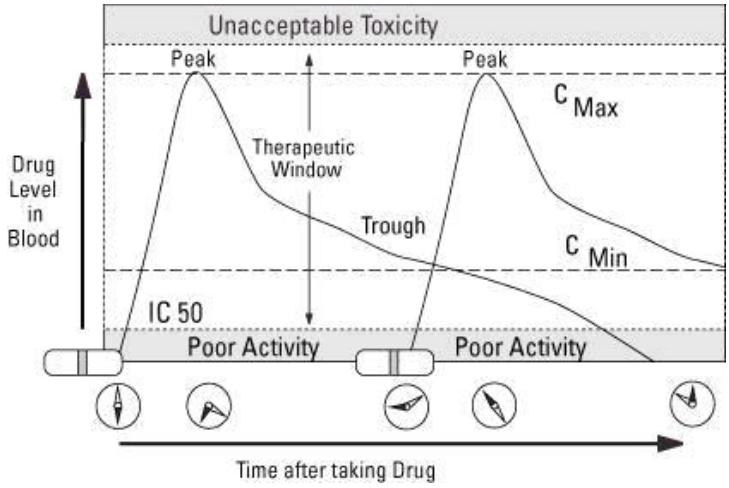
ceases, and 14C is not replenished as it decays. By comparing the abundance of 14C in an artifact, such as mummy wrappings, with the normal abundance in living tissue, it is possible to determine the artifact's age (or time since death). Carbon-14 dating can be used for biological tissues as old as 50 or 60 thousand years, but is most accurate for younger samples, since the abundance of 14C nuclei in them is greater. Very old biological materials contain no 14C at all. There are instances in which the date of an artifact can be determined by other means, such as historical knowledge or tree-ring counting. These cross-references have confirmed the validity of carbon-14 dating and permitted us to calibrate the technique as well. Carbon-14 dating revolutionized parts of archaeology and is of such importance that it earned the 1960 Nobel Prize in chemistry for its developer, the American chemist Willard Libby (1908–1980).

Drug Concentrations

Exponential functions can be used to model the concentration of a drug in a patient's body. Suppose the concentration of Drug X in a patient's bloodstream is modeled by,

$$C(t) = C_0 e - rt,$$

where $C(t)$ represents the concentration at time t (in hours), C_0 is the concentration of the drug in the blood immediately after injection, and $r > 0$ is a constant indicating the removal of the drug by the body through metabolism and/or excretion. The rate constant r has units of 1/time (1/hr). It is important to note that this model assumes that the blood concentration of the drug (C_0) peaks immediately when the drug is injected.



Drug Bioavailability

Bioavailability refers to the extent and rate at which the active moiety (drug or metabolite) enters systemic circulation, thereby accessing the site of action.

Bioavailability of a drug is largely determined by the properties of the dosage form, which depend partly on its design and manufacture. Differences in bioavailability among formulations of a given drug can have clinical significance; thus, knowing whether drug formulations are equivalent is essential.

Chemical equivalence indicates that drug products contain the same active compound in the same amount and meet current official standards; however, inactive ingredients in drug products may differ. **Bioequivalence** indicates that the drug products, when given to the same patient in the same dosage regimen, result in equivalent concentrations of drug in plasma and tissues. **Therapeutic equivalence** indicates that drug products, when given to the same patient in the same dosage regimen, have the same therapeutic and adverse effects.

Bioequivalent products are expected to be therapeutically equivalent. Therapeutic nonequivalence (eg,

more adverse effects, less efficacy) is usually discovered during long-term treatment when patients who are stabilized on one formulation are given a nonequivalent substitute.

Sometimes therapeutic equivalence is possible despite differences in bioavailability. For example, the therapeutic index (ratio of the minimum toxic concentration to the median effective concentration) of penicillin is so wide that efficacy and safety are usually not affected by the moderate differences in plasma concentration due to bioavailability differences in penicillin products. In contrast, for drugs with a relatively narrow therapeutic index, bioavailability differences may cause substantial therapeutic nonequivalence.

(See also Overview of Pharmacokinetics.)

Causes of low bioavailability

Orally administered drugs must pass through the intestinal wall and then the portal circulation to the liver; both are common sites of first-pass metabolism (metabolism that occurs before a drug reaches systemic circulation). Thus, many drugs may be metabolized before adequate plasma concentrations are reached. Low bioavailability is most common with oral dosage forms of poorly water-soluble, slowly absorbed drugs.

Insufficient time for absorption in the gastrointestinal (GI) tract is a common cause of low bioavailability. If the drug does not dissolve readily or cannot penetrate the epithelial membrane (eg, if it is highly ionized and polar), time at the absorption site may be insufficient. In such cases, bioavailability tends to be highly variable as well as low.

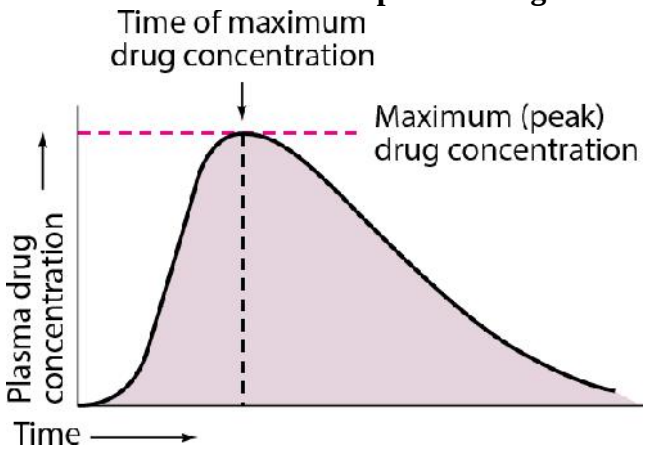
Age, sex, physical activity, genetic phenotype, stress, disorders (eg, achlorhydria, malabsorption syndromes), or previous GI surgery (eg, bariatric surgery) can also affect drug bioavailability.

Chemical reactions that reduce absorption can decrease bioavailability. They include formation of a complex (eg, between tetracycline and polyvalent metal ions), hydrolysis by gastric acid or digestive enzymes (eg, penicillin and chloramphenicol palmitate hydrolysis), conjugation in the intestinal wall (eg, sulfoconjugation of isoproterenol), adsorption to other drugs (eg, digoxin to cholestyramine), and metabolism by luminal microflora.

Assessing bioavailability

Bioavailability is usually assessed by determining the area under the plasma concentration– time curve (AUC—see figure Representative plasma concentration–time relationship after a single ora...). The most reliable measure of a drug's bioavailability is AUC. AUC is directly proportional to the total amount of unchanged drug that reaches systemic circulation. Drug products may be considered bioequivalent in extent and rate of absorption if their plasma concentration curves are essentially superimposable.

Representative plasma concentration–time relationship after a single oral dose of a hypothetical drug

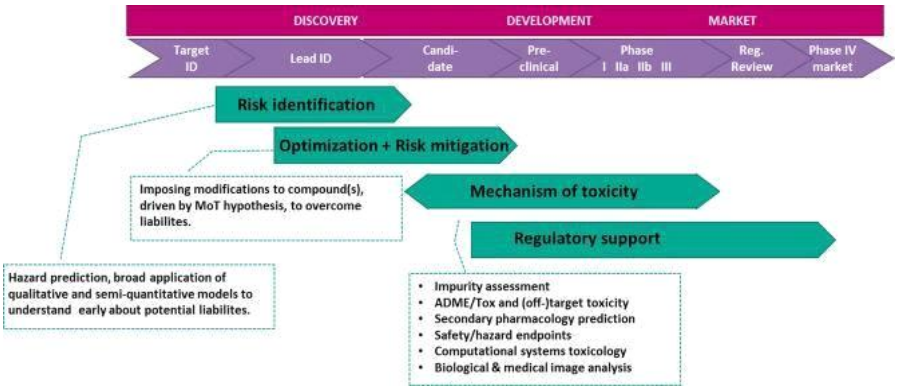


Plasma drug concentration increases with extent of absorption; the maximum (peak) plasma concentration is reached when drug elimination rate equals absorption rate. Bioavailability determinations based on the peak plasma concentration can be misleading because drug elimination begins as soon as the drug enters the bloodstream. Peak time (when maximum plasma drug concentration occurs) is the most widely used general index of absorption rate; the slower the absorption, the later the peak time.

For drugs excreted primarily unchanged in urine, bioavailability can be estimated by measuring the total amount of drug excreted after a single dose. Ideally, urine is collected over a period of 7 to 10 elimination half-lives for complete urinary recovery of the absorbed drug. After multiple dosing, bioavailability may be estimated by measuring unchanged drug recovered from urine over a 24-hour period under steady-state conditions.

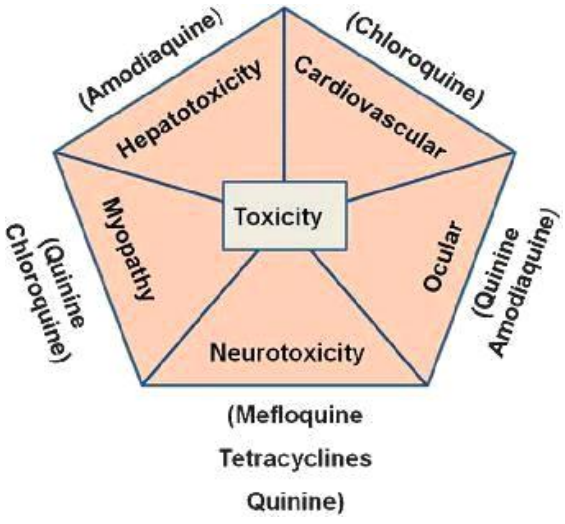
Drug Toxicity

Drug toxicity refers to the level of damage that a compound can cause to an organism. The toxic effects of a drug are dose-dependent and can affect an entire system as in the CNS or a specific organ such as the liver. Toxicity is the degree to which a chemical substance or a particular mixture of substances can damage an organism. A toxic reaction occurs when insect or spider venom acts like a poison in the body. This type of reaction can occur from one bite or sting from a highly toxic insect or spider, or from multiple bites or stings from insects or spiders not normally considered poisonous. Your age, weight, and state of health also affect your outcome. Poisoning can cause short-term effects, like a skin rash or brief illness. In serious cases, it can cause brain damage, a coma, or death. Ethanol intoxication is the commonest type of acute poisoning and suicide by medical drug overdose is the commonest type of suicide by poisoning. Death from acute poisoning is most commonly the result of either smoke inhalation or illegal drug use. If so, you could be putting yourself at risk for an accidental overdose of an over-the- counter (OTC) pain or fever medicine. Pain relief medication is generally safe if taken as directed. But taking too much of these medicines can lead to liver damage, stomach bleeding, and kidney disease.



The most toxic recreational drugs, such as GHB (gamma-hydroxybutyrate) and heroin, have a lethal dose less than 10 times their typical effective dose. By definition, a toxic relationship is a relationship characterized by behaviors on the part of the toxic partner that are emotionally and, not infrequently, physically damaging to their partner. A toxic relationship is characterized by insecurity, self-centeredness, dominance, control. Side effect is an undesirable physical symptom caused by taking a drug or undergoing a medical treatment or therapy. Side effects can range from relatively minor symptoms—such as drowsiness or an upset stomach—to serious effects such as liver damage, and sometimes even life-threatening or potentially fatal effects. The prognosis depends upon the length and degree of exposure and the severity of neurological injury. In some instances, exposure to neurotoxins or neurotoxicants can be fatal. In others, patients may survive but not fully recover. In other situations, many individuals recover completely after treatment. Thallium's toxicity has led to its use (now discontinued in many

countries) as a rat and ant poison.It has been called the “poisoner’s poison” since it is colorless, odorless, and tasteless; its slow-acting, painful and wide-ranging symptoms are often suggestive of a host of other illnesses and conditions. Overmedication is an overutilization of medication wherein a patient takes unnecessary or excessive medications. Persons who feel that they are overmedicated tend to not to follow their physician’s instructions for taking their medication. An allergy means your body sees the medicine as harmful. It rejects the drug with an allergic reaction. This may be mild or strong. It can happen a few hours after you take the drug or not until 2 weeks later. Drug toxicity may occur when a person has consumed a dose of a drug that is too high for them to handle. It may also occur when the person’s liver and/or kidneys are unable to function properly and get the drug out of the bloodstream. This can cause it to build up over time until it starts to cause problems.J the toxicity depends on a variety of factors: dose, duration and route of exposure (see Module Two), shape and structure of the chemical itself, and individual human factors. Body by inhalation (breathing), ingestion (eating), or absorption, or by direct contact with a chemical. Humans, animals, or plants; a poison. Environmental toxins can impact the developing brain through various mechanisms. Some toxins, such as mercury, cause cell death and alter cell migration and cell proliferation (101, 104). Lead disrupts neurotransmission, synaptogenesis, and synaptic trimming (101, 104, 110). Natural toxins are chemicals that are naturally produced by living organisms. These toxins are not harmful to the organisms themselves but they may be toxic to other creatures, including humans, when eaten. Mycotoxins are toxic chemical products formed by fungi that can grow on crops in the field or after harvest. Store potential poisons in their original containers. Do not transfer them to food containers like milk jugs, coffee cans, or soda bottles. Keep food and potential poisons separate; store them in different cabinets. Botulinum toxin. Scientists differ about the relative toxicities of substances, but they seem to agree that botulinum toxin, produced by anaerobic bacteria, is the most toxic substance known. Its LD50 is tiny – at most 1 nanogram per kilogram can kill a human. A toxin is a poisonous substance produced within living cells or organisms; synthetic toxicants created by artificial processes are thus excluded. Toxins vary greatly in their toxicity, ranging from usually minor (such as a bee sting) to almost immediately deadly (such as botulinum toxin). Both types of almonds bitter and sweet have amygdalin, a chemical compound that can turn into cyanide, but bitter almonds have the highest levels by far. Carbon monoxide (CO) causes the most nondrug poisoning deaths in the United States. Household products, such as cleaning agents, personal care and topical products, and pesticides, are among the top ten substances responsible for poisoning exposures annually. Pharmacology deals with drugs and their chemical properties or characteristics, their mode of action, the physiological response to drugs, and the clinical uses of drugs.



Pharmacology intersects with toxicology when the physiological response to a drug is an adverse effect. Toxicology is often regarded as the science of poisons or poisoning, but developing a strict definition for poison is problematic. A poison is any substance, including any drug that has the capacity to harm a living organism. The Renaissance physician Paracelsus (1493-1541) is famously credited with offering the philosophical definition of poisons: "What is there that is not poison? All things are poison and nothing is without poison. Solely the dose determines that a thing is not a poison." However, poisoning inherently implies that damaging physiological effects result from exposure to pharmaceuticals, illicit drugs, or chemicals. So each drug in the pharmacopeia is a potential poison, and individual dose-, situation-, environment-, and gene- related factors contribute to a drug's ability to achieve its adverse potential.

2. Drug Safety Evaluationa In Special Population

2.1 Pediatrics

Pediatrics is the branch of medicine dealing with the health and medical care of infants, children, and adolescents from birth up to the age of 18. The word "paediatrics" means "healer of children"; they are derived from two Greek words: (pais = child) and (iatros = doctor or healer). Paediatrics is a relatively new medical specialty, developing only in the mid-19th century. Abraham Jacobi (1830–1919) is known as the father of paediatrics.

What does a pediatrician do?

A paediatrician is a child's physician who provides not only medical care for children who are acutely or chronically ill but also preventive health services for healthy children. A paediatrician manages physical, mental, and emotional well-being of the children under their care at every stage of development, in both sickness and health.

Aims of pediatrics

The aims of the study of paediatrics is to reduce infant and child rate of deaths, control the spread of infectious disease, promote healthy lifestyles for a long disease-free life and help ease the problems of children and adolescents with chronic conditions.

Paediatricians diagnose and treat several conditions among children including:

- injuries
- infections
- genetic and congenital conditions
- cancers
- organ diseases and dysfunctions

Paediatrics is concerned not only about immediate management of the ill child but also long term effects on quality of life, disability and survival. Paediatricians are involved with the prevention, early detection, and management of problems including:

Related Stories

- Shifting respiratory care strategies for preterm infants could lead to improved health outcomes
- The impact of COVID-19 on dialysis patients
- Gene variant in African Americans contributes to unnecessary bone marrow biopsies
    - developmental delays and disorders

- behavioral problems
- functional disabilities
- social stresses
- mental disorders including depression and anxiety disorders

Collaboration with other specialists

Paediatrics is a collaborative specialty. Paediatricians need to work closely with other medical specialists and healthcare professionals and subspecialists of paediatrics to help children with problems.

How does pediatrics differ from adult medicine?

Paediatrics is different from adult medicine in more ways than one. The smaller body of an infant or neonate or a child is substantially different physiologically from that of an adult. So treating children is not like treating a miniature adult.

Congenital defects, genetic variance, and developmental issues are of greater concern to pediatricians than physicians treating adults. In addition, there are several legal issues in paediatrics. Children are minors and, in most jurisdictions, cannot make decisions for themselves. The issues of guardianship, privacy, legal responsibility and informed consent should be considered in every pediatric procedure.

Training

A paediatrician is a graduate from a medical school first. He or she being a primary care paediatrician then completes three years of education in an accredited pediatric residency program. They learn about caring for infant, child, adolescent, and young adults during this period.

Following the pediatric residency, the pediatrician is eligible for board certification by the American Board of Paediatrics with successful completion of a comprehensive written examination. Recertification is required every seven years.

Subspecialities in pediatrics

Subspecialities in pediatrics include:

- pediatric cardiology
- critical care medicine
- endocrinology
- gastroenterology
- hematology
- neonatal medicine
- nephrology etc.

2.2 Pregnance and Lactation

Pregnancy occurs when a sperm fertilizes an egg after it's released from the ovary during ovulation. The fertilized egg then travels down into the uterus, where implantation occurs. A successful implantation results in pregnancy.

On average, a full-term pregnancy lasts 40 weeks. There are many factors that can affect a pregnancy. Women who receive an early pregnancy diagnosis and prenatal care are more likely to experience a healthy pregnancy and give birth to a healthy baby.

Knowing what to expect during the full pregnancy term is important for monitoring both your health and the health of the baby. If you'd like to prevent pregnancy, there are also effective forms of birth control you should keep in mind.

Symptoms of pregnancy

You may notice some signs and symptoms before you even take a pregnancy test. Others will appear weeks later, as your hormone levels change.

Missed period

A missed period is one of the earliest symptoms of pregnancy (and maybe the most classic one). However, a missed period doesn't necessarily mean you're pregnant, especially if your cycle tends to be irregular.

There are many health conditions other than pregnancy that can cause a late or missed period.

Headache

Headaches are common in early pregnancy. They're usually caused by altered hormone levels and increased blood volume. Contact your doctor if your headaches don't go away or are especially painful.

Spotting

Some women may experience light bleeding and spotting in early pregnancy. This bleeding is most often the result of implantation. Implantation usually occurs one to two weeks after fertilization.

Early pregnancy bleeding can also result from relatively minor conditions such as an infection or irritation. The latter often affects the surface of the cervix (which is very sensitive during pregnancy).

Bleeding can also sometimes signal a serious pregnancy complication, such as miscarriage, ectopic pregnancy, or placenta previa. Always contact your doctor if you're concerned.

Weight gain

You can expect to gain between 1 and 4 pounds in your first few months of pregnancy. Weight gain becomes more noticeable toward the beginning of your second trimester.

Pregnancy-induced hypertension

High blood pressure, or hypertension, sometimes develops during pregnancy. A number of factors can increase your risk, including:

- being overweight or obese
- smoking
- having a prior history or a family history of pregnancy-induced hypertension

Heartburn

Hormones released during pregnancy can sometimes relax the valve between your stomach and esophagus. When stomach acid leaks out, this can result in heartburn.

Constipation

Hormone changes during early pregnancy can slow down your digestive system. As a result, you may become constipated.

Cramps

As the muscles in your uterus begin to stretch and expand, you may feel a pulling sensation that resembles menstrual cramps. If spotting or bleeding occurs alongside your cramps, it could signal a miscarriage or an ectopic pregnancy.

Back pain

Hormones and stress on the muscles are the biggest causes of back pain in early pregnancy. Later on, your increased weight and shifted center of gravity may add to your back pain. Around half of all pregnant women report back pain during their pregnancy.

Anemia

Pregnant women have an increased risk of anemia, which causes symptoms such as lightheadedness and dizziness.

The condition can lead to premature birth and low birth weight. Prenatal care usually involves screening for anemia.

Depression

Between 14 and 23 percent of all pregnant women develop depression during their pregnancy. The many biological and emotional changes you experience can be contributing causes.

Be sure to tell your doctor if you don't feel like your usual self.

Insomnia

Insomnia is another common symptom of early pregnancy. Stress, physical discomfort, and hormonal changes can be contributing causes. A balanced diet, good sleep habits, and yoga stretches can all help you get a good night's sleep.

Breast changes

Breast changes are one of the first noticeable signs of pregnancy. Even before you're far enough along for a positive test, your breasts may begin to feel tender, swollen, and generally heavy or full. Your nipples may also become larger and more sensitive, and the areolae may darken.

Acne

Because of increased androgen hormones, many women experience acne in early pregnancy. These hormones can make your skin oilier, which can clog pores. Pregnancy acne is usually temporary and clears up after the baby is born.

Vomiting

Vomiting is a component of "morning sickness," a common symptom that usually appears within the first four months. Morning sickness is often the first sign that you're pregnant. Increased hormones during early pregnancy are the main cause.

Hip pain

Hip pain is common during pregnancy and tends to increase in late pregnancy. It can have a variety of causes, including:

- pressure on your ligaments
- sciatica
- changes in your posture
- a heavier uterus

Diarrhea

Diarrhea and other digestive difficulties occur frequently during pregnancy. Hormone changes, a different diet, and added stress are all possible explanations. If diarrhea lasts more than a few days, contact your doctor to

make sure you don't become dehydrated.

Pregnancy week by week

Pregnancy weeks are grouped into three trimesters, each one with medical milestones for both you and the baby.

First trimester

A baby grows rapidly during the first trimester (weeks 1 to 12). The fetus begins developing their brain, spinal cord, and organs. The baby's heart will also begin to beat.

During the first trimester, the probability of a miscarriage is relatively high. According to the American College of Obstetricians and Gynecologists (ACOG), it's estimated that about 1 in 10 pregnancies end in miscarriage, and that about 85 percent of these occur in the first trimester.

Seek immediate help if you experience the symptoms of miscarriage.

Second trimester

During the second trimester of pregnancy (weeks 13 to 27), your healthcare provider will likely perform an anatomy scan ultrasound.

This test checks the fetus's body for any developmental abnormalities. The test results can also reveal the sex of your baby, if you wish to find out before the baby is born.

You'll probably begin to feel your baby move, kick, and punch inside of your uterus.

After 23 weeks, a baby *in utero* is considered "viable." This means that it could survive living outside of your womb. Babies born this early often have serious medical issues. Your baby has a much better chance of being born healthy the longer you are able to carry the pregnancy.

Third trimester

During the third trimester (weeks 28 to 40), your weight gain will accelerate, and you may feel more tired.

Your baby can now sense light as well as open and close their eyes. Their bones are also formed.

As labor approaches, you may feel pelvic discomfort, and your feet may swell. Contractions that don't lead to labor, known as Braxton-Hicks contractions, may start to occur in the weeks before you deliver.

The bottom line

Every pregnancy is different, but developments will most likely occur within this general time frame. Find out more about the changes you and your baby will undergo throughout the trimesters and sign up for our I'm Expecting newsletter to receive week-by-week pregnancy guidance.

Pregnancy tests

Home pregnancy tests are very accurate after the first day of your missed period. If you get a positive result on a home pregnancy test, you should schedule an appointment with your doctor right away. An ultrasound will be used to confirm and date your pregnancy.

Pregnancy is diagnosed by measuring the body's levels of human chorionic gonadotropin (hCG). Also referred to as the pregnancy hormone, hCG is produced upon implantation. However, it may not be detected until after you miss a period.

After you miss a period, hCG levels increase rapidly. hCG is detected through either a urine or a blood test.

Urine tests may be provided at a doctor's office, and they're the same as the tests you can take at home.

Blood tests can be performed in a laboratory. hCG blood tests are about as accurate as home pregnancy tests. The difference is that blood tests may be ordered as soon as six days after ovulation.

The sooner you can confirm you're pregnant, the better. An early diagnosis will allow you to take better care of your baby's health. Get more information on pregnancy tests, such as tips for avoiding a "false negative" result.

Pregnancy and vaginal discharge

An increase in vaginal discharge is one of the earliest signs of pregnancy. Your production of discharge may increase as early as one to two weeks after conception, before you've even missed a period.

As your pregnancy progresses, you'll continue to produce increasing amounts of discharge. The discharge will also tend to become thicker and occur more frequently. It's usually heaviest at the end of your pregnancy.

During the final weeks of your pregnancy, your discharge may contain streaks of thick mucus and blood. This is called "the bloody show." It can be an early sign of labor. You should let your doctor know if you have any bleeding.

Normal vaginal discharge, or leukorrhea, is thin and either clear or milky white. It's also mild- smelling.

If your discharge is yellow, green, or gray with a strong, unpleasant odor, it's considered abnormal. Abnormal discharge can be a sign of an infection or a problem with your pregnancy, especially if there's redness, itching, or vulvar swelling.

If you think you have abnormal vaginal discharge, let your healthcare provider know immediately. Learn more about vaginal discharge during pregnancy.

Pregnancy and urinary tract infections (UTIs)

Urinary tract infections (UTIs) are one of the most common complications women experience during pregnancy. Bacteria can get inside a woman's urethra, or urinary tract, and can move up into the bladder. The fetus puts added pressure on the bladder, which can cause the bacteria to be trapped, causing an infection.

Symptoms of a UTI usually include pain and burning or frequent urination. You may also experience:

- cloudy or blood-tinged urine
- pelvic pain
- lower back pain
- fever
- nausea and vomiting

Nearly 18 percent of pregnant women develop a UTI. You can help prevent these infections by emptying your bladder frequently, especially before and after sex. Drink plenty of water to stay hydrated. Avoid using douches and harsh soaps in the genital area.

Contact your healthcare provider if you have symptoms of a UTI. Infections during pregnancy can be dangerous because they increase the risk of premature labor.

When caught early, most UTIs can be treated with antibiotics that are effective against bacteria but still safe for use during pregnancy. Follow the advice here to prevent UTIs before they even start.

Pregnancy prevention

Women who have male sexual partners should consider birth control if they're not interested in becoming pregnant.

Some methods of pregnancy prevention work better for certain individuals. Talk to your doctor about birth control that's right for you. A few of the most common birth cont rol methods are discussed below:

Birth control method	Effectiveness rate
Intrauterine devices (IUDs)	Over 99 percent
The pill	99 percent with perfect use; around 91 percent with typical use
Male condom	98 percent with perfect use; around 82 percent Trusted Source Trusted Source with typical use
Female condom (or internal condom)	95 percent effective with perfect use; around 79 percent with typical use
Morning-after pill	Up to 95 percent (taken within one day of sexual contact); 75 to 89 percent (taken within three days)
Natural family planning (NFP)	75 percent when used on its own

Intrauterine devices (IUDs)

Intrauterine devices (IUDs) work by mostly by stopping fertilization. They're currently the most effective form of birth control. The downside is that they don't prevent sexually transmitted diseases (STDs).

The pill and other hormonal birth control methods

Birth control pills, patches and the vaginal ring work by controlling the hormone levels in a woman's body. They're available by prescription.

Actions that can reduce the effectiveness of these methods include forgetting to use them as prescribed. Effectiveness rates that mention "typical use" account for these types of human errors.

Other forms of hormonal birth control include the patch and the vaginal ring. They're also available by prescription, and their effectiveness rates are similar to those of the pill.

Condoms and other barrier methods

Condoms, diaphragms, and sponges are convenient and inexpensive forms of birth control that can be bought without a prescription.

They're most effective when used correctly every time you have sexual intercourse. If you're relying on these barrier methods to avoid getting pregnant, also consider using an additional method of contraception such as spermicide or a birth control pill.

Other barrier methods include diaphragms and sponges. They can be bought without a prescription.

Emergency contraception

Several morning-after pills are available, both over the counter and by prescription. These pills aren't intended as regular forms of birth control. Instead, they can act as a backup if you have unprotected sex or forget to use your regular form of birth control.

They must be used within 120 hours (five days) of sexual contact to be effective. Some pills are most effective when taken within 72 hours (three days).

Natural family planning (NFP)

Natural family planning (NFP), or fertility awareness, is the birth control method with the highest failure rate. With NFP, a woman tracks her menstrual cycle so that she can predict when she'll ovulate. She'll then avoid intercourse during her fertile window.

Accidental pregnancies can occur because there are many variables affecting a woman's cycle from month to month.

The bottom line

Condoms are the only birth control method that both prevent pregnancy and protect against STDs. Discover the safest condoms on the market here.

Lactation

What is Lactation?

"Lactation is the process of milk secretion from the mammary glands of a female after childbirth."

Lactation is the process of milk secretion from the mammary glands of a mother soon after childbirth. The milk, thus produced provides nutrition and immunity to the young one. Galactopoiesis is the stage that maintains milk production and requires prolactin and oxytocin.

Preparation for Lactation

The female is ready to produce milk during the fifth or sixth month of pregnancy. During the later stages of pregnancy, the female enters the first stage of lactogenesis. At this stage, the breasts make colostrum, a thick, yellow fluid, also known as the first milk a baby receives.

Colostrum is highly rich in immunoglobulin A that boosts the immunity of the newborn. It prevents any pathogens from invading the baby's body and also prevents food allergies.

Lactation Process

1. Due to the impact of ovarian hormones and placental hormones, breast growth begins during the period of pregnancy and it continues to get larger in size after the childbirth.
2. During this period, a certain amount of milk is produced in the breast.
3. The milk secretion increases only after the baby's birth.
4. During the process of lactation, the milk is secreted from the mammary glands.

Lactation Hormones

- Usually hormones like estrogen, placental lactogenic, progesterone, prolactin and oxytocin are involved in the process of lactation.
- Estrogen hormone helps in increasing the size of the breast during pregnancy causing the growth of breast tissue.
- The presence of a placental lactogenic hormone is higher during pregnancy as this hormone helps in stimulating the growth of the nipple, areola and breast tissue.
- Progesterone hormone helps in increasing the size of the breast tissue along with boosting milk production. During the post-pregnancy period, the progesterone hormone level tends to decrease, which stimulates milk production.
- Prolactin hormone helps in differentiating the cells that perform their own specific functions. The alveoli, which is responsible for producing milk after the baby's birth is active mainly because of the prolactin hormone. The prolactin hormone is produced once exposed to cortisol hormone.
- Once the nipples are stimulated, the oxytocin hormone is released, causing the alveoli to contract. These help in squeezing the milk out into the duct system. The entire process is called as a letdown. The letdown process begins only when the nerves of breasts are stimulated.

Can Lactation Happen without Pregnancy?

There are three hormones, which play an important role in stimulating the milk production in mammary glands of a lactating mother. Consuming medicines of these three hormones in the form of supplements would help women to produce breast milk in their mammary glands without pregnancy.

There are certain other natural tendencies were lactation happens without pregnancy. These include:

1. Imbalance of hormone.
2. Side effects from drugs/medicines.
3. Health disorders.
4. Nerve irritation in the breast region.
5. Overproduction of prolactin hormone in the brain.

Properties of milk

1. The milk produced in an initial stage of lactation varies from the milk after maturation viz. produced when lactation is well established.
2. The early milk produced in the initial stage of lactation is known as colostrum.
3. The composition of milk changes gradually after childbirth. The colostrum changes to transitional milk within four-five days from the childbirth.
4. After 14 to 15 days of childbirth, matured milk is produced in mammary glands.

The termination of lactation slowly stops with the reduced demand from the baby.

Comparison between the Elements of Colostrum, Transitional and Mature Milk with Cow's Milk (average value per 100 ml whole milk)

	Colostrum (1-5days)	**Transitional (6-14 days)**	**Mature (after14days)**	**Cow's milk**
Energy (kcal)	58.00	74.00	71.00	69.00
Total solids (g)	12.80	13.60	12.40	12.70
Fat (g)	2.90	3.60	3.80	3.70
Lactose (g)	5.30	6.60	7.00	4.80
Protein (g)	2.70	1.60	1.20	3.30
Casein (g)	1.20	0.70	0.40	2.80
Ash (g)	0.33	0.24	0.21	0.72

Minerals

Calcium (mg)	31.00	34.00	33.00	125
Magnesium (mg)	4.00	4.00	4.00	12
Potassium (mg)	74.00	64.00	55.00	138
Sodium (mg)	48.00	29.00	15.00	58
Iron (mg)	0.09	0.04	0.15	

2.3 Geriatrics

Geriatrics: The branch of medicine concerned with the diagnosis, treatment and **prevention** of disease in older people and the problems specific to **aging**.

Geriatrics, or **geriatric medicine**,is a specialty that focuses on health care of elderly people. It aims to promote health by preventing and treating diseases and disabilities in older adults.There is no set age at which patients may be under the care of a **geriatrician**, or **geriatric physician**, a physician who specializes in the care of elderly people. Rather, this decision is determined by the individual patient's needs, and the availability of a specialist. It is important to note the difference between geriatrics, the care of aged people, and gerontology, which is the study of the aging process itself. The term *geriatrics* comes from the Greek γέρων *geron* meaning "old man", and ιατρός *iatros* meaning "healer". However, geriatrics is sometimes called **medical gerontology**.

3. Cioms

3.1 CIOMS Working Groups

The report from the Working Group was published in collaboration with WHO in 2010. The report covers the activities and outputs of the CIOMS/WHO Working Group on Vaccine Pharmacovigilance (2005-2010)

The Working Group was established in November 2005 at the request of WHO to:

1. Develop general definitions strictly focused on Vaccine Pharmacovigilance
2. Contribute to the development review evaluation and approval of definitions on adverse events following immunisation as developed by the Brighton Collaboration (BC) process and to their dissemination:

   – In endorsing already existing definitions

   – In participating in the review of definitions under development

   – In proposing priorities for the development of new definitions

– Facilitating the translation and dissemination of the definitions

3. Collaborate with other CIOMS working groups especially that on Standardised MedDRA Queries (SMQs) and CIOMS VIII on Application of Signal Detection in Pharmacovigilance.

The Working Group was composed of members from the pharmaceutical industry, regulatory agencies, governmental institutions, and academia both from industrialised and developing countries as well as from international organizations. The aim of the group was to complete a final document including all general definitions as well as the Introduction and Definition sections of all endorsed Brighton Collaboration definitions by the end of 2010.

Outcomes

Published case definitions reviewed and endorsed by the WG:

Six case definitions were published in English, Spanish and French on the Brighton Collaboration website:

– Fever

– Hypotonic-Hyporesponsive Episode (HHE)

– Intussusception

– Nodule at injection site

– Persistent crying

– Seizure

New case definitions reviewed and endorsed by the WG:

– Abcess

– Anaphylaxis

– Aseptic meningitis

– Cellulitis

– Diarrhoea

– Encephalitis, myelitis, and acute disseminated encephalomyelitis (ADEM)

– Fatigue

– Fever

– Guillain-Barré Syndrome (GBS)

– Hypotonic Hyporesponsive Episode (HHE)

– Induration

– Intussuception

– Nodule

– Overall local reaction

– Rash

– Smallpox adverse events definitions

– Swelling

– Thrombocytopenia

– Unexplained sudden infant death (USID)

Comparability of SMQs and Brighton Collaboration (BC) case definitions:

The MedDRA Maintenance and Support Services Organization (MSSO) performed a mapping between concepts in the published Brighton Collaboration vaccine adverse event definitions and terms in MedDRA Version 11.1 (September 2008). The following BC definitions were mapped:

– Abscess at injection site

– Anaphylaxis

– Aseptic meningitis

– Cellulitis at injection site

– Diarrhoea

– Eczema vaccinatum

– Encephalitis, myelitis, and acute disseminated encephalomyelitis (ADEM)

– Fatigue

– Fever

– Generalized vaccinia

– Hypotonic-hyporesponsive episode

– Inadvertent inoculation

– Induration at or near injection site

– Intussusception (acute)

– Nodule at injection site

– Persistent crying

– Progressive vaccinia

– Rash (including mucosal involvement)

– Robust take

– Seizure (generalized convulsive)

– Sudden infant death syndrome

– Swelling at or near injection site

– Thrombocytopenia

During the mapping process, concepts in the case definitions that are not already part of MedDRA were identified. These findings made the WG decide to make a recommendation to the Brighton Secretariat that Brighton working groups consider MedDRA terms when developing new definitions.

CIOMS VIII Signal Detection Working Group

Comments regarding various Signal definitions were sent to CIOMS WG VIII. A vaccine- specific point-to-consider document as an annex to Signal definition in collaboration with CIOMS WG VIII was finalized.

WHO-UMC Working Group on vaccine identifiability

The WG recommended that a drug dictionary for vaccines is needed and supports the Uppsala Monitoring Centre (UMC; WHO Collaborating Center for International Drug Monitoring) in their efforts in this respect.

CIOMS-I FORM

SUSPECT ADVERSE REACTION REPORT	

I. REACTION INFORMATION

1. PATIENT INITIALS (first,last)	1a. COUNTRY	2. DATE OF BIRTH			2a. AGE	3. SEX	4-6. REACTION ONSET			9-12. CHECK ALL APPROPRIATE TO ADVERSE REACTION
		Day	Month	Year			Day	Month	Year	☐ PATIENT DIED
7 + 12 DESCRIBE REACTION(S) (including relevant tests/lab data)										☐ INVOLVED OR PROLONGED INPATIENT HOSPITALIZATION
										☐ INVOLVED PERSISTENCE OR SIGNIFICANT DISABILITY OR INCAPACITY
Narrative- *										☐ LIFE THREATENING

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG 1 or 1 (include generic name)		20. DID REACTION ABATE AFTER STOPPING DRUG? ☐ YES ☐ NO ☐ NA
15. DAILY DOSE(S)	16. ROUTE(S) OF ADMINISTRATION	21. DID REACTION REAPPEAR AFTER REINTRODUCTION? ☐ YES ☐ NO ☐ NA
17. INDICATION(S) FOR USE		
18. THERAPY DATES (from/to)	19. THERAPY DURATION	

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUG(S) AND DATES OF ADMINISTRATION (exclude those used to treat reaction)
23. OTHER RELEVANT HISTORY (e.g. diagnostics, allergies, pregnancy with last month of period, etc.)

IV. MANUFACTURER INFORMATION

24a. NAME AND ADDRESS OF MANUFACTURER		Spontaneous report
	24b. MFR CONTROL NO.	
24c. DATE RECEIVED BY MANUFACTURER	24d. BY MANUFACTURER STUDY LITERATURE HEALTH PROFESSIONAL	
DATE OF THIS REPORT	25a. REPORT TYPE INITIAL ☐ FOLLOW-UP ☐	

NI - No information available at this time. UNK - Information unknown

DRAFT

* Item completed on continuation page(s)

3.2 CIOMS Form

For most of the fields in CIOMS I there are corresponding data elements in ICH E2B. However, ICH E2B is a flexible electronic format with several data elements (both as structured information and in free text) intended for data transfer between different databases. CIOMS I is a pure reporting form with limited amount of fields (less structured and mostly in free text). This implies some challenges in the mapping of data between CIOMS I and ICH E2B and therefore the table with suggestions in this document should only work as an overview and a guideline.

4. CDSCO (India) and Pharmacovigilance

4.1.1 Drug and Cosmetic Act, 1940

Objectives

1. To regulate the import, manufacture, distribution and sale of drugs & cosmetics through licensing.
2. Manufacture, distribution and sale of drugs and cosmetics by qualified persons only.
3. To prevent substandard in drugs, presumably for maintaining high standards of medical treatment.
4. To regulate the manufacture and sale of Ayurvedic, Siddha and Unani drugs.
5. To establish Drugs Technical Advisory Board (DTAB) and Drugs Consultative Committees (DCC) for Allopathic and allied drugs and cosmetics.

Drug

All medicines for internal or external use of human beings or animals and all substances intended to be used for or in the diagnosis, treatment, mitigation or prevention of any disease or disorder in human beings or animals, including preparations applied on human body for the purpose of repelling insects like mosquitoes.

'Cosmetic'

As defined in the Act Cosmetic includes any article intended to be rubbed, poured, sprinkled or sprayed on, or introduced into, or otherwise applied to, the human body or any part thereof for cleansing, beautifying, promoting attractiveness, or altering the appearance, and includes any article intended for use as a component of cosmetic.

Administrative Structure

A) Advisory :

1) Drugs Technical Advisory Board-DTAB

2) Drugs Consultative Committee-D.C.C. B)

B) Analytical :

1) Central Drugs Laboratory - CDL

2) Drug Control Laboratory in states

3) Government Analysts

C) Executives :

1) Licensing authorities

2) Controlling authorities

3) Drug Inspectors

4.1.2. Schedule Y

Schedule Y defines **the clinical trials** as the requirements and guidelines for import and manufacture of new drugs for sale or for clinical trials. It describes the details of application process for conducting clinical trials; responsibilities of the sponsor, investigators and the Independent Ethics Committee.

4.2 Differe3nce in Indian and Global Pharmacovigilance Requirements

Pharmacovigilance Is Carried Out In India

Pharmacovigilance in India was **initiated way back in 1986 with a formal adverse drug reaction (ADR) monitoring system**, under supervision of the drug controller of India. India joined the World Health Organization (WHO) Programme for International Drug Monitoring in 1998, but was not successful.

Global Pharmacovigilance

Pharmacovigilance refers to **the monitoring, reviewing, evaluating and communicating of information on the safety of pharmaceutical products**. Global Patient Safety takes a comprehensive and rigorous approach to pharmacovigilance activities.

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