# 1. Introduction to Pharmacovigilance

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

## 1.1 Glossary of Terminologies

### 1.1.1 Absolute risk

Risk in a population of exposed persons; the probability of an event affecting members of a particular population (e.g. 1 in 1,000). Absolute risk can be measured over time (*incidence*) or at a given time (prevalence).

### 1.1.2 Adverse Event (AE)

Any untoward medical occurrence that may present during treatment with a pharmaceutical product but which does not necessarily have a causal relationship with this treatment.

### 1.1.3 Adverse (Drug) Reaction (ADR)

A response which is noxious and unintended, and which occurs at doses normally used in humans for the prophylaxis, diagnosis, or therapy of disease, or for the modification of physiological function. (WHO, 1972).

**"A response to a medicinal product which is noxious and unintended."**

### 1.1.4 Allopathy

Non-traditional, western scientific therapy, usually using synthesised ingredients, but may also contain a purified active ingredient extracted from a plant or other natural source, usually in opposition to the disease.

### 1.1.5 Association

Events associated in time but not necessarily linked as cause and effect.

### 1.1.6 Attributable risk

Difference between the risk in an exposed population (*absolute risk*) and the risk in an unexposed population (*reference risk*). Attributable risk is the result of an absolute comparison between outcome frequency measurements, such as incidence.

### 1.1.7 Biological products

Medical products prepared from biological material of human, animal or microbiologic

origin (such as blood products, vaccines, insulin).

### 1.1.8 Causal relationship

A relationship between one phenomenon or event (A) and another (B) in which A precedes and causes B. In pharmacovigilance; a medicine causing an adverse reaction.

### 1.1.9 Causality assessment

The evaluation of the likelihood that a medicine was the causative agent of an observed adverse reaction. Causality assessment is usually made according established algorithms.

### 1.1.10 Caveat document

The formal advisory warning accompanying data release from the WHO Global ICSR Database: it specifies the conditions and reservations applying to interpretations and use of the data.

### 1.1.11 Cem-Flow

Software developed by UMC for collection and analysis of data in Cohort Event Monitoring.

### 1.1.12 Clinical trial

A systematic study on pharmaceutical products in human subjects (including patients and other volunteers) in order to discover or verify the effects of and/or identify any adverse reaction to investigational products, and/or to study the absorption, distribution, metabolism and excretion (ADME) of the products with the objective of ascertaining their efficacy and safety.

### 1.1.13 Cohort Event Monitoring

Cohort Event Monitoring (CEM) is a prospective, observational study of events that occur during the use of medicines, for intensified follow-up of selected medicinal products phase. Patients are monitored from the time they begin treatment, and for a defined period of time.

### 1.1.14 Compliance

Faithful adherence by the patient to the prescriberôs instructions.

### 1.1.15 Control group

The comparison group in drug-trials not being given the studied drug.

### 1.1.16 Critical terms

Some of the terms in WHO-ART are marked as óCritical Termsô. These terms either refer to or might be indicative of serious disease states, and warrant special attention, because of their possible association with the risk of serious illness which may lead to more decisive action than reports on other terms.

### 1.1.17 Data mining

A general term for computerised extraction of potentially interesting patterns from large data sets often based on statistical algorithms. A related term with essentially the same meaning is ópattern discoveryô. In pharmacovigilance, the commonest application of data mining is so called disproportionality analysis, for example using the Information component (IC).

### 1.1.18 De-challenge

The withdrawal of a drug from a patient; the point at which the continuity, reduction or disappearance of adverse effects may be observed.

### 1.1.19 Disproportionality analysis

Screening of ICSR databases for reporting rates which are higher than expected. For drug-ADR pairs, common measures of disproportionality are the Proportional Reporting Ratio (PRR), the Reporting Odds Ratio (ROR), The Information Component (IC), and the Empirical Bayes Geometrical Mean (EBGM). There are also disproportionality measures for drug-drug-ADR triplets, such as Omega (Ý).

### 1.1.20 Effectiveness/risk

The balance between the rates of effectiveness of a medicine versus the risk of harm is a quantitative assessment of the merit of a medicine used in routine clinical practice. Comparative information between therapies is most useful. This is more useful than the efficacy and hazard predictions from pre-marketing information that is limited and based on selected subjects.

### 1.1.21 Efficacy

The ability of a drug to produce the intended effect as determined by scientific methods, for example in pre-clinical research conditions (opposite of hazard).

### 1.1.22 Epidemiology

The science concerned with the study of the factors determining and influencing the frequency and distribution of disease, injury and other health-related events and their causes in a defined human population for the purpose of establishing programs to prevent and control their development and spread.

### 1.1.23 Essential medicines

Essential medicines are those that satisfy the priority health care needs of the population. They are selected with due regard to public health relevance, evidence on efficacy and safety, and comparative cost-effectiveness.

### 1.1.24 Excipients

All materials included to make a pharmaceutical formulation (e.g. a tablet) except the active drug substance(s).

### 1.1.25 Formulary

A listing of medicinal drugs with their uses, methods of administration, available dose, dosage forms, side effects, etc, sometimes including their formulas and methods of preparation.

### 1.1.26 Frequency of ADRs

In giving an estimate of the frequency of ADRs the following standard categories are recommended:

| | |
|---|---|
| Very common* | > 10% |
| Common (frequent) | >1% and <10% |
| Uncommon (infrequent) | >0.1% and < 1% |
| Rare | >0.01% and <0.1% |
| Very rare* | <0.01% |

* *Optional categories*

### 1.1.27 Generic (multisource product)

The term ógeneric productô has somewhat different meanings in different jurisdictions. Generic products may be marketed either under the non-proprietary approved name or under a new brand (proprietary) name. They are usually intended to be interchangeable with the innovator product, which is usually manufactured without a license from the innovator

company and marketed after the expiry of patent or other exclusivity rights.

### 1.1.28 Harm

The nature and extent of actual damage that could be caused by a drug. Not to be confused with risk.

### 1.1.29 Herbal medicine

Includes herbs, herbal materials, herbal preparations and finished herbal products.

### 1.1.30 Homeopathy

Homeopathy is a therapeutic system which works on the principle that ólike treats likeô. An illness is treated with a medicine which could produce similar symptoms in a healthy person. The active ingredients are given in highly diluted form to avoid toxicity. Homeopathic remedies are virtually 100% safe.

### 1.1.31 Information component (IC)

The Information component (IC) measures the disproportionality in the reporting of a drug-ADR pair in an ICSR database, relative to the reporting expected based on the overall reporting of the drug and the ADR. Positive IC values indicate higher reporting than expected. The IC has also been implemented on electronic health records, to detect interesting temporal relationships between drug prescriptions and medical events.

### 1.1.32 Incidence

Number of new cases of an outcome which develop over a defined time period in a defined population at risk.

### 1.1.33 Individual Case Safety Report (ICSR)

A report that contains óinformation describing a suspected adverse drug reaction related to the administration of one or more medicinal products to an individual patientô.

### 1.1.34 MedDRA

MedDRA is the Medical Dictionary for Regulatory Activities. WHO-ART, the WHO Adverse Reactions Terminology, is now mapped to MedDRA.

### 1.1.35 Medical error

ñAn unintended act (either of omission or commission) or one that does not achieve its intended outcomes.ò

### 1.1.36 Member countries

Countries which comply with the criteria for, and have joined the WHO Programme for International Drug Monitoring.

### 1.1.37 National Pharmacovigilance centres

Organisations recognised by governments to represent their country in the WHO Programme (usually the drug regulatory agency). A single, governmentally recognized centre (or integrated system) within a country with the clinical and scientific expertise to collect, collate, analyse and give advice on all information related to drug safety.

### 1.1.38 Odds

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

### 1.1.39 Odds ratio

Ratio of the *Odds* in a given population and the *Odds* in another population.

### 1.1.40 Omega (Ω)

A measure of disproportionate reporting for drug-drug-ADR triplets in ICSR databases, designed to highlight potential signals of drug- drug interactions. Just like the more established disproportionality measures for drug-ADR pairs, Ý is based on a contrast between the observed and expected number of reports. A positive Ý indicates higher reporting than expected.

### 1.1.41 OTC (Over the Counter) medicine

Medicinal product available to the public without prescription.

### 1.1.42 Pani-Flow

Software developed by UMC for collection and analysis of data in relation to vaccinations in a pandemic situation.

### 1.1.43 Periodic Safety Update Report (PSUR)

A systematic review of the global safety data which became available to the manufacturer of a marketed drug during a specific time period. Produced in an internationally agreed format.

### 1.1.44 Pharmacoepidemiology

Study of the use and effects of drugs in large populations.

### 1.1.45 Pharmacology

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

### 1.1.46 Pharmacovigilance

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

### 1.1.47 Phocomelia

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

### 1.1.48 Phytotherapy

Western-style, scientific treatment using plant extracts or materials.

### 1.1.49 Placebo

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

### 1.1.50 Polypharmacy

The concomitant use of more than one drug, sometimes prescribed by different practitioners.

### 1.1.51 Post-marketing

The stage when a drug is generally available on the market.

### 1.1.52 Predisposing factors

Any aspect of the patientôs history (other than the drug) which might explain reported adverse events (genetic factors, diet, alcohol consumption, disease history, polypharmacy or use of herbal medicines, for example).

### 1.1.53 Pre-marketing

The stage before a drug is available for prescription or sale to the public.

### 1.1.54 Prescription Event Monitoring (PEM)

System created to monitor adverse drug events in a population. Prescribers are requested to report all events, regardless of whether they are suspected adverse events, for identified patients receiving a specified drug. Also more accurately named *Cohort Event Monitoring*.

### 1.1.55 Prescription Only Medicine (POM)

Medicinal product available to the public only on prescription.

### 1.1.56 Prevalence

Number of existing cases of an outcome in a defined population at a given point in time.

### 1.1.57 Prophylaxis

Prevention or protection.

### 1.1.58 Rational drug use

An ideal of therapeutic practice in which drugs are prescribed and used in exact accordance with the best understanding of their appropriateness for the indication and the particular patient, and of their benefit, harm effectiveness and risk.

### 1.1.59 Re-challenge

The point at which a drug is again given to a patient after its previous withdrawal - also see *de-challenge*.

### 1.1.60 Record linkage

Method of assembling information contained in two or more records, e.g. In different sets of medical charts, and in vital records such as birth and death certificates. This makes it possible to relate significant health events that are remote from one another in time and place.

### 1.1.61 Reference risk

Risk in a population of unexposed persons; also called baseline risk. Reference risk can be measured over time (*incidence*) or at a given time (*prevalence*). The unexposed population refers to a reference population, as closely comparable to the exposed population as possible, apart from the exposure.

### 1.1.62 Regulatory authority

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

### 1.1.63 Relative risk

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

### 1.1.64 Risk

The probability of harm being caused; the probability (chance, odds) of an occurrence.

### 1.1.65 Serious Adverse Event or Reaction

A serious adverse event or reaction is any untoward medical occurrence that at any dose:

- results in death
- requires inpatient hospitalisation or prolongation of existing hospitalisation
- results in persistent or significant disability/incapacity
- is life-threatening

### 1.1.66 Side effect

Any unintended effect of a pharmaceutical product occurring at normal dosage which is related to the pharmacological properties of the drug.

### 1.1.67 Signal

Reported information on a possible causal relationship between an adverse event and a drug, the relationship being unknown or incompletely documented previously. Usually more than a single report is required to generate a signal, depending upon the seriousness of the event and the quality of the information. The publication of a signal usually implies the need for some kind of review or action.

### 1.1.68 Summary of Product Characteristics (SPC)

A regulatory document attached to the marketing authorization which forms the basis of the product information made available to prescribers and patients.

### 1.1.69 Spontaneous reporting

System whereby case reports of adverse drug events are voluntarily submitted from health professionals and pharmaceutical manufacturers to the national regulatory authority.

### 1.1.70 Thalidomide

Drug prescribed in the 1950s as a mild sleeping pill and remedy for morning-sickness for pregnant women. Led to serious birth defects and the start of modern pharmacovigilance. Returning to favour in treatment of serious diseases such as cancer and leprosy.

### 1.1.71 Traditional medicines

Traditional medicine is 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.

### 1.1.72 Unexpected adverse reaction

An adverse reaction, the nature or severity of which is not consistent with domestic labelling or market authorization, or expected from characteristics of the drug.

### 1.1.73 Vigi-Base

The name of the WHO Global ICSR Database.

### 1.1.74 Vigi-Flow

Vigi-Flow is a complete ICSR management system created and maintained by the UMC. It is web-based and built to adhere to the ICH-E2B standard. It can be used as the national database for countries in the WHO Programme as it incorporates tools for report analysis, and facilitates sending reports to Vigi-Base.

### 1.1.75 Vigi-med

Share point based conferencing facility, exclusive to member countries of the WHO Programme for International Drug Monitoring for fast communication of topical pharmacovigilance issues.

### 1.1.76 Vigi-Mine

A statistical tool within Vigi-Search with vast statistical material calculated for all Drug-ADR pairs (combinations) available in Vigi-Base. The main features include the disproportionality measure (IC value) stratified in different ways and useful filter capabilities.

### 1.1.77 Vigi-Search

A search service for accessing ICSRs stored in the Vigi-Base database offered by the UMC to national pharmacovigilance centres and other third-party inquirers.

### 1.1.78 WHO-ART

Terminology for coding clinical information in relation to drug therapy. WHO-ART is maintained by UMC.

### 1.1.79 WHO Drug Dictionary (WHO DD)

The WHO Drug Dictionary is an international classification of drugs providing proprietary and non-proprietary names of medicinal products used in different countries, together with all active ingredients.

## 1.2 Why Pharmacovigilance in India?

The information collected during the pre-marketing phase of a medical drug is inevitably incomplete with regard to possible adverse reactions:

1. Tests in animals are insufficiently predictive of human safety
2. Patients in clinical trials are selected and limited in number, the conditions of use differ from those in clinical practice and the duration of trials is limited
3. Information about rare but serious adverse reactions, chronic toxicity, and use in special groups (such as children, the elderly or pregnant women) or drug interactions is often incomplete or not available.

## 1.3 What are the major aims of Pharmacovigilance?

Pharmacovigilance is concerned with the detection, assessment and prevention of adverse reactions to drugs. Major aims of pharmacovigilance are:

1. Early detection of hither to unknown adverse reactions and interactions
2. Detection of increases in frequency of (known) adverse reactions
3. Identification of risk factors and possible mechanisms underlying adverse reactions
4. Estimation of quantitative aspects of benefit/risk analysis and dissemination of information needed to improve drug prescribing and regulation.

## 1.4 Terms commonly used in Pharmacovigilance

**Benefits** are commonly expressed as the proven therapeutic good of a product, but should also include the patientôs subjective assessment of its effects.

**Risk** is the probability of harm being caused, usually expressed as a percent or ratio of the treated population; the probability of an occurrence.

**Harm** is the nature & extent of actual damage that could be caused. It should not be confused with risk.

**Effectiveness** is used to express the extent to which a drug works under real world circumstances, i.e., clinical practice (not clinical trials).

**Efficacy** is used to express the extent to which a drug works under ideal circumstances (i.e., in clinical trials).

# 2. Concepts and Definitions

## 2.1 Pharmacovigilance

Pharmacovigilance is the pharmacological science relating to the detection, assessment, understanding and prevention of adverse effects, particularly long term and short term side effects of medicines. Pharmacovigilance is the science of collecting, monitoring, researching, assessing and evaluating information from healthcare providers and patients on the adverse effects of medications, biologicals, herbalism and traditional medicines with a view to:

- Identifying new information about hazards associated with medicines
- Preventing harm to the patients.

Pharmacovigilance starts from the clinical stage and continues throughout the product life cycle of the drug, mainly divided as Pharmacovigilance during pre-marketing (that is clinical phase) and post-marketing. The process of collection of such information about a drug begins in phase I of the clinical trial, before approval of the drug, and continues even after approval; several post-market safety studies are conducted, with many made mandatory by drug regulatory agencies around the world.

The Pharmacovigilance effort in the India is coordinated by The Indian Pharmacopoeia Commission and conducted by the Central Drugs Standard Control Organization (CDSCO).

## 2.2 Risk Benefit

The comparative evaluation or weighing of benefits (positive effects) and risks (potential harm) of various medical options for treatment, prophylaxis, prevention or diagnosis is essential. It is done during research and development on new medical products or procedures (such as surgery), or by a regulatory authority deliberating the approval or withdrawal of a product or some intermediate action, by a physician on behalf of a patient, or by the patient. Such weighing, whether implicit or explicit, is at the heart of decision-making in medicine and health care.

This apparently straightforward concept is expressed through such terms as benefit to risk ratio, benefit-risk difference, benefit vs. risk, therapeutic margin, therapeutic index and others.

The term ôbenefit-risk ratioô is often used as a general term linked to the use of a medicine. To balance risk and benefit is, however, a very complex exercise. Usually the risks of a medicine are of a totally different nature and frequency compared with its

benefits. For most medicines the benefits are limited to a few indications and for an individual patient there is usually only a single benefit sought but the potential risks are multiple. Perceptions of risks versus benefits are influenced to a great extent by the context in which they occur. Thus, perception of risk may be different to actual risk. In the end in any given situation, the acceptable risk-to-benefit balance is. An individual judgement on the part of the patient or the prescriber,

For newer medicines, where there is likely to be limited experience, conservative estimates of the overall merit seem preferable so that the prescriber will use the drug critically. Subsequently, re-evaluation of the risk-to-benefit balance is necessary as greater knowledge of efficacy and adverse effects is acquired.

### 2.3 Adverse Event (or Adverse Experience)

An adverse event (AE) is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An adverse event (AE) can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.

AEs in patients participating in clinical trials must be reported to the study sponsor and if required could be reported to local ethics committee. Adverse events categorized as "serious" ( results in death, illness requiring hospitalization, events deemed life-threatening, results in persistent or significant disability/incapacity, a congenital anomaly/birth defect or medical important condition ) must be reported to the regulatory authorities immediately, whereas non-serious adverse events are merely documented in the annual summary sent to the regulatory authority.

The sponsor collects AE reports from the local researchers, and notifies all participating sites of the AEs at the other sites, as well as both the local investigators' and the sponsors' judgment of the seriousness of the AEs. This process allows the sponsor and all the local investigators access to a set of data that might suggest potential problems with the study treatment while the study is still ongoing.

## 2.4 Adverse Drug Reaction (ADR)

In the pre-approval clinical experience with a new medicinal product or its new usages, particularly as the therapeutic dose(s) may not be established, all noxious and unintended responses to a medicinal product related to any dose should be considered adverse drug reactions. An ADR is a response to a drug which is noxious and unintended and which occurs at doses normally used in man for prophylaxis, diagnosis, or therapy of disease or for modification of physiological function.

The old term "side effect" has been used in various ways in the past, usually to describe negative (unfavourable) effects, but also positive (favourable) effects. It is recommended that this term no longer be used and particularly should not be regarded as synonymous with adverse event or adverse reaction.

## 2.5 Serious of Adverse Event or Adverse Drug Reaction

A serious adverse event (experience) or reaction is any untoward medical occurrence that at any dose:

- Results in death,
- Is life-threatening,

NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

- Requires inpatient hospitalization or prolongation of existing hospitalization,
- Results in persistent or significant disability/incapacity, or
- Is a congenital anomaly/birth defect.

Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above. These should also usually be considered serious.

Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

## 2.6 Severity Vs Seriousness

To ensure no confusion or misunderstanding exist of the difference between the terms "serious" and "severe," which are not synonymous, the following note of clarification is provided:

The term "severe" is often used to describe the intensity (severity) of a specific event (as in mild, moderate, or severe myocardial infarction); the event itself, however, may be of relatively minor medical significance (such as severe headache). This is not the same as "serious," which is based on patient/event outcome or action criteria usually associated with events that pose a threat to a patient's life or functioning. Seriousness (not severity) serves as a guide for defining regulatory reporting obligations.

**Serious Adverse Events (SAE) Vs Severe Adverse Events**

Severity is not synonymous with seriousness. SAE is based on patient/event outcome or action criteria usually associated with events that pose a threat to a patient's life or functioning. Seriousness (not severity) serves as a guide for defining regulatory reporting obligations. In other words, the SAEs need to be fulfilling additional reporting process (reported to corporate global drug safety group or Pharmacovigilance group, regulatory authorities, EC/IRBs). Severe AE is one class of AEs with severity (old term intensity) classified as 'severe'. Severe AE is one of the AE classifications ï AE severity (other classifications are relationships/causality).

## 2.7 Causality

Causality (also referred to as causation) is the relationship between an event (the *cause*) and a second event (the *effect*), where the second event is understood as a consequence of the first.

In common usage, causality is also the relationship between a set of factors (causes) and a phenomenon (the *effect*). Anything that affects an effect is a factor of that effect. A direct factor is a factor that affects an effect directly, that is, without any intervening factors. (Intervening factors are sometimes called "intermediate factors".) The connection between a cause(s) and an effect in this way can also be referred to as a *causal nexus.*

### 2.7.1 Why causality assessment?

An inherent problem in pharmacovigilance is that most case reports concern *suspected* adverse drug reactions. Adverse reactions are rarely specific for the drug, diagnostic tests are usually absent and a rechallenge is rarely ethically justified. In practice few adverse reactions are ócertainô or óunlikelyô; most are somewhere in between these extremes, i.e. óPossibleô or óProbableô. In an attempt to solve this problem many systems have been developed for a structured and harmonised assessment of causality. None of these systems, however, have been shown to produce a precise and reliable quantitative estimation of relationship likelihood. Nevertheless, causality assessment has become a common routine procedure in pharmacovigilance. The advances and limitations of causality assessment are reviewed.

***Advances and limitations of standardised case causality assessment***

| **What causality assessment can do** | **What causality assessment cannot do** |
|---|---|
| Decrease disagreement between assessors | Give accurate quantitative measurement of relationship likelihood |
| Classify relationship likelihood | Distinguish valid from invalid cases |
| Mark individual case reports | Prove the connection between drug and event |
| Improvement of scientific evaluation; educational | Quantify the contribution of a drug to the development of an adverse event |
| | Change uncertainty into certainty |

### 2.7.2 The WHO-UMC causality assessment system

The WHO-UMC system has been developed in consultation with the National Centres participating in the Programme for International Drug Monitoring and is meant as a practical tool for the assessment of case reports. It is basically a combined assessment taking into account the clinical-pharmacological aspects of the case history and the quality of the documentation of the observation.

***WHO-UMC Causality assessment scale***

| Causality term | Assessment criteria* |
|---|---|
| **Certain** | ▪ Event or laboratory test abnormality, with plausible time relationship to drug intake<br>▪ Cannot be explained by disease or other drugs<br>▪ Response to withdrawal plausible (pharmacologically, pathologically)<br>▪ Event definitive pharmacologically or phenomenologically (i.e. an objective and specific medical disorder or a recognised pharmacological phenomenon)<br>▪ Rechallenge satisfactory, if necessary |
| **Probable/ Likely** | ▪ Event or laboratory test abnormality, with reasonable time relationship to drug intake<br>▪ Unlikely to be attributed to disease or other drugs<br>▪ Response to withdrawal clinically reasonable<br>▪ Rechallenge not required |
| **Possible** | ▪ Event or laboratory test abnormality, with reasonable time relationship to drug intake<br>▪ Could also be explained by disease or other drugs<br>▪ Information on drug withdrawal may be lacking or unclear |
| **Unlikely** | ▪ Event or laboratory test abnormality, with a time to drug intake that makes a relationship improbable (but not impossible)<br>▪ Disease or other drugs provide plausible explanations |
| **Conditional/ Unclassified** | ▪ Event or laboratory test abnormality<br>▪ More data for proper assessment needed, or<br>▪ Additional data under examination |
| **Unassessable/ Unclassifiable** | ▪ Report suggesting an adverse reaction<br>▪ Cannot be judged because information is insufficient or contradictory<br>▪ Data cannot be supplemented or verified |

***All points should be reasonably complied with**

### 2.8 Expectedness

The **WHO** defines as **Expectedness of an AE/ADR** may be product or product use specific, and separate investigators brochures may be used accordingly in different Clinical trials. However, such documents should cover all information on ADRs that applies to all affected product presentations and uses. When relevant, separate discussions of pertinent product ï specific or use specific safety information in clinical trials, should also be included in the investigators brochures.

Any ADR occurring in a clinical trials that qualifies for special attention and is observed with one product dosage form or use should be cross ï referenced in the investigators brochures for all dosage forms and uses during the clinical development of an investigational medicinal product.

### 2.9 SUSAR

An unexpected adverse reaction (UAR) is an adverse reaction that is not consistent with the product information in the SPC.

A suspected unexpected serious adverse reaction (SUSAR) is any UAR that at any dose:

- **a.** Results in death;
- **b.** Is life threatening (i.e. the subject was at risk of death at the time of the event)
- **c.** Refer to an event which hypothetically might have caused death if it were more severe
- **d.** Requires hospitalisation or prolongation of existing hospitalisation;
- **e.** Results in persistent or significant disability or incapacity;
- **f.** Is a congenital anomaly or birth defect.

SUSAR is a serious adverse drug reaction (SAR) that is unexpected or for which the development is uncommon (unexpected issue) observed during a clinical trial and for which there is a relationship with the experimental drug, whatever the tested drug or its comparator.

### 2.10 Outcome of Adverse Event

Any untoward medical occurrence that may present during treatment with a pharmaceutical product but which does not necessarily have a causal relationship with this treatment and the outcome of Adverse Event described the conditions as follows:

**Fatal-** fatal describes conditions, circumstances, or events that have caused or are destined to cause death or dire consequences: *a fatal illness.*

**Continuing**- continuing describes the condition when the treatment is going on

**Recovering-** Return to a normal state of health, mind, or strength

**Recovered-** the patient appears cured from illness or disease.

**Unknown-** Unknown describes the condition when the result is not known

### 2.11 Sources of Report

The basic principles that underlie most systems are considered ill the following sections.

#### 2.11.1 Individual reporting

Doctors are the major source of reports. Those whose practice is primarily outside hospitals tend to care for patients for prolonged periods of time and may therefore also see the occurrence of slowly developing or delayed reactions. Since most severe reactions are seen in hospitals, physicians who are hospital-based are often able to ascertain previous drug administration, link it to the reaction, and submit a report.

The physician, during an outpatient or inpatient examination, may decide that the patient has a recognizable syndrome of signs, symptoms, and/or laboratory findings and that this syndrome may be associated with a previously administered drug. He / She then report this information to the centre.

#### 2.11.2 Comprehensive monitoring

Comprehensive monitoring is typically performed in a hospital setting and the input consists of abstracts of patient identification, drug administration, and patient reactions. Specialized methods are used to ensure that this information is complete, and case reports or tabulated summary data can be supplied to the national centre.

#### 2.11.3 Population monitoring

In population monitoring the records of hospital or clinic patients, or of the entire population of a district, may be employed. Such monitoring could be effective when a large stable population is surveyed in an organized medical care system.· As rapid advances are being made in the electronic processing of patient documentation and records, there may be unusual opportunities to incorporate a drug monitoring element in these systems.

Population monitoring appears to have much to offer in that actual rates of

reactions being obtained and truly unexpected reactions may be identified. It is complex and expensive, however, and the patient population may not be large enough for the detection of rare (1 in 10 000-50 000) reactions. This system would automatically record drug use and patient syndromes or events, permitting searches for associations between the two. The results of such searches may be reported to the national centre.

### 2.11.4 Other sources

All potential sources of information should be considered. Each national centre must seize opportunities to exploit old and develop new sources of information. For example, useful information can come from poison control centres, social security records, inquest reports, and from clinical and basic pharmacology, toxicology, and pathology units.

## 2.12 Valid Report

The Individual Case Safety Report (ICSR) is a Health Level Seven standard for the capture of the information needed to support the reporting of adverse events, product problems or consumer complaints associated with the use of FDA regulated products or a report received by a company or agency which describes an adverse event.

Reports, describing serious adverse drug reactions that needed to be exchanged in pharmacovigilance between the various parties in accordance with community legislation, are referred to as ICSRs or safety reports. An ICSR has to contain the data elements as defined in the related guidance documents adopted at International level.

Any supporting information related to the Case must be sufficiently described within the ICSR with the reference to the documents that are held by the sander, which may need to provided on request, it is recognised that it is often difficult to obtain all details on specific Case, However the complete information related to an individual case, that is available to the sender, has to be reported in accordance with the legal requirements as set out in the community legislation. This may also include Causality assessment if requested by competent authorities. It is the responsibility of the sender to structure all information available in accordance with the elements as defined with in ICH E2B specifications.

In addition, whenever more recent information on an individual case to be provided and not only partial information e.g. Changes or Updates.

**The minimum information needed for a Valid Report according to ICH E2B is:-**

- **a.** One identifiable patient
- **b.** Identifiable reporter
- **c.** One reaction / event &
- **d.** One suspected Drug

### 2.13 Expedited reporting Vs Periodic reporting

It is important to harmonise the way to gather and, if necessary, to take action on important clinical safety information arising during clinical development. Thus, agreed definitions and terminology, as well as procedures, will ensure uniform Good Clinical Practice standards in this area. The initiatives already undertaken for marketed medicines through the CIOMS-1 and CIOMS-2 Working Groups on expedited (alert) reports and periodic safety update reporting, respectively, are important precedents and models.

The purpose of expedited reporting is to make regulators, investigators, and other appropriate people aware of new, important information on serious reactions. Therefore, such reporting will generally involve events previously unobserved or undocumented, and a guideline is needed on how to define an event as "unexpected" or "expected" (expected/unexpected from the perspective of previously observed, not on the basis of what might be anticipated from the pharmacological properties of a medicinal product).

An "unexpected" adverse reaction is one, the nature or severity of which is not consistent with information in the relevant source document(s). Until source documents are amended, expedited reporting is required for additional occurrences of the reaction.
The following documents or circumstances will be used to determine whether an adverse event/reaction is expected:

1. For a medicinal product not yet approved for marketing in a country, a company's Investigator's Brochure will serve as the source document in that country.
2. Reports which add significant information on specificity or severity of a known, already documented serious ADR constitute unexpected events. For example, an event more specific or more severe than described in the Investigator's Brochure would be considered "unexpected". Specific examples would be (a) acute renal failure as a labelled ADR with a subsequent new report of interstitial nephritis and (b) hepatitis with a first report of fulminant hepatitis.

Whereas, Periodic safety update reports (PSURs) are pharmacovigilance documents intended to provide an evaluation of the risk-benefit balance of a medicinal product for submission by marketing authorisation holders at defined time points during the post-authorisation phase. The main objective of a PSUR is to present a comprehensive and critical analysis of the risk-benefit balance of the medicinal product taking into account new or emerging information, in the context of cumulative information, on risks and benefits. The PSUR is therefore a tool for post-authorisation evaluation at defined time points in the lifecycle of the product.

For the purposes of lifecycle benefit-risk management, it is necessary to continue evaluating the risks and benefits of a medicine in everyday medical practice and long term use in the post-authorisation phase. This may extend to evaluation of populations and endpoints that could not be investigated in the pre-authorisation clinical trials. A different benefit-risk profile may emerge as pharmacovigilance reveals further information about safety. The marketing authorisation holder should therefore re- evaluate the risk-benefit balance of its own medicinal products in populations exposed. This structured evaluation should be undertaken in the context of ongoing pharmacovigilance and risk management to facilitate optimisation of the risk-benefit balance through effective risk minimisation.

The PSUR should not be used to provide the initial notification of significant new safety information or, as a general rule, provide the means by which new safety issues are detected, or new efficacy data are submitted.

### 2.14 Day zero

Day zero remain as the day that the first information was received.

Or

Day zero should be considered the day on which the minimum criteria for a reportable adverse reaction report becomes available.

### 2.15 Other Drug related issues such as:

#### 2.15.1 Medication Errors

Medication errors are mishaps that occur during prescribing, transcribing, dispensing, administering, adherence, or monitoring a drug. Examples of medication errors include misreading or miswriting a prescription. Medication errors that are stopped before harm can occur are sometimes called ñnear missesò or ñclose callsò or more formally, a potential adverse drug event. Not all prescribing errors lead to adverse outcomes. Some do not cause harm, while others are caught before harm can occur (ñnear-missesò).

Medication errors are more common than adverse drug events, but result in harm less than 1% of the time. About 25% of adverse drug events are due to medication errors.

### 2.15.2 Misuse

This refers to situations where the medicine is intentionally and inappropriately used not in accordance with the authorised PI or the directions for use on the medicine label.

### 2.15.3 Drug Abuse

This corresponds to the persistent or sporadic, intentional excessive use of a medicine, which is accompanied by harmful physical or psychological effects.

### 2.15.4 Beneficial effects

The adverse effect of a drug should not be considered without taking account of its beneficial effects.