INVESTIGATOR’S BROCHURE (IB)

Investigator’s Brochure (IB) summarises the main elements of the entire development programme to date, **primarily for the benefit of investigators** conducting clinical studies to assess the risks and benefits associated with an investigational product.

IB provides an overview of nonclinical and clinical findings together it is also used by independent ethics committees when deciding on ethical approval for conducting a clinical study.

General Considerations

The IB should include:

Title Page

This should provide the sponsor's name, the identity of each investigational product (i.e., research number, chemical or approved generic name, and trade name(s) where legally permissible and desired by the sponsor), and the release date. It is also suggested that an edition number, and a reference to the number and date of the edition it supersedes, be provided.

Confidentiality Statement

The sponsor may wish to include a statement instructing the investigator/recipients to treat the IB as a confidential document for the sole information and use of the investigator's team and the IRB/IEC.

SUMMARY

- Summary providing a profile of ‘physical, chemical, pharmaceutical, pharmacological, toxicological, pharmacokinetic, metabolic, and clinical information’.
- As per ICH E6 Summary should not exceed two pages.

INTRODUCTION

- Information to be covered includes the generic and trade names of the drug product, its active ingredient(s), and the pharmacological class and position of the product being investigated within this class, especially potential advantages over other products within the class. Identifying anticipated prophylactic, therapeutic, or diagnostic indications, and provide an overview of the investigational approach as already conducted or intended.

PHYSICAL, CHEMICAL, AND PHARMACEUTICAL PROPERTIES AND FORMULATION

- This is a brief section describing the chemical, physical, and pharmacological properties of the investigational product, in terms of the drug product and, where relevant, also the drug substance. The section should aim to provide the investigator with sufficient information on the investigational product so that potential risks associated with either the drug itself or any excipients can be assessed. This section should also provide information on storage and handling, preparation steps needed prior to administration, such as reconstitution or dilution.
- Typically, the information for this section will be provided by the Sponsor's Chemistry, Manufacturing, and Controls (CMC) department, but the writer may need to adapt the material provided to the required format for the IB.

NON-CLINICAL STUDIES

- This includes major subsections on nonclinical pharmacology, pharmacokinetics and metabolism, and toxicology
- When a large number of non-clinical studies are available, it can be beneficial to provide the details of each study in a tabulated format, and then provide focused summaries of results and interpretations, supported by tables and figures, within the non-clinical section.

The information provided may include the following, as appropriate, if known/available:

- Species tested
- Number and sex of animals in each group
- Unit dose (e.g., milligram/kilogram (mg/kg))
- Dose interval
- Route of administration
- Duration of dosing
- Information on systemic distribution
- Duration of post-exposure follow-up
- Results, including the following aspects:

Nature and frequency of pharmacological or toxic effects

Severity or intensity of pharmacological or toxic effects

Time to onset of effects

Reversibility of effects

Duration of effects

Dose response

(a) Nonclinical Pharmacology

- A summary of the pharmacological aspects of the investigational product and, where appropriate, its significant metabolites studied in animals, should be included. Such a summary should incorporate studies that assess potential therapeutic activity (e.g., efficacy models, receptor binding) as well as those that assess safety (e.g., special studies to assess pharmacological actions other than the intended therapeutic effect(s).

(b) Pharmacokinetics and Product Metabolism in Animals

- A summary of the pharmacokinetics and biological transformation and disposition of the investigational product in all species studied should be given. The discussion of the findings should address the absorption and the local and systemic bioavailability of the investigational product and its metabolites, and their relationship to the pharmacological and toxicological findings in animal species.

(c)Toxicology

- This section should be subdivided based on single and multiple dose toxicology studies, carcinogenicity studies, special studies (studies specific to the type of product being investigated, e.g. irritancy studies on a product applied topically), reproductive toxicity studies, and mutagenicity studies

EFFECTS IN HUMANS

- This should summarise the results obtained in all clinical studies conducted with the investigational product to date.
- ICH E6 specifies that information should be summarised on the pharmacokinetics, metabolism, pharmacodynamics, dose response, safety, efficacy, and other pharmacological activities

(a) Pharmacokinetics and Product Metabolism in Humans

A summary of information on the pharmacokinetics of the investigational product(s) should be presented, including the following, if available:

- Pharmacokinetics (including metabolism, as appropriate, and absorption, plasma protein binding, distribution, and elimination).
- Bioavailability of the investigational product (absolute, where possible, and/or relative) using a reference dosage form.
- Population subgroups (e.g., gender, age, and impaired organ function).
- Interactions (e.g., product-product interactions and effects of food).
- Other pharmacokinetic data (e.g., results of population studies performed within clinical trial(s).

(b) Safety and Efficacy

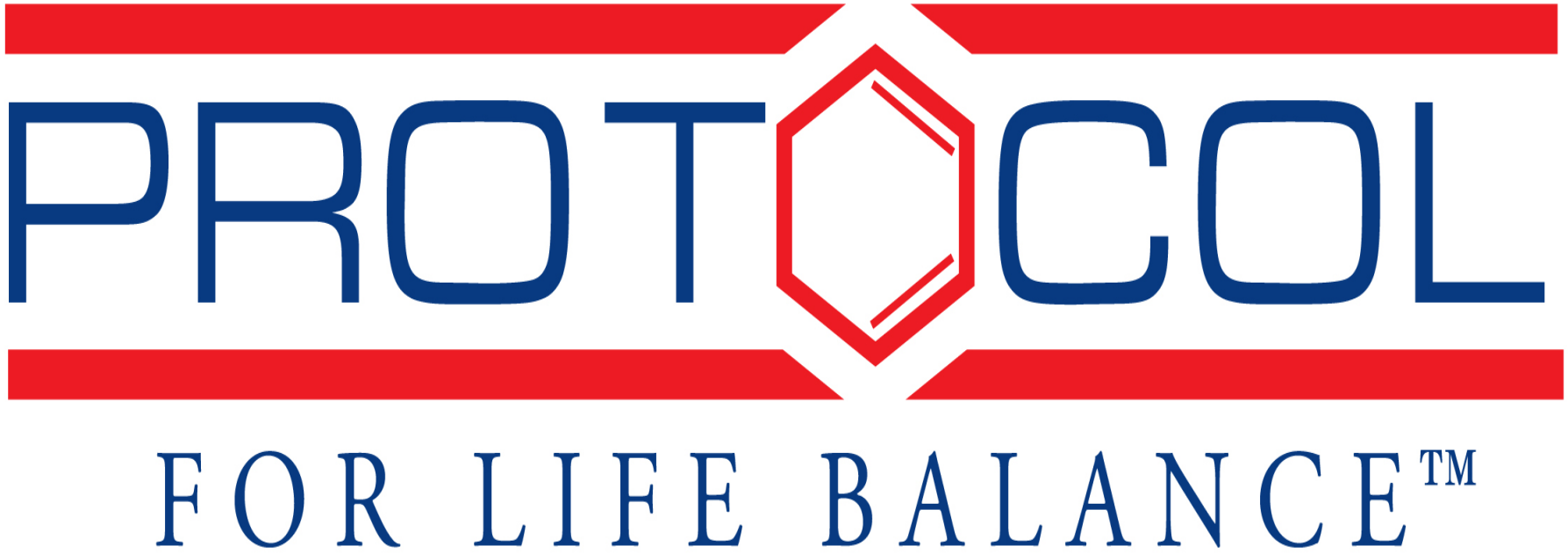
- A summary of information should be provided about the investigational product's (including metabolites, where appropriate) safety, pharmacodynamics, efficacy, and dose response that were obtained from preceding trials in humans (healthy volunteers and/or patients). The implications of this information should be discussed. In cases where a number of clinical trials have been completed, the use of summaries of safety and efficacy across multiple trials by indications in subgroups may provide a clear presentation of the data.
- Tabular summaries of adverse drug reactions for all the clinical trials (including those for all the studied indications) would be useful. Important differences in adverse drug reaction patterns/incidences across indications or subgroups should be discussed.
- The IB should provide a description of the possible risks and adverse drug reactions to be anticipated on the basis of prior experiences with the product under investigation and with related products.
- A description should also be provided of the precautions or special monitoring to be done as part of the investigational use of the product(s).

(c) Marketing Experience

The IB should identify countries where the investigational product has been marketed or approved. Any significant information arising from the marketed use should be summarised (e.g., formulations, dosages, routes of administration, and adverse product reactions). The IB should also identify all the countries where the investigational product did not receive approval/registration for marketing or was withdrawn from marketing/registration.

SUMMARY OF DATA AND GUIDANCE FOR THE INVESTIGATOR

- The guidance for the investigator can be viewed as a kind of discussion section in which the totality of the non-clinical and clinical experience is summarised and interpreted so that inferences for the use of the investigational product in future studies can be drawn.
- Thus, any non-clinical findings of potential concern will need to be discussed in terms of either what has been observed in clinical studies conducted to date or what may be anticipated in future clinical studies.
- This should also provide practical information for the management of subjects being treated with the investigational product.
- This section of the IB will generally contain subheadings such as ‘Therapeutic indications’, ‘Contraindications’, and ‘Warnings and precautions for use’.


PROTOCOL
FOR LIFE BALANCE™

PROTOCOL

A Clinical Trial Protocol is a document that describes the objective(s), design, methodology, statistical considerations, and organization of a clinical trial.

All clinical trials are based on a set of rules called a protocol.

A protocol describes :

What type of people may participate in the trial
The schedule of tests
Procedures
Medications and Dosages
Length of the study

COMPONENTS

1. General Information (Title Page)

a) Protocol title, protocol identifying number, and date.
b) Name and address of the sponsor and monitor
c) Name and title of the person(s) authorized to sign the protocol and the protocol amendment(s) for the sponsor.
d) Name, title, address, and telephone number(s) of the sponsor's medical expert for the trial.
e) Name and title of the investigator(s) responsible for the trial, and the address and telephone number(s) of the trial site(s).
f) Name(s) and address (es) of the clinical laboratory (ies) and other medical and/or technical department(s) and/or institutions involved in the trial

2. Background Information

a) A summary of findings from non-clinical studies that potentially have clinical significance and from clinical trials that is relevant to the trial.
b) Summary of the known and potential risks and benefits, if any, to human subjects.
c) Description of and justification for the route of administration, dosage, dosage regimen, and treatment period(s).
d) A statement that the trial will be conducted in compliance with the protocol and the applicable regulatory requirement(s).
e) Description of the population to be studied.
f) References to literature and data that are relevant to the trial and that provide background for the trial.

3. Trial Objectives and Purpose

A detailed description of the objectives and the purpose of the trial.

4. Trial Design

a) A specific statement of the primary endpoints and the secondary endpoints, if any, to be measured during the trial.

b) A description of the type/design of trial to be conducted (e.g. double-blind, placebo-controlled, parallel design) and a schematic diagram of trial design, procedures and stages.

c) A description of the measures taken to minimize/avoid bias, including: i. Randomization ii. Blinding.

d) A description of the trial treatment(s) and the dosage and dosage regimen of the investigational product(s). Also include a description of the dosage form, packaging, and labeling of the investigational product(s).

e) The expected duration of participation, and the sequence and duration of all trial periods, including follow-up, if any.

f) A description of the "stopping rules" or "discontinuation criteria" for individual subjects, parts of trial and entire trial.

g) Accountability procedures for the investigational product(s), including the placebo(s) and comparator(s)

h) Maintenance of trial treatment randomization codes and procedures for breaking codes.

5. Selection and Withdrawal of Subjects

a) Subject inclusion criteria.

b) Subject exclusion criteria.

c) Subject withdrawal criteria and procedures specifying:

i) When and how to withdraw subjects from the trial/investigational product treatment.

ii) The type and timing of the data to be collected for withdrawn subjects.

iii) Whether and how subjects are to be replaced.

iv) The follow-up for subjects withdrawn from investigational product treatment/trial treatment.

6. Treatment of Subjects

a) The treatment(s) to be administered, including the name(s) of all the product(s), the dose(s), the dosing schedule(s), the route/mode(s) of administration, and the treatment period(s), including the follow-up period(s) for subjects for each investigational product treatment/trial treatment group/arm of the trial.

b) Medication(s)/treatment(s) permitted (including rescue medication) and not permitted before and/or during the trial.

c) Procedures for monitoring subject compliance.

7. Assessment of Efficacy

a) Specification of the efficacy parameters.
b) Methods and timing for assessing, recording, and analyzing of efficacy parameters.

8. Assessment of Safety

a) Specification of safety parameters.
b) The methods and timing for assessing, recording, and analyzing safety parameters.
c) Procedures for eliciting reports of and for recording and reporting adverse event and intercurrent illnesses.
d) The type and duration of the follow-up of subjects after adverse events.

9. Statistics

e) A description of the statistical methods to be employed, including timing of any planned interim analysis .
b) The number of subjects planned to be enrolled.
c) The level of significance to be used.
d) Criteria for the termination of the trial.
e) Procedure for accounting for missing, unused, and spurious data.
f) Procedures for reporting any deviation(s) from the original statistical plan.
g) The selection of subjects to be included in the analyses (e.g. all randomized subjects, all dosed subjects, all eligible subjects, evaluable subjects).

10. Quality Control and Quality Assurance

a)A description of the monitoring of data collection, record retention and adverse event reporting.

11. Ethics

Description of ethical considerations relating to the trial.

12. Data Handling and Record Keeping

13. Financing and Insurance

Financing and insurance if not addressed in a separate agreement.

14. Publication Policy

Publication policy, if not addressed in a separate agreement.

15. Supplements

(NOTE: Since the protocol and the clinical trial/study report are closely related, further relevant information can be found in the ICH Guideline for Structure and Content of Clinical Study Reports.)

INFORMED CONSENT PROCESS

INFORMED CONSENT

- Informed consent is a process by which a participant voluntarily confirms his willingness to participate in the clinical trial
- Informed consent form describes the rights of the study participants and includes details about the study, such as its purpose, duration, risks and potential benefits.
- The participant then decides whether or not to sign the form.
- Informed consent form to be signed and dated by the Principal Investigator and subject, in case if he decides to join in the trial.

Goals of the informed consent process

- Give the subject, information about the research
- Make sure the subject has time to consider all options
- Answer all of the subject’s questions before the decision is made
- Make sure that all information is understood by the subject
- Obtain the subject’s voluntary informed consent to participate
- Continue to inform the subject throughout the research study
- Continue to re-affirm subject consent to participate throughout the research study

The informed consent form must be in the local language.
It is a continuous process and it is divided into three copies.
Ist copy- Subject
IInd copy – Subjects medical records
IIIrd copy – The original copy for investigator

It comprises of two parts
PART I [Information Sheet]
PART II [Consent form]

PART I

It contains basic Elements.

- A statement that the study involves research
- An explanation of the purpose of the research
- The expected duration of the subject's participation.
- Clinical trial procedures to be followed.
- Foreseeable risks or discomforts
- Expected benefits to the subject

- Alternate treatment that may be available to the subject and their benefits and risks
- Compensation and/or treatment available to the subject in the event of trial- related injury.
- That the subject's participation in the trial is voluntary
- Confidentiality of the records identifying the subject
- The person to contact for further information regarding the trial and whom to contact in the event of trial-related injury.

PART II

Consent forms must be presented to a potential participant and signed before that person can take part in the study.

Ist case: if the subject is educated

Name of the subject

Signature of the subject

The date should be mentioned in DD\MM\YY format

Name of the investigator

Signature of the investigator

The date should be mentioned in DD\MM\YY format

IInd case: If the subject is an illiterate person

Name of the subject

Thumb impression of the subject

Name of the witness

Signature of the witness

The date should be mentioned in DD\MM\YY format

Name of the investigator

Signature of the investigator

The date should be mentioned in DD\MM\YY format

IIIrd case: If the subject is a child

Name of the child

Name of the parent/guardian

Signature of the parent/guardian

The date should be mentioned in DD\MM\YY format

Name of the investigator

Signature of the investigator

The date should be mentioned in DD\MM\YY format

STANDARD OPERATING PROCEDURE

Standard Operating Procedures (SOPs)

Official, detailed, written instructions for the management of clinical trials. SOPs ensure that all the functions and activities of a clinical trial are carried out in a consistent and efficient manner.

The ICH defines SOPs as 'detailed written instructions to achieve uniformity of the performance of a specific function'.

An SOP is nothing more than a clearly written description of how particular task is to be performed.

Importance of SOPs

Consistency and control are fundamental components of a clinical research Protocol.

SOPs help to ensure the Consistency and control

They are essential for standardizing processes, for training new personnel and for managing workload.

The SOPs must cover

- A descriptive title and indication of the SOP's position in the total collection.
- Date when the SOP became operative
- The edition number and a statement that this edition replaces an earlier edition from an earlier date
- The exact distribution of SOPs
- The signature of the person responsible for writing the SOP
- The signature of the person responsible for authorizing the SOP
- In some contexts the purpose of the SOP

IRB / IEC

REGULATORY AUTHORITIES

Definition

These are the bodies having the power to regulate.

In the ICH GCP guideline the term includes the authorities that review submitted clinical data and those that conduct inspections.

These bodies are sometimes referred to as competent authorities or Regulatory Agencies.

Different Countries RA

United States.	FDA Regulations
Canada	TPD Regulations
European Union	EMEA Regulations
Israel	Regulations of Ministry of Health
India	Ministry of Health
China	SFDA Regulations
South Africa	Department of Health Regulations
Australia	TGA Regulations
New Zealand	Joint Therapeutic Products Agency
Russia	Ministry of Health
Japan	Ministry of Health and Welfare

FDA comprises of several centers and one office.

Office of the Commissioner

It is the main regulatory office.

It includes :
commissioner, deputy commissioner for foods, deputy commissioner for medicinal products & tobacco, deputy commissioner for global regulatory operations & policy, chief scientist, counselor to the commissioner, chief operating officer.

Centers

CBER: Center for Biological Evaluation & Research. To ensure the safety, purity, potency & effectiveness of biological products.

CDER: Center for Drug Evaluation & Research. It is the division of FDA that monitors the safety and efficacy of the drug.

CDRH: Center for Devices & Radiological Health. It is responsible for regulating firms who manufactures, repackages and labels medical devices.

CVM: Center for Veterinary Medicine. It regulates the manufacture and distribution of food addictives and drugs that are given to animals.

CFSAN: Center for Food Safety & Applied Nutrition. It regulates food, dietary supplements and cosmetics.

CTP: Center for Tobacco Products . It oversees the implementation of the smoking prevention & Tobacco Control Act.

NCTR: National Center for Toxicological Research. It plays a crucial role in the FDA's mission. It mainly supports FDA product centers and their regulatory roles.

Code of Federal Regulations

The Code of Federal Regulations (CFR) is the codification of the general and permanent rules published in the Federal Register by the executive departments and agencies of the Federal Government.

It is divided into 50 titles that represent broad areas subject to Federal regulation.

Each volume of the CFR is updated once each calendar year and is issued on a quarterly basis.

Titles 1-16 are updated as of January 1st
Titles 17-27 are updated as of April 1st
Titles 28-41 are updated as of July 1st
Titles 42-50 are updated as of October 1st

Each title is divided into chapters, which usually bear the name of the issuing agency.

Each chapter is further subdivided into parts that cover specific regulatory areas.

Large parts may be subdivided into subparts.

All parts are organized in sections, and most citations in the CFR are provided at the section level.

CPMP (Europeans union's Committee for Proprietary Medicinal Products) – 1977

In Europe, the first initiatives were undertaken by individual countries, each of them creating its own regulations/guidelines for conducting research in human subjects.

In the year 1990, The European Union's Committee for Proprietary Medicinal Products (CPMP) published a guideline on Good Clinical Practice for Trials on Medicinal Products in the European Community, which was the first unified standard covering all aspects of medical research in Europe.

In 1995 the Committee for Proprietary Medicinal Products was replaced by European Agency for Medicinal Products (EMEA), which was in renamed as European Medicinal Agency in 2004.

EMEA has 6 committees:

CHMP: Committee for Medical Products for Human Use. It is responsible for preparing the agencies opinions on all questions concerning medicines for human use, in accordance with regulation.

CVMP: Committee for Medical Products for Veterinary Use. It is responsible for preparing the agencies opinions on all questions concerning medicines for veterinary use.

COMP: Committee for Orphan Medicinal Products. It is responsible for reviewing applications from persons or companies seeking "orphan medicinal product designation".

HMPC: **Committee for Herbal Medicinal Products. It mainly deals with the simplified registration procedure for traditional herbal medicinal products in EU member states.**

PDCO: **Pediatric Committee. It is responsible for assessing the content of Pediatric investigation plans & adopting opinions on them.**

CAT: **Committee for Advanced Therapies. It is a multidisciplinary committee that gathers the info to assess the quality, safety and efficacy of advanced therapy medicinal products.**

DCGI: (Drug controller General of India)

DCGI is a regulatory apex body under Govt. of India.

It is responsible for regulatory approvals for conduct of clinical trials in India.

It is governed by the rules Amended in Schedule Y.

Prior to amendment of schedule Y global drug trials could be conducted only with a phase lag in India.

Currently concurrent, parallel, global clinical trials (Phase II-IV) are permitted to be conducted in India by the DCGI.

DCGI heads the Central Drugs Standard control organization (CDSCO) and discharges the functions attached to the central Govt.

The DCGI also has the responsibility of laying down regulatory measures and amendment of Acts and Rules, laying down standards for drugs, cosmetics, diagnostics and devices and updating the Indian Pharmacopoeia.

T-License:

A license given to export/import drug/ raw materials/ Ip from other countries. It is also called as shipping license.

There are two types of Drug approval process in the DCGI:

Type A:

it is also known as fast track process.

The protocol is already approved in other regulation board.

Duration of approval is 2-6 weeks.

Type B:

it is conducted only to single country concern.

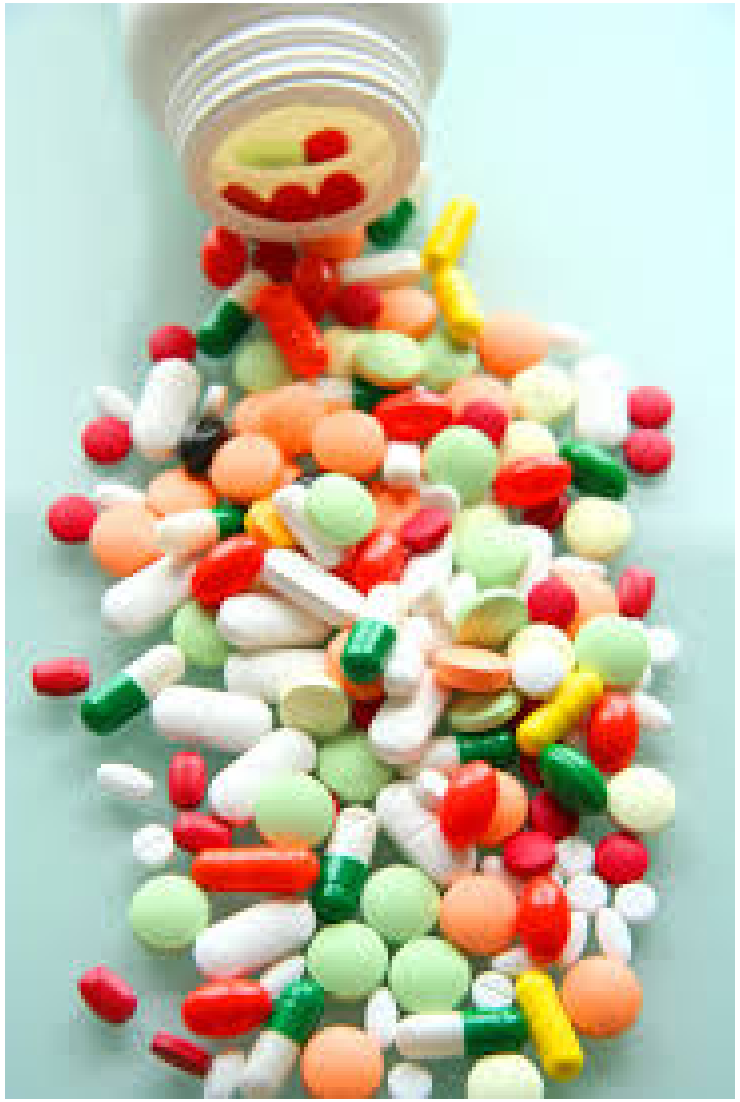
Duration of approval is 8-12 weeks.

Introduction

Drug:

✓ Substance or mixture of substances used for diagnosis, treatment or prevention of disease or disorders.

✓Used for restoring , correcting or modifying organic functions in Human beings or animals.



DEFINITION:

- It 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.

- Pharmacon=drug, vigilare=to keep awake, alert, or to keep watch.

- The purpose is to identify new information about hazards related to medicines and preventing harm to patients

- concerned with the ADR (Adverse Drug Reaction) "Any unfavorable and unintended sign, symptom

  or a disease temporarily associated with the use of medicinal product (drug)."

- branch of Pharmacoepidomology- the study of use and effects of drugs in huge population.

- It uses the methods of epidemology and is concerned with all aspects of benefit – risk ratio for populations.

Need of Pharmacovigilance

There is a need to monitor the effects of drugs during the clinical trials and after its launch in the market.

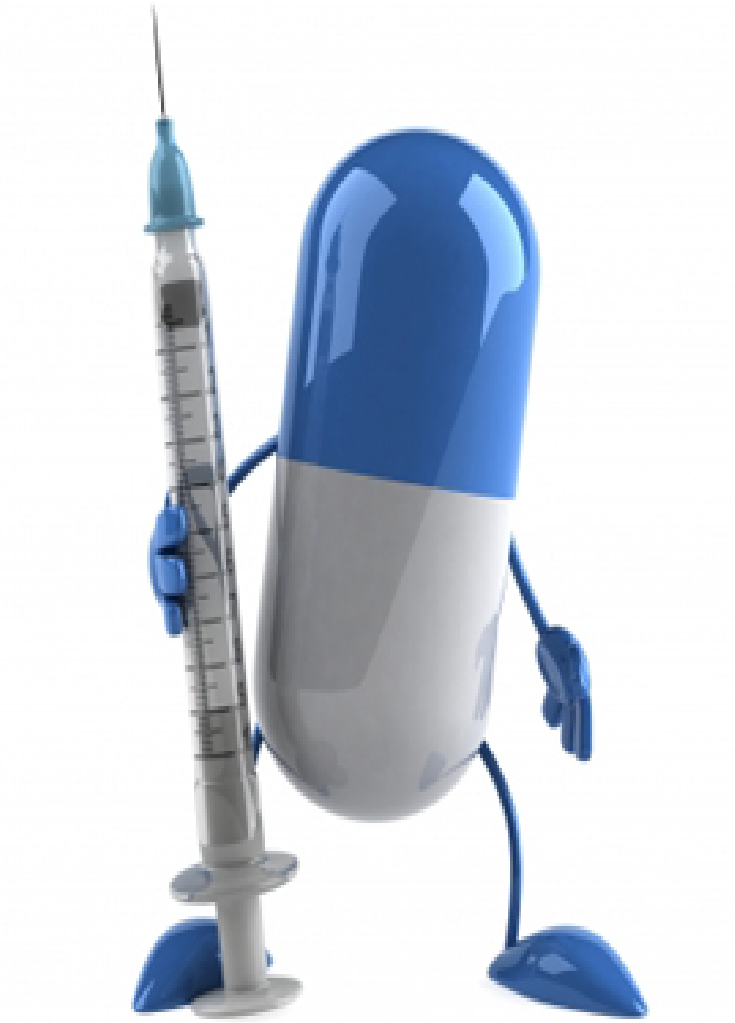
Because Adverse events can happen during the clinical trials and even after its launch in market

Why Pharmacovigilance in Clinical Trials

- **After completing Pre-Clinical studies in animals, first time trial drug will be administered to the Human.**

- **At this time the drug will act in different way to the Human body**

- **Chances of Adverse events will also persist**



Pharmacovigilance in Post Marketing – Why?

- **At the time of approval, clinical trial data is available on limited number of patients treated for relatively short periods.**

- **Once a product is marketed, large number of Patients may be exposed, including :**

  - **Patients with Co-morbid illness**

  - **Patients using concomitant medications**

  - **Patients with chronic exposure**

What to report?

1. **ADR associated with vaccines, diagnostics, drugs used in traditional medicine, herbal remedies, cosmetics, medical devices and equipment.**

2. **Lack of efficacy and suspected pharmaceutical products**

3. **Overdose**

4. **Every single problem related to the use of a drug**

Terms commonly used

1. ***Adverse drug reaction (ADR)*** *is a side effect occurring with a drug where a positive causal relationship between the event and the drug is thought, or has been proven, to exist.*

2. ***Adverse event (AE)*** *is a side effect occurring with a drug. By definition, the causal relationship between the AE and the drug is unknown.*

3. ***Benefits*****:** *proven therapeutic good of a product but should also include patient's subjective assessment of its effect.*

4. ***Causal relationship*** *is said to exist when a drug is thought to have caused or contributed to the occurrence of an adverse drug reaction.*

5. ***Dechallenge and Rechallenge*** *refer to a drug being stopped and restarted in a patient, respectively. Dechallenge and rechallenge play an important role in determining whether a causal relationship between an event and a drug exists.*

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

7. ***Efficacy***: *it is used to express the extent to which a drug works under ideal circumstances i.e., clinical trials.*

8. ***Harm:*** *it is the nature and extent of actual damage that could be caused.*

9. ***Individual Case Study Report*** *(ICSR) is an adverse event report for an individual patient.*

10. ***Risk***: *it is the probability of harm being caused usually expressed as a percent or ratio of the treated population.*

11. ***Triage*** *refers to the process of placing a potential adverse event report into one of three categories: 1) non-serious case; 2) serious case; or 3) no case (minimum criteria for an AE case are not fulfilled).*

Types of Adverse Reactions

Type A Effects (Augmented)

- Due to Pharmacological effects
- Are common
- Dose dependent
- Are dose related – may often be avoided by using doses which are appropriate to the individual patient
- On over dosage cause : loss of appetite, lethargy, breathlessness etc…..

Type B Effects (Bizzard, idiosyncratic reactions)

- Generally rare and unpredictable
- Non Dose related
- Unrelated to Pharmacology
- Occur in predisposed, intolerant patients
- Example : Pencillin allergies

Type C effects (Continuous)

- Adverse reactions after long term therapy
- There is often no suggestive time relationship and the connection may be very difficult to prove.
- Example : Carcinogenesis
- Related to cumulative drug use

Type D Effects (Delayed)

- **Adverse effect may be presented years after a drug was used**

- **Apparent only sometime after use of drug.**

- **Example: Thalidomide Episode, where the children were effected when their mother was treated with the sedative.**

Type E Effects (Ending)

- Absence of drug after withdrawal – Rebound Effect
- Example : corticosteroids in asthma treatment

Type F Effects (Failure of therapy)

- results from the ineffective treatment
- Example : Accelerated hypertension because of insufficient control

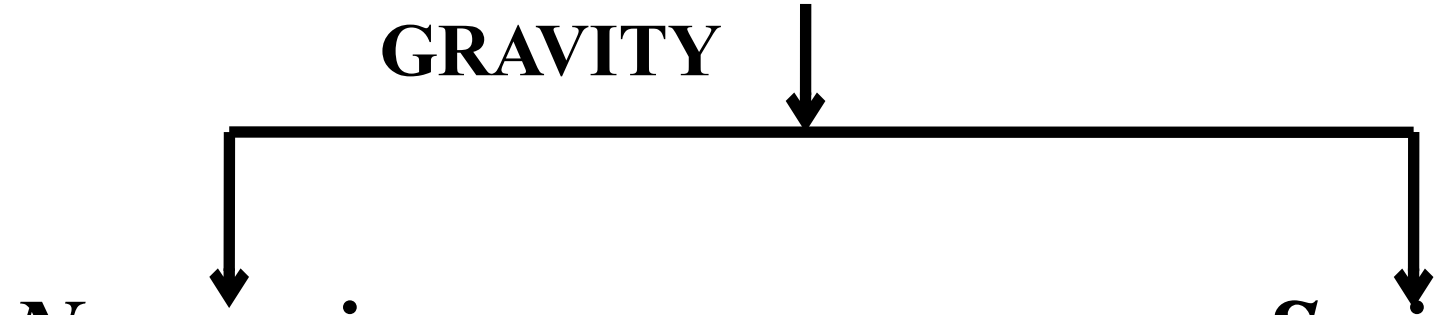
Classification of Adverse Events based on its severity

- ***Mild*: No changes in the therapy are needed**
- ***Moderate*: Change of therapy is desired but the events are not life – threatening or causing disability**
- ***Serious :* is either life-threatening, fatal, Cause persistent disability, cause of prolong hospital admission**
- ***Lethal :* An ADR directly or indirectly contributes to a patients death**

Classification of AE based on Frequency

- **Very Common : > 1/10 (>0.1)**
- **Common (frequent) : > 1/100 and < 1/10 (b/w 0.1 and 0.01)**
- **Uncommon (infrequent) : > 1/1000 and < 1/100**
- **Rare : > 1/10000 and < 1/1000**
- **Very Rare : < 1/10000**

CLASSIFICATION OF ADR



Non-serious

This does not require significant medical intervention.

Serious

death of a patient
life threatening
Hospitalization
permanent disability

Based on avoidability of the ADR's

- ✓ ***Definitely avoidable :*** **The ADR was due to a drug treatment procedure inconsistent with present day knowledge of good medical practice.**

- ✓ ***Possibly avoidable :*** **The ADR could have been avoided by an effort exceeding the obligatory demands of present day knowledge of good medical practice.**

- ✓ ***Unavoidable :*** **The ADR could not have been avoided by any reasonable means.**

Unexpected Adverse Drug reaction

- **An Adverse reaction, the nature or severity of which is not consistent with the applicable product information**

- **were not previously observed and are not documented**

Expected Adverse Drug Reactions

Expected are those adverse events that were observed during clinical trails or post – approval observations and are mentioned in summary of Product Characteristics.

Spontaneous reporting

A spontaneous report is an unsolicited communication by healthcare professionals or consumers that describes one or more adverse drug reactions in a patient who was given one or more medicinal products.

Throughout the world spontaneous reporting is the most common method of surveillance.

It is the easiest to establish and the cheapest to run, but reporting rates are generally very low and subject to strong biases and there is no database of all users or information on overall drug utilization.

These problems prevent the accurate assessment of risk, risk factors or comparisons between drugs

Adverse reactions:
It should be noted that this method is for the reporting of suspected adverse reactions.
The definition of an adverse reaction is: a response to a medicine which is noxious and unintended, and which occurs at doses normally used in man. (WHO).

Serious Adverse Reaction:
A serious adverse reaction is any untoward medical occurrence that at any dose results in death, is life threatening, requires or prolongs patient hospitalisation, results in persistent disability/incapacity, or is a congenital anomaly/birth defect (International Conference on Harmonisation (ICH)).

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 was more severe.

The aims of spontaneous reporting are to:

- improve patient care and safety in relation to the use of medicines and all medical and paramedical interventions;

- improve public health and safety in relation to the use of medicines;

- detect problems related to the use of medicines and communicate the findings in a timely manner;

- contribute to the assessment of benefit, harm, effectiveness and risk of medicines, leading to the prevention of harm and maximization of benefit;

- encourage the safe, rational and more effective (including cost-effective) use of medicines

Minimum reporting requirements

According to WHO criteria, the following basic information is required before a report is acceptable:

- An identifiable source of information or reporter;
- An identifiable patient;
- name(s) of the suspected product(s);
- A description of the suspected reaction(s).

How to report

Reporting form:

Over 100 different reporting forms are available. These have been individually developed by each country that has set up a Pharmacovigilance Centre.

Other options for reporting

Reporting needs to be made as convenient as possible. If other methods are available, they may be preferred by some health professionals.

Preferences may vary between clinics and hospitals, private or government facilities and public health programmes.

Where to report:

- Reports should be sent to the Pharmacovigilance Centre.

- If it is not practical to send the forms directly to the centre, it may be necessary to arrange points of collection at other sites as e.g. specific hospitals or clinics.

- They should be stored securely to maintain confidentiality.

Cohort event monitoring

Event monitoring:

An event is any new clinical experience that occurs after commencing a medicine regardless of its severity or seriousness and without judgement on its causality.

Cohort Event Monitoring (CEM) records all clinical events and not just suspected adverse reactions.

Event monitoring involves

- Actively asking for reports of the events
- Systematically asking for reports of the events.

Cohort event monitoring (CEM) is a prospective, observational, cohort study of adverse events associated with in one or more medicines.

A CEM programme is essentially an observational study of a new medicine in the early post marketing phase, but it can be used for older medicines.

Its basic function is to act as an early warning system of problems with new medicines, although it will provide much more.

Objectives:

- The objectives of spontaneous reporting are also objectives of CEM. The aims of CEM include the following, either in addition, or more effectively than for spontaneous reporting.
- Provide incidence rates for adverse events as a measure of risk.
- Characterize known adverse reactions.
- Detect signals of unrecognized reactions.
- Detect interactions with other medicines, complementary and alternative medicines, foods and concomitant diseases.
- Identify risk factors and thus provide evidence on which to base effective risk management.
- Assess safety in pregnancy and lactation.
- Provide a measure of comparative risks between medicines.
- Provide cohorts for further study of safety issues if required in the future.
- Detect inefficacy, which might be due to:
  - faulty administration; poor storage conditions; poor quality product;
  - counterfeit product; interactions.

Basic processes

•Establishing a cohort of patients for each drug and/or drug combination.

•Recording adverse events experienced by patients in the cohort(s) for a defined period.

Programme duration

CEM is done for a limited length of time.

The length depends on the time it takes to achieve the cohort size that is necessary

Epidemiology

The key epidemiological features of CEM studies are that they are:

Observational:

This means that the studies are “non-interventional” and are undertaken in real-life situations. Patients are not selected according to any criteria: all patients who are treated for disease with the medicine being monitored are included. This includes patients of all ages, those with other diseases and those on other medicines. Treatment is given according to the usual local guidelines.

Prospective:
This means that the monitoring is planned before the patients are treated and the patients are studied and followed up from the time they begin their treatment

Inceptional :
This has a similar meaning to prospective: that every patient is studied from the time of commencement of their treatment.

Dynamic:
This means that new patients are added as the study continues until such time as there are sufficient numbers in the cohort.

Longitudinal :
This means that the patients are studied over a period of time. For therapy used for acute treatment this is a matter of only a few days although monitoring may continue longer if looking for delayed effects.

Descriptive :
This means, that the events are identified and described, their frequency is measured and their distribution in different subgroups of the cohort is recorded.

First step – Implementation

The implementation step has to be done well if a CEM study is to succeed. It is necessary to do the following:

- Appoint a full-time CEM coordinator.
- Aim at having an initial pilot study.
- Select appropriate sentinel sites, with trained teams and adequate resources to perform CEM.
- Using the most appropriate means, all stakeholders must be fully informed of:
  - ❖ The reasons for monitoring .
  - ❖ The methodology as it involves them.
  - ❖ The value of safety monitoring and the advantages of CEM.
  - ❖ The contribution it will make to the health of the population (improving benefit and reducing risk).
  - ❖ The potential for increasing the effectiveness of public health programmes.
  - ❖ The potential for reducing health costs for the community and government.

Second step – establishing the cohort

Numbers of patients

- In general, the aim is to have 10 000 patients in the cohort.

- If a comparator study is being undertaken, greater numbers will be needed

- Concomitant medicines: larger numbers might be needed to detect differences in patients on specific medicines compared with the other patients.

Other health problems e.g. malnutrition: larger numbers might be needed to detect differences in these patients.

Selection of patients

Logistics:

Decisions will need to be made as to where the patients will be recruited and the monitoring to be performed

The patients might be recruited from all health facilities

Patients might be recruited from selected health facilities that are representative of the whole country, designated as "sentinel monitoring sites".

Inceptional :

Patients must be monitored from the inception of treatment. Patients not seen at the beginning of treatment should be excluded from the study

Subgroups of interest :

Children

HIV/AIDS

Pregnancy

Patient identification

It is vital that patients can be identified accurately. Inaccurate identification will result in:

- duplicate entries in the database leading to inflated numbers in the cohort and inaccurate statistics;
- difficulties in follow-up.

Other patient data

- Age at the time of treatment. (date of birth to help identification).
- Sex.
- Weight and height.

Background data

- History of significant illness (e.g. liver disease, kidney disease).
- Other diseases present at the time of treatment (e.g. HIV/AIDS, tuberculosis, anaemia).

Third step – acquiring the data

The medicines

Details of administration of medicine

The following should be recorded:

- brand name, e.g. Coartem;
- dose and schedule of administration;
- date of commencement of treatment;
- date of completion of course of therapy or date of withdrawal;
- record of incomplete adherence;
- record reason(s) for incomplete adherence

Concomitant medicines

All medicines taken during the 2 weeks prior to treatment and at any time from day 0 of treatment until the follow-up appointment should be recorded

Record the following information on concomitant medicines:

- name: brand (preferred) or generic;
- any traditional medicine(s) (“yes” or “no”);

•indication for use;
•dose and frequency of administration;
•date started;
•date stopped (record “continues” if not stopped).

The events

Principles of event reporting

•All adverse events are requested to be reported and not just suspected adverse reactions. Clinicians should be asked to make no judgement on causality.

•“Adverse events” are requested to be reported because there are always unexpected or unrecognized adverse reactions. If only suspected reactions are reported, then those which are unexpected and unrecognized are likely to be missed.

- All clinical events experienced by each patient should be recorded on the questionnaire provided. This includes unexpected improvement of concomitant disease (favourable event) as well as adverse events.

- Pretreatment: Each patient who attends a health care facility should be asked if any health events have occurred in the previous 7 days and these should be recorded as having occurred during the control period.

- Post-treatment: At the follow-up visit any new events or worsening of pre-existing conditions that have occurred since treatment began should be recorded.

Reporting requirements

Health professionals should be asked to record the following types of events:

- All new events even if minor.
- Change in a pre-existing condition.
- Abnormal changes in laboratory tests.
- Admission to hospital with date and cause.
- Pregnancy of any duration.
- Accidents.
- All deaths with date and cause.
- Possible interactions.

Recording event details

A brief description of each event is usually all that is necessary. These event descriptions will be reviewed later by pharmacovigilance staff and standard adverse event terminology will be applied by them. The clinician does not need to know the standard event terminology.

Reporting forms (questionnaires)

- The CEM questionnaires have two sides
- Side A is the Pretreatment questionnaire. This information is used to record patient details, treatment and the events during the pretreatment control period.
- Side B is the post-treatment (or follow-up) questionnaire. This provides the follow-up information on events and outcomes of treatment since treatment began.
- It is important to make the recording of data as easy as possible.
- The patient details should be recorded by an assistant before the patient is seen by the clinical worker.
- The questionnaire may need to be adapted for local use.
- Consideration should be given to printing the questionnaires on duplicate self-copying (NCR) paper.

- There would need to be a “pad A” for questionnaire A and “pad B” for questionnaire B.
- It would be an advantage to have them colour-coded.

- When completed, the top copy of each form should be sent to the Pharmacovigilance Centre and the duplicate copy retained in the health facility with the patient's record, where possible, or in another convenient location.

- Questionnaire A would then be sent to the Pharmacovigilance Centre, according to local procedures, without waiting for questionnaire B to be completed.

- This policy should result in a reduced likelihood that forms will be lost; copies of the questionnaires would be retained in the health facility for reference

Who should report?

•Health workers with clinical responsibility should record the events.

•It is desirable that the health worker who treated the patient at the first visit should also see the patient at follow-up.

How and where to send the completed questionnaires

•The completed questionnaires need to be sent to the National Pharmacovigilance Centre where the events will be assessed and the information entered into a database.

•The method of sending the questionnaires needs to be planned with each health facility, from hospitals to rural clinics.

•It may be desirable for rural clinics to send their reports to district hospitals and for district hospitals to send them to referral hospitals which will send them to the Pharmacovigilance Centre.

•The questionnaires should be stored securely so that they cannot be accessed by unauthorized people.

•An appropriate frequency for sending the reports needs to be established, e.g. weekly

Fourth step – Clinical review

This involves the following activities in the Pharmacovigilance Centre:

• Assessing the clinical details and determining the appropriate event terms.
• Determining the duration to onset of each event.
• Recording data on dechallenge and rechallenge (if any).
• Determining severity and seriousness.
• Recording the outcome of each event.
• Undertaking a relationship assessment for each event as the first step in establishing causality.

The event should be specific to be acceptable for recording

For example, sometimes a “stomach upset” is reported, but this description is too vague. It could mean dyspepsia, nausea, vomiting, diarrhoea, or some other specific event.

Determining the event term

•A person with clinical expertise (the CEM Clinical Supervisor) in the Pharmacovigilance Centre should review the details of the events described.

•The first decision to be made is which clinical group(s), e.g. alimentary or respiratory, would be the most appropriate in which to record the event(s).

•The most appropriate term should then be selected from the particular system organ class (SOC) in the WHO-ART dictionary.

•The selected terms should be recorded for later data entry on a coding sheet

Seriousness

•Each event should be routinely recorded as either serious or not serious.

•If serious, then the reason for this choice of description should be given. The coding sheet allows for a code to be entered, e.g. “H” for hospitalized or prolonged hospitalization.

Severity

•Severity does not have the same meaning as seriousness. A patient can experience a severe event that is not serious.

•Severity is a subjective assessment made by the patient and/or the clinician. Although subjective, it is nevertheless useful in identifying reactions that may affect adherence.

•It can be recorded on the coding sheet as “1” for severe or “2” for not severe.

Outcome

The types of outcome to be recorded are listed on the coding sheet (with codes for entry), and are:

• recovered without sequelae;
• recovered with sequelae;
• not yet recovered;
• died due to adverse reaction;
• died – medicine may be contributory;
• died – unrelated to medicine;
• died – cause unknown.