Module 2 – Pharmacovigilance Methods - Drug discovery onwards

Contents

List of Abbreviations

ADME	Absorption, Distribution, Metabolism, Excretion
ADR	Adverse Drug Reaction
AE	Adverse Event
CRO	Clinical research organizations/ Contact research organizations
EMA	European Medicines Agency
EU	European Union
FDA	Food and Drug Administration
IITs	Investigator-initiated trials
IND	Investigational New Drug
MA	Marketing Authorization
NDA	New Drug Application
PEM	Prescription Event Monitoring
SAE	Serious Adverse Event
SUSAR	Serious Unexpected Serious Adverse Reaction
US	United States

1. Premarketing Pharmacovigilance

Introduction

To obtain approval to market a new drug in the United States (US), Canada, the European Union (EU), and most other countries, a series of clinical trials on patients is required. Drug discovery and development is long, costly and complex process, requiring coordinated collaboration of different Teams which includes research, development, manufacturing, medical, regulatory, marketing and business management. Clinical research is an indispensable part of drug discovery process. The scope and duration of these trials will vary widely, depending on the nature of the drug and its therapeutic application. Clinical trials on patients in the different countries are approved and monitored by different regulatory agencies.

After the appropriate pharmacology and toxicology testing in vitro and in animals, development of small-scale and sometimes (even at this early stage) larger-scale manufacturing procedures, and other preparatory testing, the drug is ready to be used in humans in the so-called first in man, or first in humans, study. In the US, a company (sometimes an individual or an academic center) submits an Investigational New Drug Application (IND) to the Food and Drug Administration (FDA) (or the equivalent to a health authority outside the US) containing the preparatory data. IND application contained results of preclinical testing, candidate drug's chemical information, manufacturing information and detailed clinical trial plan. This is, in most cases, data that are proprietary and not available to the public. In addition, the submitter includes in the package a protocol for a clinical trial in humans. The FDA reviews the application to make sure people participating in the clinical trials will not be exposed to unreasonable risks.

Drug trials are heavily regulated, and multiple layers of protections and precautions have been developed to protect the patients. These include investigational review boards, data safety monitoring boards, sponsor and health authority scrutiny, and some level of public notification and publicizing of the study on the internet (clinical trial registries).

Clinical Trial is a systematic study of new drug (s) in human subject (s) to generate data for discovering and/or verifying the clinical, pharmacological (Pharmacokinetic and Pharmacodynamics), and/or adverse effects with the objective of determining safety and /or efficacy of a new drug

The need for Clinical Trials is:

- ✓ To evaluate new drugs, medical devices, biologics or other interventions on patients in strictly scientifically controlled settings
- ✓ Required for regulatory authority approval of new therapies.
- ✓ To assess the safety and efficacy of an experimental therapy
- ✓ To evaluate whether the new intervention is better than standard therapy
- ✓ To compare the efficacy of two standard or marketed interventions

Trials are divided into four phases, although there is usually some overlap.

1.1 Phase I

Phase I trials belong to human pharmacology, in contrast to animal pharmacology. These are the first steps in determining the profile of both the beneficial and the untoward effects in humans. They are designed mainly to find the maximum tolerated dose and the pathways for metabolizing and eliminating the drug. Safety is more important in this phase than efficacy. The first study is often a single-dose trial in a small number (e.g., a dozen) of healthy, often male (to avoid any possible pregnancy issues), volunteers. If tolerated, a multiple-dose study and a rising-dose study follow. The aim of phase I trials is to study absorption, distribution in the body, metabolism, and excretion (so-called ADME studies) as well as safety and toxicity.

Other things that may be examined include the proposed formulation to be used in subsequent trials and marketing (as they may be different) and the dosing frequency or schedule. Drug interaction studies may be done in phase I or later in phase II. If the drugs are known to be toxic or have severe and predictable Adverse Drug Reactions (ADRs), these studies are often done for ethical reasons in patients with the disease to be treated rather than in healthy volunteers (e.g., cancer chemotherapy or Acquired Immunodeficiency Syndrome). Each study is short, often running no more than a few days to a few weeks at

most. The trial design is usually simple and open label. They may or may not be controlled. Several phase I studies often take a year or so and may include around 100 patients in total.

There is usually no benefit to the subjects in the trial, and they participate either because of generosity of spirit or because they are paid. Because there is no gain to the individual subjects, all efforts are made to minimize the risk of toxicity. Serious adverse events are usually rare in phase I trials. Subjects are often "housed" for these studies in special clinical research centers run by academic medical centers or clinical research organizations (CROs).

Note that the term "subjects" in this context usually refers to "normal people," not patients. The term "patients" is usually used to refer to people with the disease in question and not "normal" people. Hence, phase I trials usually involve healthy subjects, and phase II, III, and IV trials involve patients. This distinction is not always followed, and some use the terms interchangeably.

Adverse events (AEs) seen in phase I trials are always noteworthy because the subjects are usually normal and a low starting dose of the drug in question is usually used.

Because few subjects are studied in phase I, any AE should be investigated thoroughly. Serious Adverse Events (SAEs) and the rare death seen in phase I trials should be looked at immediately, and if the event is severe, stopping further dosing or enrollment should be considered. Note that the FDA now requires all serious AEs (whether labeled or not, whether felt to be due to the drug or not) to be submitted as expedited reports. In addition to the toxicity of the drug preparation, subjects have been known to hide serious medical problems or medical history to participate in the study, especially if the subjects are compensated.

1.2 Phase II

Phase II trials are done after the drug has successfully passed through all or parts of phase I trials. Phase II trials are usually performed in patients afflicted with the disease for which that drug was developed. Whereas phase I trials are usually done for safety, phase II trials are done for both efficacy and safety. The goal is to find the minimal effective dose that

retains efficacy with the minimum of AEs. These studies may also continue the Absorption, Distribution, Metabolism, Excretion (ADME) investigations of phase I as well as develop safety and efficacy markers and tests for subsequent larger phase III trials. The studies may include up to hundreds of patients and are usually double blinded. They may run several weeks or months.

Sponsors and investigators participating in phase II trials must pay attention to toxicity because unexpected SAEs and even deaths may occur. Severe and unexpected toxicity may force the immediate stopping of the study or a midstream alteration of the protocol and informed consent to decrease toxicity. Patients in phase II trials usually are not compensated for their participation. Special studies may be done in phase I, II, III, or IV, such as drug-interaction studies (sometimes in healthy volunteers, sometimes in patients with the disease), food or alcohol interaction studies, and evaluation studies in renal failure or liver failure patients. These special studies, however, are usually required for the Marketing authorization (MA) or New Drug Application (NDA) submission and so must be done at some point. Some drugs or products (e.g., oncology drugs or herbals) may not fully undergo phase I and phase II testing as is classically done and as described above. Oncology drugs, which are often very toxic, are rarely studied in normal subjects but are used directly in patients with malignancy. Similarly, “orphan drugs,” which are drugs developed for rare diseases, may undergo abbreviated testing.

1.3 Phase III

Phase III is often divided into phases IIIA and IIIB. Phase III trials include hundreds to thousands of patients, and the whole phase may take several years to complete, depending on the treatment duration and outcomes of the disease studied. Each individual trial may include multiple sites on one or more continents and run months to a year or more. (Survival studies may take even longer because the study does not end until the last patient dies.) The goal is regulatory approval to market the drug.

Phase IIIA trials are usually the key (the old term is “pivotal”) studies to be submitted for regulatory approval, and they are incorporated in the NDA submission or “MA dossier.” The design used in these trials is usually double blind, but many other varieties are used. Depending on the drug and disease under study, the comparator is either the known and accepted therapy called the “standard of care” (e.g., obligatory in almost all cancer, infection, severe pain trials) or placebo (e.g., in treating mild headache or nasal congestion). In some cases, the FDA and other agencies may require a placebo- controlled trial.

This is becoming more and more controversial in terms of the ethics of using placebo. Many health agencies often prefer trials against the standard of care rather than placebo.

Although both have a place in drug development, placebo trials are felt to be less and less acceptable. Phase IIIB trials are additional (usually) large-scale studies that may be started during the examination of the initial dossier by the health agency (the reviewing process) and may end before or after the approval for marketing (NDA or MA). Because the total elapsed review time by the health agency may take a year or more, sponsors may continue studies during this review period.

These studies may focus on pharmacoeconomic or risk evaluation issues as well as cost-effectiveness and studies against competitor drugs. Sometimes surprising or unexpected results of phase IIIA studies force late changes in phase IIIB studies. As most products now have full life cycle risk evaluation and management programs in place, additional testing may be added to phase III trials to evaluate risks that are unclear or that need further evaluation.

By doing such testing in phase III, it may be possible to achieve more rapid marketing approval though post-marketing studies, and other commitments for risk evaluation, management, and mitigation may continue in phase IV.

Sponsors and investigators participating in phase III trials continue to focus on unexpected SAEs, deaths and other SAEs. Since the sample size is bigger in Phase III every effort is made to determine the frequency of SAE's and to characterize the SAEs from a severity perspective. Therefore, from a pharmacovigilance perspective, larger scale studies are preferable to more fully establish the safety profile of any drug.

However, there are inevitable limitations. Clinical studies conducted prior to drug registration usually do not include sufficient patients to identify uncommon or rare adverse reactions; include specific inclusion and exclusion criteria; do not mirror real life post-marketing scenarios; the frailest patients and various populations (e.g. women, ethnic minorities) may be under-represented; and the duration of treatment may be limited. Thus, there is a need for pharmacovigilance activities to continue after a medicine is marketed and is referred to as Post Marketing Pharmacovigilance.

1.4 New Drug Application

Through the NDA application, pharmaceutical companies formally propose that the FDA to approve a new pharmaceutical for sales and marketing. The goals of the NDA are to provide enough information to permit FDA reviewer to reach the following key decisions:

- Whether the drug is safe and effective in its proposed use(s), and whether the benefits of the drug outweigh the risks.
- Whether the drug's proposed labeling (package insert) is appropriate, and what it should contain.
- Whether the methods used in manufacturing the drug and the controls used to maintain the drug's quality are adequate to preserve the drug's identity, strength, quality, and purity.

1.5 Pharmacovigilance Activities

Pharmacovigilance activities during this stage of drug development are not extensive as those conducted during the post marketing phase. The primary reason for this is that during the drug development stage the molecule is evaluated in a controlled environment and is not exposed to the entire population. Moreover, the molecule is only studied for a limited period of time.

Nevertheless, there is a vast amount of critical safety data generated during the drug development stage. And while the molecule may gain MA for one indication, there may be developmental activities ongoing for other indications. This makes it all the more important to collect, collaborate and construct the safety profile of the molecule or the drug as the case may be.

Specifically, is a summary of the activities performed during the drug development stage:

- The SAE/Serious Unexpected Serious Adverse Reaction (SUSAR) Collection & Reporting
- AE Collection
- Authoring and Reporting of the Developmental Safety Update Reports
- Preparation of the Developmental Safety Profile of the molecule and ongoing monitoring of the safety profile through co-relation with the non-clinical and clinical findings, structure activity relationship, mechanistic action of the drug and class effect.
- Modification of the Clinical developmental plans, clinical study protocols, investigator's brochure, informed consent forms, Investigator notifications based on the updated safety data.
- Work closely with the medical monitoring teams and ensuring the health, safety and wellbeing of the participating subjects/patients.

2. Post Marketing Pharmacovigilance

Pharmacovigilance methods deployed during the post marketing stage are even today the main stay for decision making and action.

The primary reason for this is that vast numbers of patients consume the drug in a relatively short period of time. Also, the post marketing set up is a real-life scenario.

Principles of epidemiology are applied when designing these methodologies. Post marketing pharmacovigilance activities are classified as Active Methods, Passive Methods and Other Methods.

2.1 Active Methods:

- **Cohort Event Monitoring (CEM)/Prescription Event Monitoring (PEM):** This is a prospective observational cohort study of adverse events associated with one or more medicines. This monitoring is deployed alongside routine clinical practice and aims at detecting early warnings and precautions typically in the early stages of marketing.

  Government nominated institutes are usually involved in this activity.

  Example: Drug Safety Research Unit (DSRU) in the United Kingdom has been instrumental in running a number of PEM studies and has supported decision making of the MHRA and other regulatory authorities on various safety issues.

- **Registry:** A registry is a record of patients with same characteristics. A registry captures information on standardized questionnaires.
  A registry is used to measure disease burden (disease registry), monitor safety of drug or device (drug/device registry) or monitor the outcome of pregnancy when receiving a certain drug.
- **Record Linkage:** is a method of assembling information contained in two or more records. Health records are linked to the safety assessment of medicines and are useful for studying the long-term impact of drugs.

These methods can be typically used in closed settings such as hospitals or specific regions but are seldom used.

2.2 Passive Methods:

- **Spontaneous Reporting:**

  While there are the various methods within post marketing pharmacovigilance the Spontaneous Reporting methodology has been traditionally the mainstay for the collection of safety data.

  This method relies on collection of safety data spontaneously from healthcare professionals or consumers. It is an unsolicited communication by a healthcare professional or consumer that describes one or more Adverse Drug Reaction (ADR) in a patient who was given one or more medicinal product and is not derived from an organized data collection scheme or trial or study.

- **Targeted Reporting:** These are methods used to know more about the ADR profile of a specific medicine in the population or to estimate the incidence of a known ADR for a specific medicine in a population

- **Intensified Reporting:** An extension of the spontaneous reporting and aims to enhance the ADR reporting of specific medicines in the early post marketing phase.

2.3 Other Methods

- **Phase IV**

Phase IV studies include different types of studies. They are done after the approval and marketing of the drug.

Note that a drug may not always be marketed immediately after approval. Sometimes the company receiving the approval may choose to sell or out-license the drug, or timing may make it wiser to wait (e.g., new seasonal allergy drugs should be marketed near the time for the allergy season to hit). The health authority may require that certain phase

IV studies be done as “commitments” immediately after marketing as a requirement of marketing approval. This may be done to clarify some safety and efficacy issues that remained after phase III but which the health agency believed were not sufficient to prevent or delay marketing of the drug. In the United States, the FDA now has the legal authority to require phase IV commitments, including Risk Evaluation and Mitigation Strategies (REMS) and formal clinical or observational studies. Similarly, the European Medicines Agency (EMA) and member states may require further studies in their Risk Management Plans (RMPs). Failure to perform such tasks may result in penalties to the company or even withdrawal or limitation of the marketing approval.

Phase IV studies may also be marketing or pharmacoeconomic studies to aid in selling the product by studying head-on comparisons with competitor drugs. They may be studies looking at subgroups of the approved group and indication (e.g., testing a drug approved for diabetes on diabetics who are elderly or are also in heart failure).

They may be done in children, not only to evaluate the usefulness and safety but also to obtain, in various markets, additional patent exclusivity.

Phase IV studies may be done for specific safety reasons to investigate an AE or a signal that has unexpectedly occurred after marketing. Such studies may be classical clinical trials, or they may be observational or epidemiologic studies done in large databases. The design and size are very variable, ranging from small open-label trials to massive, multicenter, double-blind comparator trials or “large simple safety studies” with simple protocols and minimal record-keeping. Sometimes patients are compensated for participation.

So-called market-driven phase IV “seeding studies” are now forbidden in most parts of the world. These were pure marketing projects designed to encourage physicians to prescribe a particular product in place of a competitor’s product. A protocol was usually written (to justify calling the endeavor a study) but was often of poor quality.

Results were not always collected by the sponsor and, if collected, were often not analyzed. Prescribers were sometimes compensated. In a more subtle way, postmarketing trials for entirely legitimate purposes may include elements aimed at

getting physicians to use the new drug in place of another product ("stealth seeding trials"). By doing this, the prescriber becomes familiar with the product, and the company hopes he or she will prescribe it for other patients after the trial is completed.

- **Late Phase Studies**

A term that has appeared in the last few years is late phase studies, referring to the grab bag of requirements that agencies and companies are doing both for registration, risk, and marketing reasons. They include registries (product, disease, safety/ADR), postmarketing observational studies, classic phase IV trials as discussed earlier, clinical effectiveness trials, Over The Counter (OTC) trials, community-based trials, health economic and outcomes studies (retrospective, prospective, observational), cost effectiveness, burden of illness, patient reported outcome (PRO, quality of life [QoL], chart review, survey (physicians, patients), health economic piggyback trials, risk management, expanded access, drug safety, and others.

- **Investigator-Initiated Trials or Studies**

Investigator-initiated trials (IITs) or studies (IISs), also called investigator-sponsored trials (ISTs), are usually new ideas thought up by researchers in the academic world or occasionally suggested by the pharmaceutical company. New uses or ways of administering drugs are frequently proposed by academic researchers to pharmaceutical companies. Many companies actually have physicians, PhDs, or pharmacologists on staff (often called "medical liaisons") who travel to academic medical centers and seek out such clever new uses. Such trials are usually done at single centers. Sometimes the investigator will come up with the idea and approach the company (sponsor or patent holder) for assistance with either a grant or product supply (especially if the product is costly).

This type of study can be instrumental in the scientific development of a drug. The advantages of IITs are that new ideas are found and explored, costs are usually fairly small, and the studies can be done fairly quickly. The disadvantage is that many details that should be determined before the trials are not addressed (e.g., effective dose and safety in this population). An IIT that fails usually ends that idea. Thus, if too low a dose

is chosen, one might never know that a higher dose would produce positive results. Funding is usually from the pharmaceutical company in the form of a grant-in-aid, drug supply, protocol, or case report form support. A contract or agreement is usually signed by both parties. The legal sponsor of the study is not the pharmaceutical company but rather the investigator. It is he or she who opens the IND with the FDA or the equivalent in other countries (often with the help of the pharmaceutical company). The usual safety provisions are followed: Good Clinical Practices, investigational review boards, and SAE reporting to the health agency by the investigator. Note that FDA in its 2011 IND regulatory rules requires the investigator/sponsor to handle safety reporting to the FDA, IRB etc. as if he/she were a sponsor such as a pharmaceutical company. Most pharmaceutical companies also require the investigator to report SAEs to the company (in addition to the health authority) so that the company maintains a full safety database for all uses of a product. It is less clear from FDA regulations whether the pharmaceutical company should also submit the cases if the company receives them from the investigator of an IIT who is required to submit them directly to FDA. These trials would technically be phase I if a new indication, formulation, or delivery is being studied. If not, they would most probably be considered phase IV trials. Not all studies require an IND (if the use of the drug is fully covered within the approved labeling).

Such studies usually have to be registered with the appropriate health authority and clinical trial database (e.g., clinicaltrials.gov in the United States and EudraCT in the European Union).

Phases in Clinical Trials

	Objective	Duration	Population	Sample Size
Phase I Human Pharmacology	Determine the metabolic and pharmacological actions and the maximally tolerated dose	Upto 1 month	Healthy volunteers or individuals with the target disease (such as cancer or HIV)	20-100
Phase II Therapeutic Exploratory	Evaluate effectiveness, determine the short-term side effects and identify common risks for a specific population and disease	Several months	Individuals with target disease	100-500
Phase III Therapeutic Confirmatory	Obtain additional information about the effectiveness on clinical outcomes and evaluate the overall risk-benefit ratio in a demographically diverse sample	Several Years	Individuals with target disease	Hundreds to thousands
Phase IV Post-marketing trials/studies	Monitor ongoing safety in large populations and identify additional uses of the agent that might be approved by the regulatory authority	Ongoing (following approval)	Individuals with target disease, as well as new age groups, genders, etc.	Thousands