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Review on Pharmacovigilance

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Abstract: *Pharmacovigilance plays a significant part in the healthcare system by keeping track of drug interactions and the impact of those interactions on the human body. The purpose and methods of pharmacovigilance, the goals of the Pharmacovigilance Program of India (PvPI), the list of national adverse drug monitoring centres (AMCs), and their roles are all outlined in this article. The Indian Pharmacopoeia Commission, which serves as the country's national coordination centre for the pharmacovigilance programme, may prioritise promoting safe drug usage. This article discusses the significance of good clinical practise from the perspective of Indian clinical research, while defining and outlining the GCP Protocol designing for clinical trial, Process of Clinical Trial Application (CTA), Elements of the non-clinical and clinical safety specification, Design and conduct of clinical trial, and Goals and Objectives of the GCP Protocol.*

Keywords: Pharmacovigilance, Clinical Trial, New Drugs and Clinical trials Rules 2019, India, ICH-GCP, Regulatory Applications, PvPI

I. INTRODUCTION

Clinical research includes pharmacovigilance as a crucial and vital component. Throughout the lifecycle of a product, post-marketing pharmacovigilance and clinical trial safety are both essential. "Defined as the pharmacological science dealing to the identification, assessment, understanding, and prevention of adverse effects, particularly long-term and short-term adverse effects of medicines," is how pharmacovigilance is described. In India, pharmacovigilance is still in its infancy and there is very little understanding of the field. While the field of pharmacovigilance has made significant strides in the west, India has not made as much progress. It is crucial to comprehend the significance of pharmacovigilance and how it affects the product's life cycle. This will make it possible to incorporate effective pharmacovigilance practises into the systems and practises toA clinical trial is a research study that examines whether a novel medical procedure or a novel application of an existing procedure will be a more effective means of disease prevention, detection, diagnosis, or treatment1. Any novel medication must pass preclinical testing in order to begin a clinical trial. Preclinical research includes experiments on animal populations and in vitro (also known as test-tube or laboratory) research. To gather preliminary information on the research drug's efficacy, toxicity, and pharmacokinetics, a wide variety of dosages of the study drug are administered to animal subjects or to an in-vitro substrate.

II. CLINICAL RESEARCH

A clinical trial is a research study that examines whether a novel medical procedure or a novel application of an existing procedure will be a more effective means of disease prevention, detection, diagnosis, or treatment1. Any novel medication must pass preclinical testing in order to begin a clinical trial. Preclinical research includes experiments on animal populations and in vitro (also known as test-tube or laboratory) research. To gather preliminary information on the research drug's efficacy, toxicity, and pharmacokinetics, a wide variety of dosages of the study drug are administered to animal subjects or to an in-vitro substrate.

2.1 Phases of Clinical Trials

Pharmaceutical companies carry out significant pre-clinical research before beginning clinical trials on a medicine. 3. Pre-clinical research Pre-clinical research includes experiments on animals and in vitro (also known as test tube or laboratory) research. To obtain preliminary information on the study drug's efficacy, toxicity, and pharmacokinetics and to help pharmaceutical companies decide whether it is worthwhile to move forward with further testing, a variety of dosages of the study drug are administered to the animal subjects or to an in-vitro substrate.

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Phase 0

Phase zero may be a more modern term for an experimental, first-in-human trial carried out in compliance with the 2006 exploratory guidance issued by the U.S. Food and Drug Administration (FDA). The administration of a single subtherapeutic dose of the study drug to a small group of individuals (10–15) in part zero studies is a distinctive alternative for gathering preliminary data on the agent's pharmacological medicine (how the body processes the drug) and pharmacodynamics (how the drug add the body).

Phase I

First level of testing on human subjects is the Phase I path. Typically, a small (20–80) group of healthy volunteers would be considered elite. This section contains tests intended to evaluate a drug's pharmacological medicine, pharmacodynamics, and security (Pharmacovigilance). Clinical trial trials come in a variety of totally diverse forms.

SAD:

Single ascending dosage studies are ones in which a small group of individuals receive one dose of the medication while they are observed and examined for a period of time.

MAD:

Studies on multiple ascending doses are carried out to better understand the pharmacological effects of several doses of medication.

Phase II

Clinical trial trials are conducted on large clusters (20–300) and are intended to evaluate how well the drug works in addition to continuing clinical trial safety assessment in a very larger cluster of volunteers and patients after the initial safety of the study drug has been confirmed in clinical trial trials. The two types of clinical trial investigations are typically referred to as clinical trial A and clinical trial B. Clinical Trial A is especially meant to determine dosing requirements (what dosage of the drug should be administered), whereas Clinical Trial B is specifically designed to determine efficacy (how well the treatment functions at the specified dose(s)). Some studies combine clinical trials with other clinical trials to examine both the effectiveness and toxicity of each.

Phase III

Depending on the disease or medical condition being studied, phase III studies involve irregular controlled multi-centre trials on sizable patient groups (300–3,000 or more) and are intended to provide the final determination of how effective the drug is in comparison to the current "gold standard" of care.

Phase IV

The Post Promoting Police Work Trial is another name for Phase IV trial. When a medicine is given the go-ahead to be commercialised, phase IV trials involve security police work (Pharmacovigilance) and ongoing technological assistance.

Table 3: Phases of Clinical Trial

Phase	Group
0	10-15
1	22-80
1A	Single Ascending Dose(SAD)
1B	Multiple Ascending Dose (MAD)
2	20-300
3	300-3000
4	Post Marketing Clinical Trial

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The security police work is intended to observe any uncommon or semi-permanent adverse outcomes over a far larger patient population and longer period of time than was possible throughout the harmful outcomes discovered by phase IV trials might result in a drug being not sold, or restricted to bound uses. Baycol (branch names Bicol and lip bay) and trogelitazone (Resulting and Vioxx-vioxx) are two recent example

Functions of Drug Controller General of India (DCGI) and Central Drugs Standard Control Organization (CDSCO):

The Drug Controller General of India (DCGI) is in charge of the Central Drugs Standard Control Organization (CDSCO).

2.2 Functions of DCGI

- To create and maintain the nation's national reference standard for medications, as well as to control the country's use of medical and pharmaceutical devices.
- To create and maintain the national reference standard for medications; to ensure that the Drugs and Cosmetics Act's provisions are applied consistently across the nation; to teach medical professionals; and
- Control the nation's medical and pharmaceutical equipment and education
- To ensure that the Drugs and Cosmetics Act's provisions are applied consistently across the nation, State Drug Control Laboratories and other institutions send out analysts.
- To serve as the appellate authority in the event that a disagreement develops about the quality of the drugs;
- To inspect and evaluate samples of cosmetics and medications that CDSCO has provided

The Drugs Controller General of India has been given authority under the Medical Device Rules 2017 to serve as the Central Licensing Authority for medical devices that are subject to these regulations. These regulations cover four different types of medical devices: Class A, Class B, Class C, and Class D. For Class C and D, the DCGI will direct licencing power and for Class A and B, it will coordinate licencing. For Class A and B, the State Licensing Authority will be the State Drug Controllers.

2.3 Types of Regulatory Applications

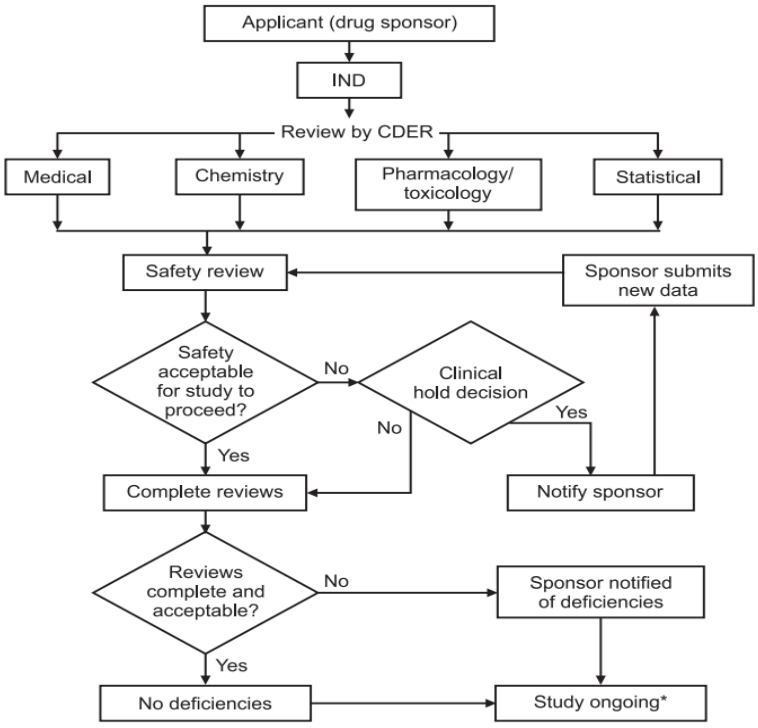

Figure 1

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Investigational New Drug (IND) Application

If the results of the preclinical trials indicated that the medicine was safe, an application would be submitted to the FDA to begin human clinical trials. The person or organisation responsible for submitting the IND application is known as the Sponsor. The FDA can be contacted to set up a pre-IND meeting to go through a variety of topics, including The proposed methodology for carrying out the clinical Trial; the design of the animal studies that are necessary to support the clinical studies Chemistry, production, and oversight of the experimental medication Such a conference will assist the Sponsor in planning animal research, gathering information, and developing the clinical protocol in accordance with the FDA's recommendations. An illustration of the IND process flow chart is provided.

New Drug Application (NDA)

A new drug's producer submits a New Drug Application (NDA), which is the formal request to manufacture and market the drug in the United States, if clinical trials show that it is generally safe, effective, and won't put patients at undue risk. Figure 2 provides an illustration of the NDA procedure.

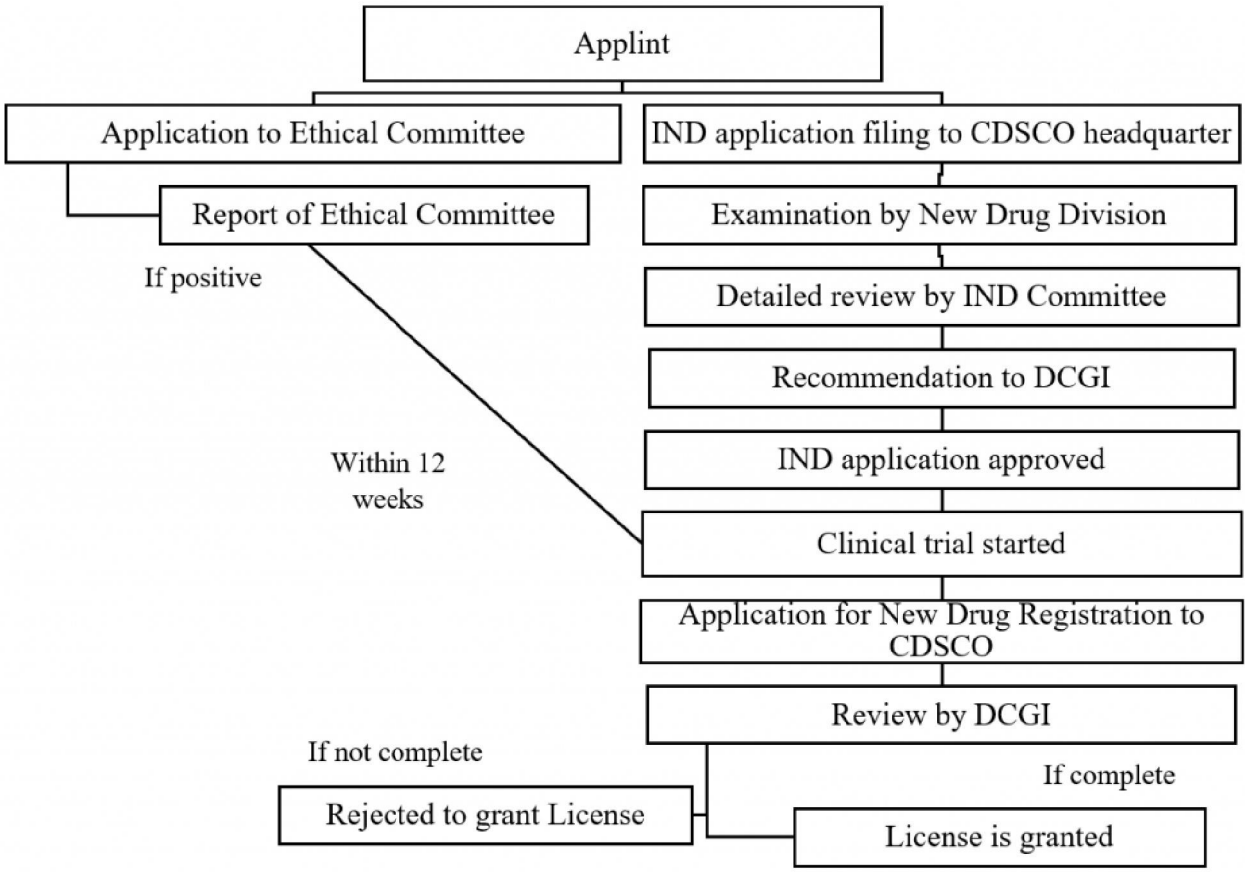

Figure 2

Abbreviated New Drug Application (ANDA)

It is an application submitted for generic drug approval. The sponsor is not compelled to conduct clinical trials for the identical brand-name product in a similar manner. Instead, generic medication makers must show that their product is identical to and bioequivalent to a brand-name product that has already received approval. Figure 3 shows the ANDA procedure in detail.

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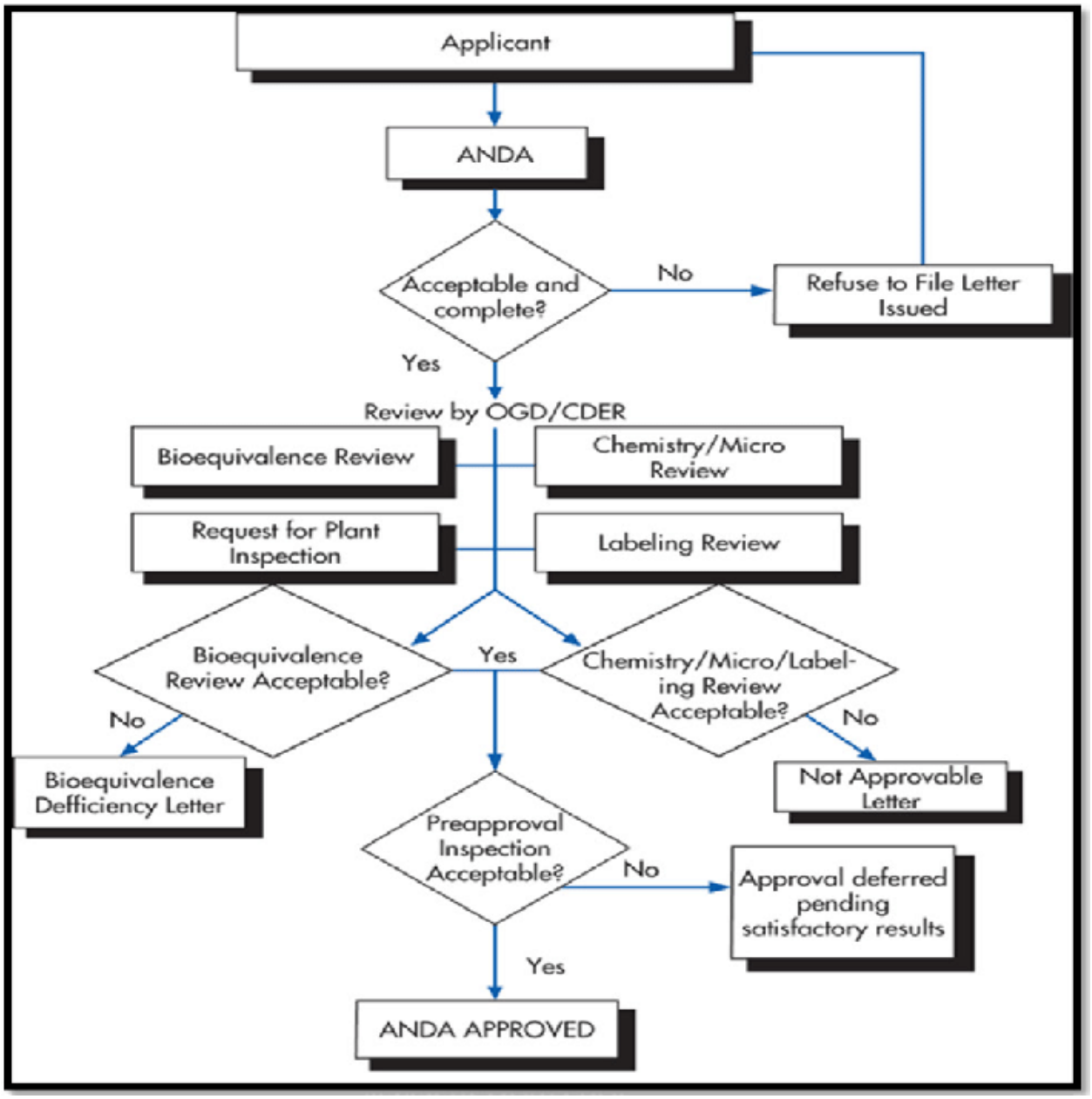

Figure 3

III. GOOD CLINICAL PRACTICE

Objectives and scope of "ICH-Good Clinical Practice" and "New Drugs and Clinical Trial Rules 2019"

ICH-Good Clinical Practice:

- To enable the mutual recognition of clinical data by the authorities in the jurisdictions by the European Union (EU), Japan, and the United States, and to preserve the rights of human subjects participating in clinical trials.
- Avoiding trial duplication will save time, money, and resources.
- Mutual acceptance of data will also facilitate worldwide submissions and specify technical standards for pharmaceuticals including innovative technologies.

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New Drugs and Clinical Trial Rules 2019

Objective:

- The Drugs and Clinical Trial Rules were announced by the Union Ministry for Health and Family Welfare with the goal of advancing clinical research in India.
- The new regulations will alter the country's regulatory environment for the approval of new drugs and the conduct of clinical trials.

Scope:

- These regulations will apply to human use NDs, INDs, CTs, BAs, and BEs as well as the regulation of ethics committees for CT, BA/BE studies, and biomedical health research.
- The definition of new pharmaceuticals has been updated to include engrafts, stem cells, gene therapy products, novel drug delivery systems (NDDS), living modified organisms, and monoclonal antibodies.

Protocol Designing for Clinical Trial

- It is an exhaustive written account and scientific justification of a study project involving human beings.
- In order to conduct the procedure and receive approval from the health authority or ethics committee in the nation where approval of the drug or device is requested, sufficient information must be acquired on the calibre of the non-clinical safety.
- A document known as a clinical trial protocol contains the goals and design of the clinical experiment. It is a document that outlines the study's background, goals, justification, design, technique (including how to handle adverse events, withdrawals, etc.), and statistical considerations. Additionally, it outlines the guidelines for how the study will be conducted and run.
- Look for more effective ways to avoid illness in those who have never experienced it.

The Protocols Means:

- To make the research question more clear.
- To assemble current knowledge.
- To develop a hypothesis and goals.
- To make a research design decision.
- To make ethical issues more clear.
- Making a funding request.
- To provide the research team with a manual and a tool.

Parts of the Protocol:

1. Title Page
2. Page with the signature.
3. Page of Content.
4. A list of acronyms.
5. An overview or introduction.
6. The goals.
7. Background and justification.
8. Qualification Standards.
9. Study Design/Methods (Inclusive of Information on Drug/Device).
10. Adverse Events and Safety.
11. Regulatory Instructions.
12. Statistical Section (Including Analysis and Monitoring).
13. Human Subjects Protection/Informed

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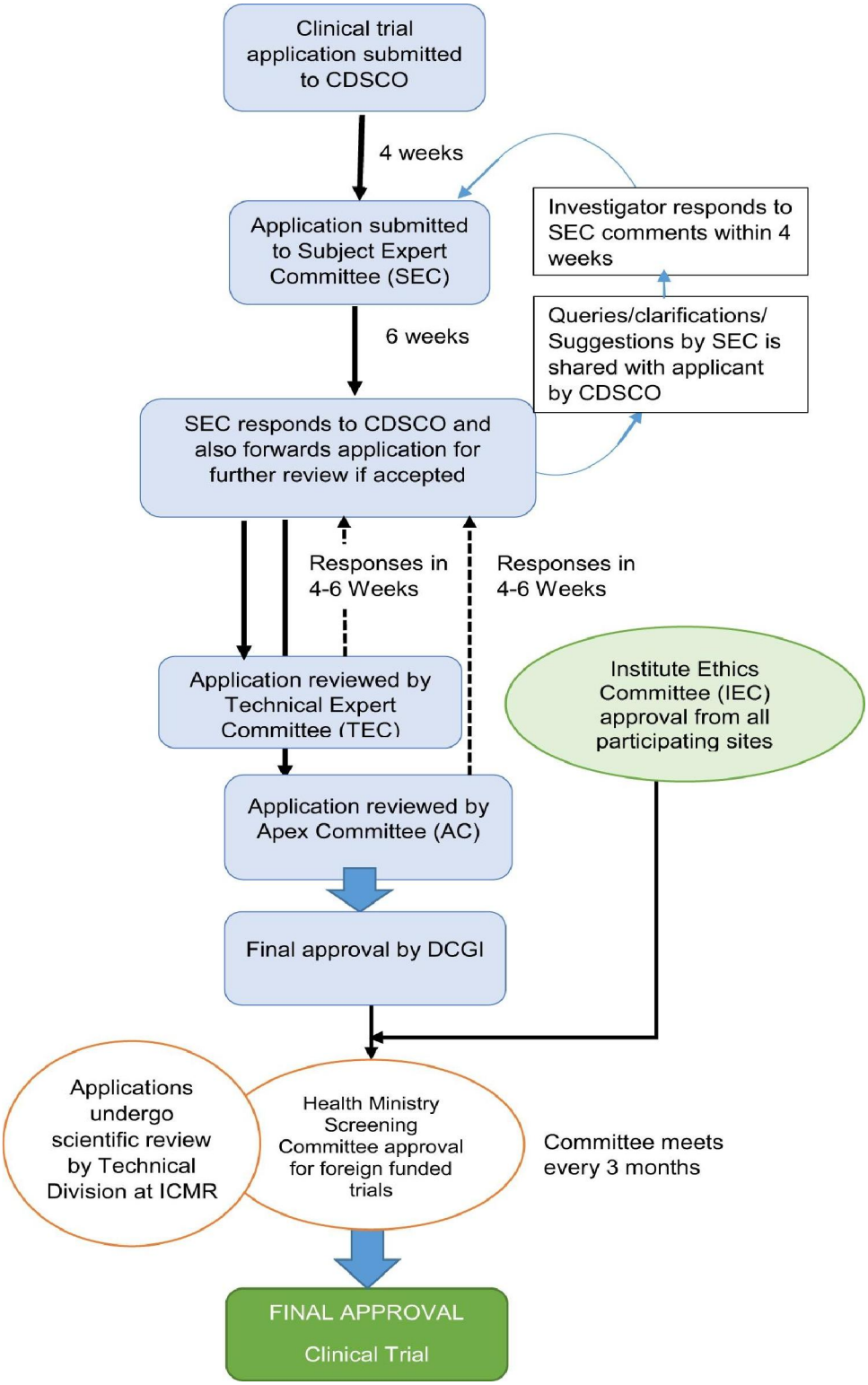
Process of Clinical Trial Application (CTA)

A clinical trial application gives regulatory authorities detailed information regarding investigational medical product (s) and the intended trial , enabling them to to decide whether the study should be carried out. The investigational medicinal product's qualities, the study's benefit/risk balance, the calibre of the information given to trial participants, and the suitability of the clinical locations and investigators are all included in the health authorities' review.



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IV. CONCEPT OF PHARMACOVIGILLANCE

The science and practices involved in the identification, evaluation, and mitigation of negative drug reactions in people are referred to as pharmacovigilance. Pharmacovigilanceis oftenthought of acontinuous examination of adverse effects and other safety-related features of medications that have previously been approved for sale.

4.1 Objective of Pharmacovigilance

Improvements in patient care and safety with regard to the use of medications with medical and paramedical interventions continue to be a crucial factor. The main goals of pharmacovigilance include demonstrating the efficacy of drugs by tracking their adverse effect profile over many years from the lab to the pharmacy; monitoring any drastic effects of drugs; improving public health and safety in relation to the use of medicines; encouraging the safe, logical, and cost-effective use of medicines; promoting understanding, education, and clinical training in pharmacovigilance; and effectively communicating to the general public. Additionally, creating processes and procedures for gathering and analysing reports from patients and clinicians, as well as supplying information to consumers, practitioners, and regulators on the successful use of pharmaceuticals, conclude to the objective of pharmacovigilance.

Types and Components of Pharmacovigilance:

- Passive surveillance
- Active surveillance
- Cohort event monitoring
- Targeted Clinical Investigations

Passive Surveillance:

Utilizing spontaneous adverse event reports voluntarily reported to the marketing authorization holder or regulatory body is a component of passive surveillance approaches. Here, information on the negative effects is gathered and stored in a national or local database. Although the reporter's name is kept secret, the reporting forms can be used to retrieve patient-related information such as country, age, gender, and co-morbidities that already existed.

Active Surveillance:

This approach intends to track particular adverse drug events and determine the total number of adverse drug reactions using a pre-planned procedure. It is often referred to as safety monitoring or toxicity monitoring.

Cohort Event Monitoring:

In this approach, the monitoring study is prepared before the drug therapy even starts. A group of individuals is exposed to a drug for a predetermined amount of time and is closely monitored throughout treatment. Monitoring is done for adverse drug interactions or those connected to one or more medications taken along with the target drug.

Targeted Clinical Investigations:

These types of studies are carried out to identify and define the negative effects of a medicine among certain populations, such as those with certain genetic abnormalities, pregnant women, and senior citizens.

Components of Pharmacovigilance:

- PvOI (chief pharmacovigilance officer)
- Support for Safety System (Database), Processing and Review of Safety Cases, and Medical Writing Team (Aggregate reports and Labels
- SOPs, training, and quality standards
- signal
- Team for Medical Writing (Aggregate reports and Labels)
- PvOI (chief pharmacovigilance officer)
- Safety case processing and case reviewer services

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- Safety system (database) support
- SOPs, quality standards, training signal, and risk analysis
- Team for global safety reporting

Constitution and Objective of Pharmacovigilance Program of India

The Pharmacovigilance Program of India's mission is to gather, compile, and analyse data in order to draw conclusions and suggest regulatory measures, as well as to inform the public and healthcare professionals about hazards.

Objectives of Pharmacovigilance Programme of India:

1. To establish a national mechanism for reporting patient safety
2. To find and examine novel signal ADR from the reported cases
3. To evaluate the benefit-risk ratio of commercially available drugs.
4. To produce evidence-based data on the safety of medications
5. To assist regulatory bodies in making decisions about the use of pharmaceuticals
6. To minimise risk, inform diverse stakeholders on the safety of using medications.
7. To become a recognized national leader in pharmacovigilance operations
8. To different parties to reduce the danger
9. 7. To become a recognized national leader in pharmacovigilance operations
10. Work together with other national centres for information sharing and data management

V. INTERNATIONAL CONFERENCE ON HARMONIATION (ICH) E2e GUIDELINES

5.1 Elements of the Specifications

It is advised that sponsors create the Safety Specifications using the format of the elements listed below. The Safety Specifications' mentioned components are solely intended as a guide. Depending on the nature of the product and its development plan, the Safety Specifications may include other components. On the other hand, only a portion of the criteria may be pertinent for items that are currently on the market but have newly discovered safetyissuesThe Safety Specifications should concentrate on the known dangers, significant potential risks, and significant gaps in knowledge. The following components must to be taken into account for inclusion.

Non-Clinical:

This portion of the Specification should present non-clinical safety findings that the clinical data have not sufficiently addressed, such as:

- Toxicity (including carcinogenicity, nephrotoxicity, hepatotoxicity, genotoxicity, repeat-dose toxicity, and reproductive/developmental toxicity);
- Basic pharmacology (cardiovascular, including QT interval prolongation; nervous system; etc.)
- Additional facts or information pertaining to toxicity.
- Adverse drug reactions

Consideration should be made to whether specific non-clinical data requirements exist if the product is intended for usage in special populations.

Clinical:

- Adverse Events (AEs)/Adverse Drug Reactions (ADRs)
- Identified and Potential Interactions, Including Food-Drug and Drug-Drug Interactions
- Epidemiology
- Pharmacological Class Effects
- Limitations of the Human Safety Data Base
- Populations not Studied in the Pre-Approval Phase

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Design and Conduct of Observational Studies:

Pharmacoepidemiological studies that are well planned and carried out, particularly observational (non-interventional, non-experimental) studies, are crucial instruments inpharmacovigilance. The investigator "observes and assesses results of continuing medical care without 'controlling' the therapy beyond standard medical practise" in observational studies. A protocol should be finalised before the observational study included in a pharmacovigilance plan gets started. It is best to consult professionals from related fields (such biostatisticians, pharmacoepidemiologists, and pharmacovigilance experts). Before the study begins, it is advised that the protocol be discussed with the regulatory authorities. Additionally, it is advised that the conditions under which a study should be stopped early be addressed with regulatory authorities and recorded beforehand. After the study is finished, a report should be sent to the authorities, along with intermediate reports if necessary.

VI. CONCLUSION

To handle the issues posed by the expanded variety and potency of drugs, pharmacovigilance is crucial. The PV in India is still expanding, changing, and getting better. India is the world's largest pharmaceutical producer and is quickly becoming a major global centre for clinical trials. By establishing the National PV programme, the DCGI has demonstrated its dedication to ensuring the safe use of pharmaceuticals. PV might not rely on just one technique; it needs a plan for a variety of complimentary techniques. PV has simultaneously expanded a number of additional initiatives, frequently in partnership with other departments. The following is just one illustration: selecting the first safe dose; supporting patient safety during the conduct of clinical trials through well-developed patient consent forms and institutional review board papers.

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