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# A REVIEW ON PHARMACOVIGILANCE IN CLINICAL TRIALS AND DRUG DEVELOPMENT

**Shubham Ghosh[a*], Moutoshi Singh[a], Partha Pratim Maiti[a] and Rupak Das[a]**

[a]Department of Pharmaceutical Technology, University of North Bengal, Raja Rammohunpur, Darjeeling, West Bengal-734013, India.

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***Corresponding Author**
**Shubham Ghosh**
Department of Pharmaceutical Technology, University of North Bengal, Raja Rammohunpur, Darjeeling, West Bengal-734013, India.

## ABSTRACT

Pharmacovigilance and clinical trials operate in tandem, any adverse events reported by trial participants are forwarded to the pharmacovigilance team. Safety in clinical trials is a crucial aspect of pharmacovigilance. Before being put on the market, all medications must successfully finish a clinical trial program that provides sufficient proof of their efficacy and safety. Here, we'll talk about clinical trials and pharmacovigilance and their relationships. Recent developments and trends have brought about revolutionary changes in pharmacovigilance, a discipline that is essential to guaranteeing the safety of pharmaceutical products. Real-world evidence has broadened the scope of medication safety monitoring by offering insights into the larger patient population. This evidence comes from a variety of sources, including electronic health records and pragmatic studies. Signal detection and predictive analytics have been transformed by artificial intelligence and machine learning, which has improved risk management techniques and expedited the discovery of possible safety issues. Patient safety monitoring is an essential part of the medication development life-cycle. At the lowest stages of medication development, the highest importance is placed on patient safety monitoring since patients must be treated according to their needs and conditions. For the purpose of approaching safety monitoring, such monitoring may be a dynamic process. A proactive and cooperative attitude with all stakeholders is required of pharmaceutical sponsors to guarantee a methodical approach to safety monitoring. The fundamentals of medication safety, regulatory aspects of drug safety, patient appropriateness for trial safety, post-marketing

safety, and causation risk assessment of the drug products are all areas that require our attention throughout clinical trials.

**KEYWORDS:** Pharmacovigilance, Clinical trials, Drug safety, Post-marketing safety, Artificial intelligence.

## 1. INTRODUCTION

Pharmacovigilance is "the pharmacological science relating to the detection, assessment, understanding, and prevention of adverse effects, particularly long term and short-term adverse effects of medicines," according to the definition given. The field of pharmacovigilance is still relatively new in India, and little is known about it.[1] In India, hardly much has been accomplished in the field of pharmacovigilance, despite significant improvements occurring in western nations. The significance of pharmacovigilance and its effects on the product's life cycle must be fully understood. In addition to improving clinical trial safety and post-marketing surveillance, this will make it possible to incorporate strong pharmacovigilance practices into processes and procedures to assist guarantee regulatory compliance. Pharmacovigilance is not new to India; it has been practiced since 1998.[2] When India made the decision to join the adverse event monitoring centre in Uppsala. The media and regulatory bodies have become increasingly aware of the hazards and benefits of medications, which highlights the significance of pharmacovigilance. "Any unfavourable medical event that may occur during drug treatment but is not necessarily related to its use is considered an adverse event".[3] Clinical research includes pharmacovigilance as a crucial and essential component. Safety in clinical trials and post-marketing pharmacovigilance are essential throughout the duration of a product's lifecycle. "An adverse drug reaction is any unpleasant, unexpected, and undesirable side effect of a medication that happens at a dosage used in humans for diagnosis, treatment, prophylaxis, or alteration of physiological function." In order to collect safety data for early detection, spontaneous reporting of adverse drug reactions and events is a crucial tool.[5] One of the most important aspects of the entire drug development life cycle may be safety evaluation.

Pharmaceutical sponsors must provide a sufficient description of the product's security profile in order to receive marketing authorization and regulatory approval.[5] The required details regarding the advantages and hazards of the product are included in the authorized product label. As more information and statistics are obtained from a larger patient group after the product is on the market, ongoing safety vigilance becomes increasingly important.

Sometimes, the initial benefit-risk analyses may be uncertain due to newly developing safety profiles. Some status market withdrawals, including as Troglitazone (Rezulin), Rofecoxib (Vioxx), and Rosiglitazone (Avandia), provide proof of these. Guidelines for risk management activities, including as pre-market risk assessment, post-marketing pharmacovigilance, and pharmacoepidemiologic evaluations, were released by the US Food and Drug Administration (FDA) in 2005.[6]

ADRs are unpleasant and unanticipated medication reactions that happen at levels typically used for disease diagnosis, treatment, or prevention, or for altering physiological function. Pharmacovigilance (PV) is especially concerned with these reactions. To optimize benefits and reduce dangers, it is imperative to continuously monitor pharmacological effects, side effects, contraindications, and overtly adverse effects that may result in a significant degree of morbidity, and in certain situations, mortality. When a drug is marketed and prescribed to huge populations both domestically and abroad, care and caution during the pre-clinical and clinical testing stages can ensure complete safety. At most, thousands of individuals participate in clinical studies, and when a medication first hits the market, its adverse drug reactions (ADRs) and less frequent side effects are frequently unknown.[7] To determine the connections between medications and adverse drug reactions (ADRs), post-marketing pharmacovigilance (PV) use techniques including data mining and case report analysis. It is the duty of drug regulatory bodies to maintain a robust pharmacovigilance (PV) system to track adverse drug reactions (ADRs) both during the drug development stage and later on in a marketed drug's life. Drug safety monitoring involves a wide range of partners, including the government, business, healthcare facilities, hospitals, academic institutions, pharmaceutical and medical associations, poisoning information centres, patients, consumers, and the media. These relationships are intricate and crucial. If PV is to grow and thrive in the face of upcoming challenges, sustained cooperation and dedication are essential.[8]

## 2. Pharmacovigilance

Pharmacovigilance (PV) is "the science and activities relating to the detection, assessment, understanding, and, prevention of adverse effects or any other drug-related problem," according to the World Health Organization (WHO). PV aims to improve patient safety in regard to medication use by offering a mechanism for gathering, evaluating, and disseminating drug safety data.[9] Investigational medicinal products (IMPs) and authorized medications are monitored as part of PV efforts in order to:

- ✓ Identify side effects that were previously unknown.
- ✓ Acknowledge variations in the unidentified negative impacts' frequency and intensity.
- ✓ Evaluate a medication's risk and benefit to see whether any steps need to be taken to increase safety.
- ✓ Verify the correctness of the information conveyed to patients and medical professionals, as well as the timeliness of the data in patient information leaflets (PILs).[9]

Monitoring the effects of medications both before and after they are properly evaluated and put on the market is necessary. Pharmacovigilance is the monitoring and evaluation of pharmaceutical quality as well as the identification and avoidance of any negative medication effects. To comprehend the dangers and advantages associated with a specific medication, pharmacovigilance entails analysing data from patients, pharmaceutical companies, and healthcare professionals. Pharmaceutical companies invest a significant amount of effort and money in creating new medications.[10] PV operations include monitoring approved drugs and experimental pharmaceutical products (IMPs) to: Find any adverse effects that haven't been found yet. Acknowledge that the severity of known side effects varies. Examine a medication's advantages and disadvantages to see if more steps are required to improve safety. Ensure that patient information booklets (PILs) contain up-to-date information and that patients and healthcare professionals are receiving accurate information.[6]

## 3. Aim of Pharmacovigilance

Pharmacovigilance's primary goals for human medications have been determined.[11] and they are:

1. Finding and measuring adverse medication responses that were previously unknown
2. Identification of patient subgroups, such as those based on species, breed, age, gender, physiological state, and underlying disease, that are particularly vulnerable to adverse medication reactions.
3. Continuous evaluation of a product's safety in each species for which it is approved in order to make sure that the advantages and dangers are still tolerable. Monitoring should be expanded to include additional species and indications.
4. Contrasting the adverse reaction profile within and between species with those of products in the same therapeutic class.

5. Identification of improper prescription and administration-in the case of the latter, monitoring of administration by particular groups, such as farmers or the general public, may be necessary.
6. More research on the pharmacological, toxicological, or microbiological characteristics of a product or drug in order to comprehend, if at all feasible, the processes behind adverse drug responses.
7. Drug-drug interaction detection. For new medications that are subsequently taken in combination with well-known goods or even other novel medications, this is especially crucial.
8. Giving veterinarians and other people who handle animals, such as farmers, other animal owners, and veterinarians, the proper information on adverse drug reaction data and drug–drug interaction data.

## 4. Methods involved in Pharmacovigilance

Pharmacovigilance-related activities can be broadly categorized into three groups: academic, industrial, and regulatory. The goal of regulatory pharmacovigilance is to give the public access to medications with a favorable benefit-harm balance. In this context, some of the issues surrounding regulatory post-marketing surveillance will be covered, after which the techniques for identifying novel ADRs will be described, together with an analysis of the benefits and drawbacks of each technique.

### 4.1 Clinical trial data insufficient to evaluate drug risk

Clinical trials are currently the primary means of gathering data on a medicine during the pre-marketing stage. There are three stages to pre-marketing clinical testing. Phase III investigations, which are frequently double blind randomized controlled trials, are thought to be the most thorough method for establishing if a therapy and an outcome are causally related. Nevertheless, this study design is not the best for tracking a drug's safety. The population that a medicine is tested on is another drawback of clinical trials. Therefore, extrapolating the findings from clinical trials to the general population may be challenging because participant characteristics do not always match those of the community in whom they will be employed.[12] This is particularly true for women, members of minority ethnic groups, and the elderly. Careful drug monitoring during the post-marketing phase is crucial for researching unusual ADRs, ADRs with a long latency, and ADRs in particular

groups.[13],[14] Two forms of descriptive studies- spontaneous reporting and intensive monitoring will be discussed here.[15]

### 4.2 Spontaneous reporting

The Australian doctor WG McBride wrote a letter that was published in the Lancet in 1961. In this letter, he reported his finding that children born to moms who had taken thalidomide during pregnancy were more likely to have congenital defects than children not exposed to the drug during pregnancy.[16] It became clear in the next years that the usage of thalidomide by mothers had resulted in the birth of thousands of infants with limb abnormalities. Since their creation, spontaneous reporting systems (SRS) have emerged as the main means of gathering post-marketing data on medication safety. Early detection of signs of novel, uncommon, and dangerous ADRs is the primary purpose of SRS. Physicians and, more frequently, pharmacists and patients can report suspected ADRs to a pharmacovigilance centre through a spontaneous reporting mechanism.

Since their creation, spontaneous reporting systems (SRS) have emerged as the main means of gathering post marketing data on medication safety. Early detection of signs of novel, uncommon, and dangerous ADRs is the primary purpose of SRS. Physicians and, more frequently, pharmacists and patients can report suspected ADRs to a pharmacovigilance centre through a spontaneous reporting mechanism.[17],[18] When indications of novel ADRs appear, the pharmacovigilance centre's job is to gather, evaluate, and notify stakeholders of the possible danger. The pharmaceutical business also uses spontaneous reporting to get data regarding their products. All medications on the market can be monitored for a comparatively small fee over the course of their whole life cycle using an SRS. The primary objection to this strategy is that it may result in underreporting and selective reporting.[19]

### 4.3 In spontaneous reporting, data mining

Signal detection in spontaneous reporting has traditionally mostly relied on case-by-case reports. However, data mining techniques have gained importance in recent years. The process of analysing data from many angles and gleaning pertinent information is known as "data mining." In huge databases, algorithms are frequently employed to uncover hidden patterns of correlations or unexpected events, or signals. Despite differences in approach, all of the data mining techniques used in pharmacovigilance express the degree to which the number of observed instances deviates from the number of expected cases.[20]

The proportion of reports for a particular adverse drug reaction (ADR) reported for a drug is compared to the proportion for that ADR in all other pharmaceuticals using proportional reporting ratios, or PPRs. The computation is comparable to the relative risk calculation. It is also feasible to compute a "reporting odds ratio" using the same data.[21] As of right now, no data-mining technique can tell the difference between known and unknown relationships. Furthermore, a reviewer is still required to analyse these events because clinical information from the case reports is not taken into consideration.

### 4.4 Intensive monitoring

A novel approach to active monitoring was created in the UK (Prescription Event Monitoring) and New Zealand (Intensive Medicines Monitoring Programme) in the late 1970s and early 1980s. These rigorous surveillance methods detect drug users based on prescription data. Any adverse events that occur during the usage of the drug under observation are reported to the drug's doctor. In order to find new signals, these data are gathered and examined. This intense monitoring systems' technique has been thoroughly explained elsewhere.[22],[23],[24],[25]

In contrast to spontaneous reporting, which merely tracks specific medications over a predetermined amount of time, extensive monitoring is based on a non-interventional observational cohort. Because intense monitoring is non-interventional, it offers real-world clinical data that does not involve inclusion or exclusion criteria during the data collection period. Selection bias is eliminated since it is not impacted by the types of exclusion and selection criteria that define clinical studies. The methodology's ability to detect signals for occurrences that were not first thought to be adverse drug reactions (ADRs) of the medicine under study stems from its foundation in event monitoring. Quantification of the risk of specific ADRs is made possible by intensive monitoring programs, which also make it possible to determine the incidence of adverse events. But this strategy also has acknowledged drawbacks. It is unknown what percentage of side effects are not reported to physicians. Additionally, the research yield reported event rates as opposed to actual incidence rates. This holds true for all research utilizing data from medical records, including computer databases and record linking. Standard intensive monitoring studies lack a control group, so it is impossible to determine the actual background occurrence of incidents.[26]

### 4.5 Database studies

A study must be conducted in order to evaluate a hypothesis. Numerous techniques, such as cohort studies and case-control studies, can be used to carry out the investigation. These approaches' drawbacks include research design and power considerations. Data that has been routinely and reliably collected must be available in order to do retrospective cohort and case-control studies. Two distinct categories of European databases are represented by the General Practice Research Database (GPRD) and the PHARMO Record Linkage System, which will be covered in more detail in the upcoming sections. There are more database and record linkage systems available for study in North America and Europe.[27]

### 4.6 General Practice Research Database

In the UK, general practitioners (GPs) oversee essentially all patient care, and information from these sources offers a nearly comprehensive picture of a patient, his conditions, and his course of treatment. About 3 million patients, or roughly 5% of the UK population, have their data collected by GPs who are members of the GPRD in any given year. These patients' age, sex, and regional distribution are all quite typical of the UK population as a whole. Age and sex demographics, medical diagnoses that are part of routine treatment or that come from hospitalizations, consultations, or emergency care, as well as the event's date and location, are among the data gathered. Additionally, free text, hospital and specialist referrals, all prescriptions (including the date of prescription, formulation strength, quantity, and dosing instructions), treatment indications for all new prescriptions, and events that result in the withdrawal of a medication or treatment are all options. Additionally, vaccination data and other information are gathered, including laboratory results, smoking, height, weight, immunizations, pregnancy, birth, death, date of entry into the practice, date of departure from the practice, and other data.[28],[29]

## 5. Pharmacovigilance Terms

### 5.1 Adverse Events Reactions (AERs)

According to the ICH E2A guideline, an adverse event is any "untoward medical occurrence" that occurs to a patient or study participant after they have been administered a pharmaceutical product. This includes any symptoms, such as aberrant test results, that are unfavourable and unanticipated for the patient or subject. These symptoms or illnesses may be temporarily linked to the usage of a medication; they are not always related to the product in the past. They also don't need to be known to be causally related to the treatment plan.[30]

### 5.2 Adverse Reactions (ADRs)

Adverse Reactions are classified by ICH E2A based on the stage of the medication's life cycle. Any "noxious and unintended responses" to the product at any dose are considered adverse reactions if the product has not yet been sold. This classification has the effect of logically proving that a connection between the reaction and the product "cannot be ruled out." Once the product has been placed on the market, “Adverse Reactions” encompass responses which are again “noxious and unintended” but occur at the established routine dosages which have been defined for use in humans to prevent, diagnose, or treat disease or modify “physiological function”. Responses to doses and uses that are not advised are included in some more recent definitions, though.[31]

### 5.3 Serious Adverse Events (SAEs)

These are "any untoward medical occurrence," as the name suggests, that:

1. Is fatal
2. Is a threat to life
3. Results in inpatient hospitalisation
4. Prolongs an existing hospital stay
5. Results in persistence or significant disability
6. Results in a congenital anomaly or birth defect

Depending on their type, events that necessitate action to keep the patient or subject from suffering from any of the aforementioned consequences or that put the patient in danger in any other way should also be categorized as serious. In certain situations, it will be obvious that expedited reporting is appropriate. Suspected infectious agent transmission is also considered a major adverse occurrence in the EU.[32]

### 5.4 Suspected Adverse Drug Reaction (SADRs)

This word, which is covered in ICH E2A and ICH E2D, refers to situations in which there is a plausible chance that the product was the cause of the incident. Since most dangerous drug responses require some sort of additional evidence, like "dechallenge and rechallenge," to be proven, they are always treated as "suspected" rather than "confirmed." This would entail the patient taking the medication, experiencing a reaction, recovering after stopping it, and then taking it once more to confirm the reaction. Rechallenge as a test may be unethical given the seriousness of such reactions, yet it may occur in clinical practice.[33]

### 5.5 Unexpected Serious Adverse Reactions (USARs) and Expected Drug Reactions (EDR)

Any suspected adverse event that is serious and does not match the information on adverse reactions provided in the current investigator brochure1 is considered a Suspected Unexpected Serious Adverse event prior to a product being marketed. Although the investigator brochure may also serve as the reference document for post-marketing studies, unexpected reactions are defined as those whose nature or severity deviates from the undesirable effects listed in the standard product information (Package Insert or Summary of Product Characteristics) after a product has been marketed.[34]

## 6. What is an adverse event?

Any reaction a patient experiences as a result of a medicine or candidate molecule is referred to as an adverse event. A significant adverse event is a potentially fatal side effect that results in hospitalization, incapacity, irreversible harm, or, in the worst situations, patient death. Even if the side effects are just suspected, all clinical study investigators are required to record adverse events.

Pharmacovigilance's job is to figure out which side effects go beyond a medication's limit of effectiveness. That is, weighing the effectiveness of a treatment against the side effects to determine which are worth the risk to patients. Chemotherapy, for example, is known to have some extremely dangerous adverse effects, yet given the chance to treat a patient with life-threatening cancer, these side effects are deemed tolerable.[35]

## 7. Pharmacovigilance in clinical research

Clinical trials that offer information about a drug's advantages and disadvantages are the first step in pharmacovigilance. Pharmacovigilance in clinical research is to ascertain whether the advantages outweigh the dangers; if so, pharmaceutical companies take action to secure authorization to sell the new medication. Before a pharmaceutical company may submit an application for the market authorization of a novel medicine, phase I, II, and III clinical studies are required. The primary point of contact at the trial site for these trials is the principal investigator. They are in charge of carrying out the study and reporting the results. In order to ascertain whether the drug in question was the cause of the serious adverse events (SAEs), the researcher gathers and examines data on SAEs during clinical trials. They are classified as adverse drug responses (ADRs) if they determine that the adverse side effects were the cause.[35]

The pharmaceutical company in charge of the drug's R&D (research and development) receives this data from the investigator. The in-house PV team of the pharmaceutical business evaluates this, and the patient files are reviewed by a physician. The PV team decides whether the medication is safe and effective enough to move on to the following stage of clinical research or to apply for approval to enter the market from the regulatory body. The final say on whether the drug's safety and efficacy characteristics are acceptable rests with these regulatory bodies. If authorized, the pharmaceutical corporation may carry out Phase IV clinical trials to gather more information about a drug's efficacy and safety profile. These studies are useful because they offer information in an uncontrolled setting that is indicative of how patients are taking the medication.[36]

**8. Pharmacovigilance outside of clinical research**

Pharmacovigilance data from clinical research is limited due to study restrictions. PV data from clinical research poorly identifies:

1. Potential drug interactions
2. Long term risk
3. Risks that come from higher doses
4. Dangers that come from drug misuse and abuse.

Therefore, it is essential to update the potential hazards of drugs through continuous PV from consumers and healthcare providers. To keep an eye on the "real world," the pharmaceutical corporation may support post marketing medication safety surveillance, a particular kind of Phase IV study. Efficacy and safety of the product because preapproval studies cannot predict every potential side effect of a medication. There are other strategies that can be used, including electronic health records, drug registries, and spontaneous reporting systems.[37]

**9. Drug discovery and development process**

The thalidomide tragedy in the early 1960s marked the beginning of modern drug safety and pharmacovigilance. After the 1959 release of the medication Thalidomide, which was intended to prevent morning sickness, more than 10,000 children were born with birth abnormalities in 46 different countries. The World Health Organization (WHO) established the Programme for International Drug Monitoring (PIDM) in response to thalidomide. Over 16 million Adverse Event Reports (ADRs) have been gathered by PIDM, which currently has more than 150 participating countries.[38]

The Kefauver-Harris Drug Amendments were voted concurrently by the US Congress in 1962. These regulations were the first to compel pharmaceutical companies to demonstrate the safety of their products before the FDA would allow them to be sold. These modifications marked the beginning of a series of regulatory revisions intended to guarantee solid proof of a drug's efficacy, safety, and chemical purity before it is put on the market. Although the primary reason for drug attrition is a lack of clinical efficacy, a poor safety profile also plays a big role in why medications fail throughout development.

From early drug discovery through preclinical research, clinical trials, and post-marketing surveillance (pharmacovigilance), this can happen at any point in the development process.[39]

### 9.1 Stages of Drug Discovery and Development include

1. Discovery and Development
2. Pre-clinical research
3. Clinical research
4. FDA Review
5. Post Market Drug Safety Monitoring

#### 9.1.1. Discovery and Development

The process of finding novel drugs is called drug discovery. In the past, most pharmaceuticals were discovered by coincidence or by discovering the active compounds in traditional treatments. Afterwards, chemical libraries containing small compounds, natural products, or plant extracts were examined using conventional pharmacology to identify those with therapeutic benefits. Through the cycle below, drug discovery is fuelled by disease processes, molecular compound testing, current treatments with unexpected side effects, and new technology.

These days, drug discovery entails medicinal chemistry, hit screening, and hit optimization to minimize possible adverse drug reactions (raising affinity and selectivity). This stage of the medication development process also enhances oral bioavailability, metabolic stability (half-life), and efficacy or potency.[40]

#### 9.1.1(a) Target Discovery/Identification

Finding the disease's biological cause and possible intervention targets is the first stage in the medication discovery process. Determining the function of a potential therapeutic target

(gene, nucleic acid, or protein) and its role in the illness is the first step in target discovery.[41] Characterization of the molecular pathways that the target addresses come after target identification. An ideal target should be "druggable," safe, effective, and compliant with commercial and clinical standards. Molecular biology, biochemistry, genetics, biophysics, and other fields may serve as the foundation for the target identification methods.[42]

**Approaches**

1. Data mining using bioinformatics: identifying, selecting and prioritizing potential disease targets.
2. Genetic association: genetic polymorphism and connection with the disease.
3. Expression profile: changes in mRNA/protein levels.
4. Pathway and phenotypic analysis: In vitro cell-based mechanistic studies.
5. Functional screening: knockdown, knockout or using target specific tools.[43]

**9.1.1(b) Target Validation**

The process of certifying the intended molecular target, such as a small molecule's gene, protein, or nucleic acid, is known as target validation. Target validation entails creating a drug-resistant mutant of the suspected target and figuring out the structure activity relationship (SAR) of the small molecule's analogues. the presumptive target's overexpression or knockdown; and keeping an eye on the established signalling pathways downstream of the presumptive target.[44]

The process of proving the discovered target's functional significance in the illness manifestation is known as target validation. Although it is very beneficial to validate a drug's toxicity and efficacy in a variety of disease-relevant cell and animal models, the final test is whether the drug functions in a clinical context.[45]

**9.1.1(c) Identification of Lead**

A synthetically stable, practicable, and drug-like molecule that exhibits appropriate specificity, affinity, and selectivity for the target receptor in primary and secondary testing is referred to as a chemical lead. Determining the synthetic feasibility, defining the structure-activity connection, and obtaining initial proof of in vivo efficacy and target engagement are all necessary for this. Characteristics of a chemical lead are:

1. SAR defined
2. Drug ability (preliminary toxicity, hERG)

3. Synthetic feasibility
4. Select mechanistic assays
5. In vitro assessment of drug resistance and efflux potential
6. Evidence of in vivo efficacy of chemical class
7. PK/Toxicity of chemical class known based on preliminary toxicity or in silico studies.

A drug ability assessment is frequently carried out to reduce the number of compounds that fail during the medication development process. When turning a chemical from a lead molecule into a medication, this evaluation is crucial. A chemical must have the capacity to bind to a particular target in order to be deemed druggable; nevertheless, the compound's pharmacokinetic profile which includes its absorption, distribution, metabolism, and excretion is also crucial. The Ames test and the cytotoxicity assay are two other tests that will assess the compound's possible toxicity in screening.[46]

**9.1.1(d) Lead Optimization**

The process of designing a drug candidate following the identification of an initial lead molecule is known as lead optimization. To develop a picture of the relationship between chemical structure and activity in terms of interactions with targets and metabolism, a prospective medication is subjected to an iterative series of synthesis and characterization. Lead optimization is used in early drug discovery to find potential compounds from the leads obtained from hit to lead high throughput screening studies. During lead optimization, the last phase of early-stage drug discovery, potential leads are assessed for a variety of characteristics, such as selectivity and binding processes. Maintaining advantageous characteristics in lead compounds while addressing structural flaws in lead is the aim of lead optimization. The chemical structures of lead compounds (small molecules or biologics) must be changed to increase target specificity and selectivity in order to create a pre-clinical therapeutic candidate. Additionally assessed are toxicological characteristics as well as pharmacodynamic and pharmacokinetic aspects. To properly characterize the molecule and determine the optimization path, labs need to gather information on the toxicity, effectiveness, stability, and bioavailability of leads.[47]

Pharmaceutical and biopharmaceutical drug development labs are increasingly using automated screening technologies. Metabolite identification and measurement are accomplished by the use of mass spectrometry. One important method for quickly and precisely assessing drug candidates and their metabolites in tissue structure is MALDI

imaging. Additionally, NMR Fragment-based Screening (FBS) in the pharmaceutical industry has become a widely applied method for the discovery and optimization of lead molecules in targeted screening campaigns.[48]

### 9.1.1(e) Product Characterization

Size, shape, strength, weakness, use, toxicity, and biological activity are characteristics of any novel pharmacological molecule that exhibits promise therapeutic action. Early phases of pharmacological research are useful for describing the compound's mode of action.

### 9.1.1(f) Formulation and Development

The physicochemical characteristics of active pharmaceutical ingredients (APIs) are described during the pharmaceutical formulation stage of medication development in order to create a dosage form that is stable, bioavailable, and ideal for a particular mode of administration.

## 9.2 Preclinical Research

The examination of a medicine's safety and effectiveness in animal species that leads to potential human outcomes is known as pre-clinical research in the drug development process. Additionally, the relevant regulatory bodies must approve the pre-clinical investigations. Only medications that have been proven to be both safe and effective will be approved by the regulatory bodies, who must also make sure that trials are carried out in an ethical and safe manner. A set of fundamental guidelines for the technical requirements of acceptable preclinical drug development has been established by ICH.[49]

The pre-clinical trials can be conducted in two ways: a) General pharmacology and b) Toxicology.

**a) Pharmacology:** The pharmacokinetic and pharmacodynamic characteristics of drugs are the focus of pharmacology. Unwanted pharmacological effects must be investigated in appropriate animal models and tracked in toxicological investigations. To determine the safety and effectiveness parameters in terms of absorption, distribution, metabolism, and excretion, pharmacokinetic studies are crucial. These studies provide data on the rate of absorption for various routes of administration, which aids in the distribution, metabolism, and excretion rates, as well as the choice of dose form, all of which affect the drug's half-life.[50]

**b) Toxicology:** In-vitro and in-vivo tests that assess the drug's toxicological effects can be used to conduct toxicological research. To examine the direct impact on cell proliferation and phenotypic, in-vitro experiments can be conducted. Toxicological effects can be determined both qualitatively and quantitatively by in-vivo research. Choosing the right animal species for toxicity research is crucial because many medications are species specific. Clinical studies frequently use in-vivo research to assess pharmacological and toxicological properties, including mode of action, to bolster the product's suggested use.[51]

### 9.2.1 The Investigational New Drug Process (IND)

Before starting clinical testing, drug developers must submit an application to the FDA for an investigational new drug.[52] In the IND application, developers must include:

1. Preclinical and toxicity study data
2. Drug manufacturing information
3. Clinical research protocols for studies to be conducted
4. Previous clinical research data (if any)
5. Information about the investigator/ developer.[53]

### 9.3 Clinical Research

In order to provide specific answers regarding the safety and effectiveness of medications, vaccines, other therapies, or novel approaches to use existing treatments, clinical studies are carried out on volunteers. A particular study protocol created by the manufacturer, researcher, or investigator is followed during clinical trials. Before clinical research commences, the developers must go through the Investigational New Drug Process (IND), which they will do as they plan the clinical study, taking into account what they intend to accomplish for each of the many Clinical Research Phases. Researchers create study questions and objectives by reviewing existing data regarding the medication before a clinical trial starts.[54] Then, they decide:

1. Selection criteria for participants
2. Number of people take part of the study
3. Duration of study
4. Dose and route of administration of dosage form
5. Assessment of parameters
6. Data collection and analysis.

### 9.3.1 Phase 0: Clinical Trial

Phase 0 refers to first-in-human (FIH) investigations that are carried out in compliance with FDA regulations. In addition to being known as human microdose studies, phase 0 trials involve administering single subtherapeutic doses to 10–15 volunteers in order to get pharmacokinetic data or assist in imaging certain targets without utilizing pharmacological activities. Phase 0 investigations are conducted by pharmaceutical companies to determine which of their medication candidates has the best human pharmacokinetic characteristics.[55]

### 9.3.2 Phase 1: Safety and dosage

Phase I trials are the initial drug studies that involve fewer healthy human participants. Phase 1 typically involves 20 to 80 healthy volunteers who have the illness or condition. Patients are often only utilized when a drug's mechanism of action suggests that healthy individuals will not tolerate it. However, researchers perform Phase 1 trials on individuals with that type of diabetes if a new medication is suggested for use in those people. Phase 1 investigations gather data on pharmacodynamics in the human body under strict observation. To determine what amount of a drug the body can tolerate and what are its acute side effects, researchers modify the dosing schedule based on data from animal studies. As a Phase 1 trial progresses, scientists learn more about the effectiveness, adverse effects that come with increasing dosage, and the mechanism of action. This is essential to Phase 2 study design. Nearly 70% of medications advance to the following stage.[56]

### 9.3.3 Phase 2: Efficacy and side effects

Larger patient groups (few hundreds) participate in phase II trials, which are intended to test the drug's effectiveness and withstand Phase I safety evaluations. To determine if the medication will be therapeutic, these studies are insufficient. Researchers can obtain more safety information from phase 2 investigations. These data are used by researchers to create new Phase 3 study procedures, improve research topics, and build research methodologies. Roughly one-third of medications advance to the next stage. The most significant contribution of Phase II clinical investigations is the discovery of therapeutic dosages for the extensive Phase III research.[56]

### 9.3.4 Phase 3: Efficacy and adverse drug reactions monitoring

Phase 3 studies are planned by researchers to demonstrate whether or if a product offers a particular action advantage to a particular person. These studies, which include 300–3,000 people, are sometimes referred to as pivotal studies. The majority of the safety data is

provided by phase 3 trials. Less frequent adverse effects might have gone undetected in the earlier trial. However, because phase 3 studies are longer and involve a larger number of volunteers, the findings are more likely to identify rare or long-term negative effects. About 25–30% of medications advance to the following stage of clinical trials. The industry can submit an application to commercialize a medication if a drug developer provides evidence from preclinical, clinical, and prior testing that the medication is safe and effective for its intended use. After carefully reviewing all of the drug's submitted data, the FDA review team decides whether or not to approve it.[57]

### 9.3.5 New Drug Application

The complete story of a therapeutic molecule is expressed in a New therapeutic Application (NDA). Its goal is to confirm that a medication is both safe and effective for the intended use in the subjects of the study. All information regarding a medicine, from preclinical data to Phase 3 trial results, must be included in the NDA by the drug developer. Developers are required to provide reports on all research, data, and analysis.[58] In addition to the results of clinical trials, developers need to include:

1. Proposed labelling
2. Safety updates
3. Drug abuse information
4. Patent information
5. Institutional review board compliance information
6. Directions for use.
7. Proposed labelling

## 9.4 FDA Review

The FDA review panel may need six to ten months after receiving a completed NDA before making a decision regarding whether to approve it. If the FDA team of review receives an incomplete NDA, they will reject it. Working with the developer to update prescribing information is crucial if the FDA determines that a medicine has been found to be safe and effective for its intended use. We refer to this as "labelling." The label clearly outlines the criteria for approval and provides instructions on how to use the medication. However, there are still problems that need to be resolved before the medication can be authorized for sale. In other situations, the FDA requires more research. The developer can decide at this point

whether or not to carry out additional work. There are procedures for filing an official appeal if a developer disagrees with an FDA ruling.[59]

### 9.5 Post-Market Drug Safety Monitoring

After the FDA has approved a medicine or device, phase 4 studies are carried out. These studies are also known as post-marketing surveillance, which includes ongoing technical support and pharmacovigilance following clearance. Phase 4 trials employ a variety of observational techniques and evaluation patterns to gauge the safety, cost-efficiency, and effectiveness of an intervention in real-world situations. The regulatory authorities may mandate phase IV studies. As a result, the months and even years that make up a drug's shelf life are crucial for providing a realistic picture of its safety. The FDA may choose to include precautions in dose or practice advice, as well as other events for more severe adverse drug responses, after reviewing reports of problems with both prescription and over-the-counter medications.[60]

## 10. CONCLUSION

In order to face the challenges presented by the ever-increasing variety and strength of medications all of which entail an unavoidable and occasionally unanticipated potential for harm pharmacovigilance is essential. When toxicity and negative consequences do manifest, particularly when they were previously unknown, it is crucial that they be documented, examined, and their importance clearly conveyed to the audience who are equipped to understand the material. Every medication has a trade-off between its possible advantages and disadvantages. By making sure that medications of high quality, safety, and effectiveness are used sensibly and that the patient's expectations and concerns are taken into consideration when therapy decisions are made, the harm can be reduced. In order to accomplish this, it is necessary to promote public health, ensure that drug use risks are anticipated and managed, improve communication between the public and health professionals, educate health professionals about the effectiveness or risk of the medications they prescribe, and help patients develop a sense of trust in the medications they use. This will increase patients' confidence in the health service as a whole. The fundamental foundation of pharmacovigilance is the qualitative and quantitative analysis of reports of spontaneous adverse drug reactions, which is then followed by a clinical evaluation or assessment of the effect on the medicine's overall safety profile. In order to enhance patient care and lower the possibility of adverse side effects, pharmacovigilance makes sure that clinical medications

are rigorously tested. PV is present at every stage of a drug's lifecycle and confirms its efficacy and safety.

## 11. Conflict of Interest

There are no conflicts of interest for the authors and co-authors in relation to this research purposes. This thesis paper's writing and content are solely the authors' responsibility.

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