IJCRT.ORG ISSN : 2320-2882

INTERNATIONAL JOURNAL OF CREATIVE RESEARCH THOUGHTS (IJCRT)

An International Open Access, Peer-reviewed, Refereed Journal

PHARMACOVIGILANCE

Ms.Sonali Mali[1], Ms.Pranali Patil[2], Ms.Tejaswini Shinge[3], Mr.Vaibhav Randive[4], Mr.Pravin Patil[5].

Nootan College of Pharmacy, Kavathemahankal, Sangli, Maharashtra

Abstract:

Pharmacovigilance (PV) plays a key role in the healthcare system through assessment, monitoring and discovery of interactions amongst drugs and their effects in human. For safety of medication ADRs monitoring required for each medicine throughout its life cycle, during development of drug such as pre-marketing including early stages of drug design, clinical trials, and post-marketing surveillance. PV is concerns with the detection, assessment, understanding and prevention of ADRs. PV analysis conducted in Phase I, Phase II, and Phase III clinical trials gives drug companies' data on the drug's safety profile. On the basis of different criteria such as commercial availability, selling of drug we select the ant diabetic drug from BCS classification (Biopharmaceutical Classification System) and identify that the Sitagliptin is medicine which is prescribed widely from this class by approaching pharmacy stores. And also monitor the ADR of selected sitagliptin medicine and prepared a ADR monitoring form. We visit the nearest hospital and take a patient interview for identification of unreported ADR.

Keywords: Pharmacovigilance, Clinical trial, ADR, BCS, Ant diabetic, Sitagliptin.

Introduction:

WHO medicine monitoring was laid in 1971 during the 20th world health assembly established National pharmacovigilance center with WHO collaboration. Pharmacovigilance refers to the wisdom and conditioning related to the discovery, evaluation, understanding, and forestallment of adverse medicine responses and other medicine- related safety issues. In relation to this general description, the introductory end of pharmacovigilance is to help detriment caused by adverse goods in humans arising from the use of medical products within or outside the terms of the marketing authorization and in relation to the life cycle of these medical products.[1] The main thing of pharmacovigilance is thus to support the safe and effective use of medical products, in particular by furnishing timely information about the safety of medical products to cases, healthcare workers and the public. Pharmacovigilance is thus an exertion contributing to the protection of cases and the preservation of public health. The top part of pharmacovigilance is to insure the safer operation of medicines . But the pressure is adding on this field to dissect data about the adverse effect, cover threat more astronomically, and directly reports patient events. Pharmacovigilance remains a dynamic clinical and scientific discipline. It continues to play a pivotal part in meeting the challenges posed by the ever adding range and energy of drugs, all of vitamins changeable implicit for detriment. When adverse goods and toxin do appear especially when preliminarily unknown it's essential that these are reported, analyzed and their significance communicated effectively to an followership that has the knowledge to interpret the information.[2]

Pharmacovigilance (PV) plays a key role in the healthcare system through assessment, monitoring and discovery of interactions amongst drugs and their effects in human. For safety of medication ADRs monitoring required for each medicine throughout its life cycle, during development of drug such as pre-marketing including early stages of drug design, clinical trials, and post-marketing surveillance. PV is concerns with the detection, assessment, understanding and prevention of ADRs. PV analysis conducted in Phase I, Phase II, and Phase III clinical trials gives drug companies' data on the drug's safety profile. On the basis of different criteria such as commercial availability, selling of drug we select the ant diabetic drug from BCS classification (Biopharmaceutical Classification System) and identify that the Sitagliptin is medicine which is prescribed widely from this class by approaching pharmacy stores. And also monitor the ADR of selected sitagliptin medicine and prepared a ADR monitoring form. We visit the nearest hospital and take a patient interview for identification of unreported ADR.[3]

History and Overview of Pharmacovigilance:

1848: fifteen-year-old Hannah Greener dies under chloroform during a surgical procedure to remove an ingrown toenail. Chloroform had been brought into use in clinical practice the previous year, replacing ether, which caused more intense nausea and vomiting;
1937: sulfanilamide elixir leads to the poisoning of more than one hundred people in the USA;
1938: the United States Congress passes the Federal, Drug and Cosmetic Act;
1955: acetylsalicylic acid is confirmed as a cause of gastrointestinal diseases;
1961: a letter from an Australian doctor, William McBride, is published in the "The Lancet". His subject is the increased frequency of malformed lower limbs in babies born to women who took thalidomide during pregnancy;
1964: the UK launches the Yellow Card scheme for the spontaneous reporting of adverse drug reactions;
1965: Council Directive 65/65/EEC of 26 January 1965 on the approximation of provisions laid down by Law, Regulation or Administrative Action relating to proprietary medicinal products is introduced;
1968: the World Health Organisation institutes its Programme for International Drug Monitoring;
1995: the European Medicines Agency is established;
2001: the EudraVigilance database is created;
2012: Directive 2010/84/EU of the European Parliament and of the Council of 15 December 2010 amending, as regards pharmacovigilance, Directive 2001/83/EC on the Community code relating to medicinal products for human use;
2017: the new EudraVigilance system is launched.[4]

❖ Clinical trials:

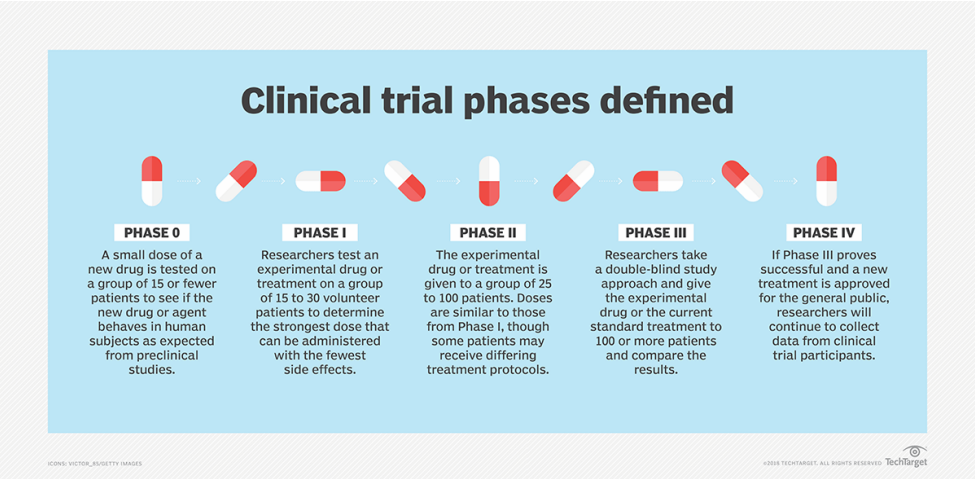
The World Health Organization (WHO) defines a clinical trial as "any exploration study that prospectively assigns mortal actors or groups of humans to one or further health- related interventions to estimate the goods on health issues. Interventions include but aren't confined to medicines, cells and other natural products, surgical procedures, radiological procedures, bias, behavioral treatments, process- of- care changes, preventative care etc. "

Importance of clinical trials:

Clinical trial is the mainstay for bringing out new drugs to the market. Clinical trials can vary in size and cost, and they can involve a single research center or multiple centers, in one country or in multiple countries. Costs for clinical trials can range into the billions of dollars per approved drug. Clinical trials are important because they improve medical research in terms of usefulness and safety. They teach investigators what does and does not work when analyzing new ways to detect, diagnose and treat disease. A clinical trial can also determine what side effects are associated with the drug; how to best manage these side effects; if the drug has any undesirable interactions with food, drink or other drugs; and how these effects can be avoided.[5]

Phases of clinical trials

The phases of clinical exploration are the stages in which scientists conduct trials with a health intervention to gain sufficient substantiation for a process considered effective as a medical treatment. Clinical trials involving new medicines are generally classified into five phases. Each phase of the medicine blessing process is treated as a separate clinical trial.[6]



Phase 0:

Researchers test an experimental drug or treatment with a small group of volunteers, from 10 to 15 patients. Phase 0 also referred to as Early Phase I. Even though phase 0 studies are done in humans, this type of study isn't like the other phases of clinical trials. Phase 0 trials are optional first-in-human trials. Single sub therapeutic doses of the study drug or treatment are given to a small number of subjects (typically 10 to 15) to gather preliminary data on the agent's pharmacodynamics (what the drug does to the body) and pharmacokinetics (what the body does to the drugs?). For a test drug, the trial documents the absorption, distribution, metabolization, and clearance (excretion) of the drug, and the drug's interactions within the body, to confirm that these appear to be as expected.

Aim: pharmacokinetic and pharmacodynamic particularly oral bioavailability and half life of the drug.

Purpose: The purpose of this phase is to help speed up and streamline the drug approval process. Phase 0 studies may help researchers find out if the drugs do what they're expected to do. This may help save time and money that would have been spent on later phase trials.[5]

Phase I:

Researchers test an experimental drug or treatment with a small group of volunteers, from 20 to 80 patients. Phase I studies are done to find the highest dose of the new treatment that can be given safely without causing severe side effects. These studies also help to decide on the best way to give the new treatment. Phase I trials carry the most potential risk. But phase I studies do help some patients. For those with life-threatening illnesses, weighing the potential risks and benefits carefully is key. Phase I trial also normally include dose ranging, also called dose escalation studies, so that the best and safest dose can be found and to discover the point at which the compound is to poisonous to administer,

Aim: To assess the safety (pharmacovigillence) tolerability, pharmacokinetic, pharmacodynamic of a drug.

Purpose: The purpose of Phase 1 is to ensure that the treatment is safe in humans and to determi sitagliptine phosphate ne how and where it distributes within the body. It may also test the best way to give a new treatment (for example, by mouth, infusion into a vein, or injection) and how the treatment affects the body.[7]

Phase II:

This testing normally takes place with a larger number of volunteers from 100 to 300. A phase 2 clinical trial is conducted to evaluate the effectiveness and safety of a new drug or drug combination for a particular indication. Phase II trials, also referred to as "therapeutic exploratory" trials, are usually larger than phase I studies. Phase II studies may be done at major cancer centers, community hospitals or even doctors' offices. Larger numbers of patients get the treatment in phase II trials, so less common side effects may be seen. These groups may get different doses or get the treatment in different ways to see which provides the best balance of safety and response. Phase II studies evaluate potential efficacy and characterizes treatment benefit for the disease in a convincing manner.[7]

Aim: A phase 2 clinical trial is conducted to evaluate the effectiveness and safety of a new drug or drug combination for a particular indication.

Purpose: The purpose of a Phase 2 Clinical Trial is to determine the right dosage and effectiveness in treating that particular disease. A study that tests how well a new treatment works for a certain type of cancer or other disease and compares the new treatment with a standard treatment. Phase II clinical trials may also provide more information about the safety and side effects of the new treatment.

Phase III:

This testing normally takes place with a large number of volunteers from 1000 to 3000. This phase is designed to assess the effectiveness of the new intervention and, thereby, its value in clinical practice. Phase III clinical trials compare the safety and effectiveness of the new treatment against the current standard treatment. Phase 3 compares the new treatment to existing treatments. This is done with an even larger group of volunteers, and generally for a longer period of time. As a result, rare and/or long-term side effects are more likely to be discovered. Phase 3 is the final phase before a treatment receives FDA approval.

Aim: The main aim of phase 3 trials is to demonstrate and confirm the prelimary evidence gathered in the previous trials that the drug is, a safe, beneficial and effective treatment for the intended indication.

Purpose: The purpose of phase III is to evaluate how the new medication works in comparison to existing medications for the same condition. Testing with large groups of people to confirm its efficacy, evaluate its effectiveness, monitor side effects, compare it to commonly used treatments, and collect information that will allow it to be used safely.

Phase IV: The phase 4 trials is also referred to as post marketing surveillance and as the name suggests, it is conducted after the drug is already marketed and available to the general public. This testing normally takes place with a large number of volunteers from 1000 to 3000. Phase IV studies look at drugs that have already been approved by the FDA. These Phase IV studies include "all studies (other than routine surveillance) performed after drug approval and related to the approved indication" These are post-marketing surveillance studies. The medicine or therapy has been approved by the Food and Drug Administration (FDA) to be given to the public. Researchers continue to look at the new medicine or therapy's benefits and risks (side effects) and at the way to best use it.

Aim: The focus of the trials is on how drugs work in the real world & Safety studies during sales.

Purpose: The main purpose of the phase 4 trial is to check the drug's performance in real life scenarios, to study the long-term risks and benefits of using the drug and to discover any rare side effects. A type of clinical trial that studies the side effects caused over time by a new treatment after it has been approved and is on the market.[8]

❖ Function of drug controller General of India (DCGI) and Central Drug Standard Control Organization (CDSCO):

Functions of DCGI:

Medicines Controller General of India (DCGI) is the head of department of the Central medicines Standard Control Organization of the Government of India responsible for blessing of licenses of specified orders of medicines similar as blood and blood products, IV fluids, vaccines, and sera in India. Medicines Controller General of India comes under the Ministry of Health & Family Welfare. DCGI also sets norms for manufacturing, deals, import, and distribution of medicines in India. With the announcement of Medical Device Rules 2017 by the Government of India, DCGI'll also act as Central Licensing Authority (CLA) for the medical bias which falls under the horizon of these rules.

1. Preparation and conservation of public reference standard.
2. To bring about the uniformity in the enforcement of the medicines and Cosmetics Act.
3. Training of medicine Judges deputized by State Drug Control Laboratories and other Institutions
4. To survey and dissect samples of cosmetics and medicines entered from CDSCO
5. To serve as the appellate authority if any disagreement arises regarding the quality of the medicines
6. Regulate medical and pharmaceutical bias in the country.
7. DCGI also sets norms for manufacturing Deals, Import and Distribution of medicines in India.[9]

Functions of CDSCO:

CDSCO It is the central drug regulatory authority in India headed by Drug Controller General of India and Functions under the ministry of Health and Family Welfare. Head quarter is located at FDA Bhawan, Kotla Road, New Delhi 110002 and function under the Directorate General of Health Services. So the functions of CDSCO are following:

1. Approval of new drugs and clinical trials.
2. Import Registration and licensing
3. License approving of Blood Bank, LVPs, Vaccines, r-DNA products and some Medical devices (CLAA Scheme).
4. Amendment to D & C Act & Rules.
5. Banning of drug and cosmetics.
6. Grant of Test Licenses, Personal Licenses, NOCs for export.
7. Testing of New Drugs.
8. Oversight and Market Surveillance through Inspectorate of Centre Over and above the State Authority.
9. Registration of foreign manufacturers of drugs and medical devices whose products are to be imported into the country.[9]
10. Grant of licenses to import drugs by Government hospitals or Medical Institutions for the use of their patients.
11. Recommend banning of drugs considered harmful or sub-therapeutic under section 26A drugs and Cosmetics Act.

❖ Types of Regulatory application

1. Investigational New Drug (IND)
2. New Drug Application (NDA) and
3. Abbreviated New Drug Application (ANDA)

1. Investigational New Drug (IND)

The IND is the launching point for the clinical disquisition in the united countries It's an essential step along the path toward getting a new medicine on the request. The primary purpose of an original IND submission is to insure as well as possible, From the FDA's perspective the safety and rights of clinical trial actors. INDs may be distributed as either marketable or exploration. Marketable INDs allow for the development of a medicine or birth with the thing of eventually submitting a marketing operation. Besides allowing clinical examinations, the IND also performs an fresh legal function. Because civil law states that only retailed medicines are permitted to be transported across countries lines. The IND provides a legal frame that allows guarantors to transport their investigational products to clinical investigators in different countries.[10]

2. New Drug Application (NDA)

The NDA is a formal request made by a Sponsor to vend a new medicine in the United States. NDAs are generally regulated by FDA's Center for medicine Evaluation and exploration (CDER).
The pretensions of the NDA are to give enough substantiation to support the safety and effectiveness of the medicine and to show that the benefits of its use overweigh the pitfalls.
It's a comprehensive document with 15 sections. The purpose of an NDA is to give the FDA critic acceptable data to insure the safety and efficacity of the medicine, labeling, and manufacturing process. For decades, the regulation and control of new medicines in the United States has been grounded on the New Drug Application (NDA). Since 1938, every new medicine has been the subject of an approve NDA before U.S. commercialization.

3. Abbreviated New Drug Application (ANDA):

An ANDA is submitted to the FDA for the review and approval of a generic drug product. ANDAs are regulated by FDA's Office of Generic Drugs (OGD) and are considered abbreviated, as they generally are not required to include pre-clinical (animal) and clinical (human) data to establish safety and effectiveness. Specifically, the generic drug must deliver the same amount of active ingredients into the bloodstream in the same amount of time as the reference product this is known as bioequivalence. In addition to the ANDA approval pathway, generic drug companies gained the ability to challenge patents in court prior to marketing as well as 180-day generic drug exclusivity. Goal of ANDA is to reduce the price of drug, to reduce the time development and increased the bioavailability of drug in comparison to references list drug. [10]

❖ Objective and scope of ICH –

" Good Clinical Practices " and New Drug Clinical Trial Rule 2019 description-Good Clinical Practice(GCP) is an transnational ethical and scientific quality standard designed to conduct, performance, examiner, inspection, record, analyses and report clinical trials. It protects the rights, integrity and confidentiality of trial subjects ideal-

1. To cover the rights of mortal subject sharing in clinical trials.
2. To insure the scientific validity and credibility of data collected in mortal clinical studies.
3. Further provident use of mortal, beast and material coffers.
4. To give a unified standard for the Europian union, Japan and the united countries to grease the collective acceptance of clinical data by the nonsupervisory authorities in this governance.[11]

Scope:

To the extent possible, the principles of GCP should generally apply to all clinical exploration involving mortal subjects, and not just probe involving pharmaceutical or other medical products. Included then are
1. Studies of a physiological, biochemical, or pathological process, or of the response to a specific intervention – whether physical, chemical, or cerebral;
2. Controlled studies of individual, preventative or remedial measures, designed to demonstrate a specific generalizable response to these measures against a background of individual natural variation;
3. Studies designed to determine the consequences for individualities and communities of specific preventative or remedial measures;
4. Studies concerning mortal health-affiliated geste in a variety of circumstances and surroundings;
5. Studies that employ either observation or physical, chemical, or cerebral intervention. Similar studies may induce records or make use of being records containing biomedical or other information about individualities that may or may not be identifiable from the records or information. The use of similar records and the protection of the confidentiality of data attained from those records are bandied in the "International Guidelines for Ethical Review of Epidemiological Studies"(CIOMS, 1991, presently being streamlined). Although some principles of GCP may not apply to all types of exploration on mortal subjects, consideration of these principles is explosively encouraged wherever applicable as a means of icing the ethical, methodologically sound and accurate conduct of mortal subject's exploration New Drug clinical trial Rule 2019 [12]

Protocol designing for clinical trial:

What is meant by clinical protocol?

Every clinical disquisition begins with the development of a clinical protocol. The protocol is a document that describes how a clinical trial will be conducted (the ideal, design, methodology, statistical considerations and association of a clinical trial,) and ensures the safety of the trial subjects and integrity of the data collected. The protocol demonstrates the guidelines to conduct a trial. It represents what will be made in the study by explaining each essential part of it and how it's carried out. It also describes the eligibility of the actors, the study duration, the specifics, and the affiliated tests. The protocol contains complex details for trials assessing pharmacological medicines, medical bias, and surgical instruments, which describe the ethical, medical, and nonsupervisory functions of the clinical trial. A principal experimenter governs the protocol.[13]

Purpose of clinical protocol:

• It formulates thesis and objects.
• Protocol raises the exploration question and defines its significance.
• It collects being knowledge and discusses the sweats of other experimenters who have worked on the affiliated questions (known as literature review).
• Protocol clarifies ethical considerations.
• It suggests the methodology necessary to break the question and achieve the objects.
• It helps to bandy the conditions and limitations to achieve these objects.

Tips to write a best protocol:

Protocol writing is grueling and a professed job. In protocol jotting, the experimenter reviews and critically evaluates the published literature on the intriguing content, plans and reviews the design way, and serves as a companion throughout the disquisition.

Then are some tips to write an ideal protocol for exploration.

• It's always important to follow guidelines for protocol content and address all essential points in the guidelines.
• The protocol shall contain all the exploration- related in the protocol and the informed concurrence form. Both these documents shall maintain the thickness.
• Include all applicable preclinical and clinical data, including published and unpublished data.
• Protocol shall contain all the study conditioning that actors will suffer.
• Taking review of protocol form people who aren't directly involved in the exploration will be veritably helpful. This helps to identify unclear aspects, where nonsupervisory agencies and the IRB may have difficulties as well.
• You need to consider the perspectives of the nonsupervisory agencies and the IRB. Both perspectives are reciprocal but distinct. Invasive procedures or treatments should be minimized.
• Consider threat minimization which is particularly important in children and other vulnerable populations.
• In some cases, if necessary, you may need to seek advice from an IRB nonsupervisory advice.[14]

Challenges in protocol writing:

The clinical trial protocol is a precise procedure of the study, and it must give a clear picture and terse design to meet the end and objects of the study. While developing a protocol design, there should be a great collaboration with medical experts, nonsupervisory experts, statisticians, pharmacokinetics and functional experts.

Contents of clinical trial protocol:

An exploration protocol is a document that describes the background, explanation, objects, design, methodology, statistical considerations, and association of a clinical exploration design. According to the ICH Good Clinical Practice guidelines, a protocol should include the following topics:

Title Page (General Information)
Background Information
Objectives/Purpose
Study Design
Selection and Exclusion of Subjects
Treatment of Subjects
Assessment of Efficacy
Assessment of Safety
Adverse Events
Discontinuation of the Study
Statistics
Quality Control and Assurance
Ethics
Data handling and Recordkeeping
Publication Policy
Project Timetable/Flowchart
References
Supplements/Appendices [15]

Process of Clinical Trial Application:

A Clinical Trial Application (CTA) is a submission to the competent National Regulatory Authority for obtaining authorization to conduct a clinical trial in a specific country. It is an application with necessary information on investigational medicinal products. The purpose of a CTA is to provide all the important details about the clinical trial to the health authorities in order to obtain the product approval.
In the European Union (EU), the CTAs are regulated under the Clinical Trial Regulation EU No. 536/2014. The regulation intends to set high standards of safety and transparency for the clinical trials conducted.[16]

Definition, Objective, types & components of pharmacovigilance:

Definition: - Pharmacovigilance (PV, or Ph V), also known as drug safety, is the pharmaceutical science relating to the "collection, detection, assessment, monitoring, and prevention" of adverse effects with pharmaceutical products.

The word "pharmacovigilance" are: pharmakon (for drug) and vigilare (for to keep watch). Pharmacovigilance is concerned with identifying the hazards associated with pharmaceutical products and with minimizing the risk of any harm that may come to patients. Companies must conduct a comprehensive drug safety and pharmacovigilance audit to assess their compliance with worldwide laws, regulations, and guidance.[17]

Objective:-

1. Enhancement of patient care and safety in relation to the use of drugs with medical and paramedical interventions remains to be an important parameter.
2. The main objects of pharmacovigilance involve flaunting the efficacity of medicines by covering their adverse effect profile for numerous times from the lab to the drugstore;
3. Tracking any drastic goods of medicines perfecting public health and safety in relation to the use of drugs
4. Encouraging the safe, rational and cost-effective use of medicines promoting understanding, education and clinical training in pharmacovigilance; and effective communication to the general public.
5. In addition, furnishing information to consumers, interpreters and controllers on the effective use of medicines along with designing programs and procedures for collecting and assaying reports from cases and clinicians conclude to the objective pharmacovigilance studies.[18]

Types of Pharmacovigilance:-

There are five important methods in Pharmacovigilance such as,

1.Passive Surveillance 2. Active surveillance

3.Cohort event monitoring 4. Targeted clinical examinations

5. Relative experimental studies.

1. Passive surveillance:

It includes a. Robotic reports b. Case series.

a. Robotic (spontaneous) reports:

Voluntary communication by healthcare professionals or consumers to a company.

Non supervisory authority or other associations. It define one or further adverse medicine responses in a case who was given one or further medicinal products. Identification of safety signals once a drug is retailed. It can watchful a company to rare adverse events that weren't noticed in earlier clinical trials or other per marketing studies. It can also deliver important information on at threat groups, threat factors and clinical features of known serious ADRs.

b. Case series:

A series of case reports can deliver sign of an association between a drug and an adverse event. But they're typically more precious for producing propositions than for attesting a relationship between drug exposure and outgrowth.[19]

2. Active surveillance:

The World Health Organization defined active surveillance as the collection of case study information as a continouspre-organized process.

Three types of Active surveillance

1. Medicine grounded relating adverse events in cases taking pharmaceutical products,
2. Setting grounded relating adverse events in certain health care settings where cases are likely to present for treatment(e.g., exigency departments etc.), or
3. Event grounded relating adverse events that are likely to be associated with medical products (e.g. acute liver failure).[20]

3. Cohort event monitoring:

Cohort event monitoring (CEM) is a ferocious system of post-marketing surveillance for drugs safety. The system is grounded on tradition event monitoring, which began in the 1970s, and has ago been acclimated by WHO for covering the safety of drugs used in Public Health Programmes. CEM aims to capture all adverse events that do in a defined group of cases after starting treatment with a specific drug during the course of routine clinical practice.[21]

4. Targeted clinical examinations:

When significant pit falls are linked from pre blessing clinical trials. Farther clinical studies might be needed to estimate the medium of action for the adverse responses. In some cases, pharmacodynamic and pharmacokinetics studies might be conducted to determine whether a particular cure can put cases at an increased threat of adverse events. Inheritable testing can give suggestions about the group of cases at an increased threat of adverse responses Specific studies to probe implicit medicine relations and food medicine relations might also be needed. Studies can include populations pharmacokinetic studies and attention monitoring in cases and normal levies. This population might include the senior, children or cases with renal or hepatic complaint. [22]

5. Relative experimental studies:

There are number of experimental study Designs that are useful in Validating Signals from robotic reports or case series. Major types of this design are Cross sectional studies, Case control studies, and Cohort studies, Observation l studies. Fall under The order of Analytic study Designs and are farther classified as. Experimental or experimental study designs. The thing of logical studies is to identify and estimate causes or threat Factors of conditions or health affiliated events the secreting characteristics between observation and experimental design, experimental study designs is that in the letter, the presence or absence of witnessing an intervention defines the groups.[23]

Constitutional objectives of Pharmacovigilance Program of India (PvpI):

The Central medicines Standard Control Organization (CDSCO), Directorate General of Health Services under the aegis of Ministry of Health & Family Welfare, Government of India in association with Indian Pharmacopeia commission, Ghaziabad is initiating a nation-wide Pharmacovigilance programme for guarding the health of the cases by promising medicine safety. The Pharmacovigilance Programme of India (PvPI) was started by the Government of India on 14th July 2010 with the All India Institute of Medical Stores AIIMS), New Delhi as the National Coordination Centre for covering Adverse medicine responses (ADRs) in the country for safe- guarding Public Health. In the time 2010, 22 ADR monitoring centers including AIIMS, New Delhi was set up under this Programme. [24,25]

Objectives:

1 .To create a nation-wide system for patient safety reporting
2. To identify and analyze the new signal (ADR) from the reported cases
3. To analyses the benefit - risk ratio of marketed medications
4. To generate the evidence based information on safety of medicines
5. To support regulatory agencies in the decision making process on use of medications
6. To communicate the safety information on use of medicines to various stakeholders to minimize the risk
7. To emerge as a national center of excellence for pharmacovigilance activities
8. To collaborate with other national centers for the exchange of information and data management
9. To provide training and consultancy support to other national pharmacovigilance centers located across globe.
10. To create awareness amongst health care professionals about the importance of ADR reprting in India.[26]

List of National Adverse Drug Monitoring Centers (AMCs) and their function:

1. Department of Pharmacology, Therapeutics & Toxicology, Govt. Medical College, Bakshi Nagar, Jammu.
2. Department of Pharmacology, PGIMER, Chandigarh
3. Department of Pharmacology, R.G. Kara Medical College, Kolkata
4. Department of Pharmacology, Lady Herding Medical College, New Delhi
5. Department of Clinical Pharmacology, Seth GS Medical College & KEM Hospital, Parel, Mumbai
6. Department of Clinical & Experimental Pharmacology, School of Tropical Medicine, Chittaranjan Avenue, Kolkata
7. Department of Pharmacology, JIPMER, Pondicherry
8. Department of Clinical Pharmacy, JSS Medical College Hospital , Karnataka
9. Department of Pharmacology, Medical College, Guwahati. Assam
10. Institute of Pharmacology, Madras Medical College, Chennai
11. Department of Pharmacology, SAIMS Medical College, Indore-Ujjain
12. Department of Pharmacology, GSVM Medical College, Swaroop Nagar, Kanpur, U.P.
13. Department of Pharmacology, Pundit Bhagwat Dayal Sharma, Post Graduate Institute of Medical Sciences, Rohtak, Haryana.

Elements of non-clinical and clinical safety specifications:

Nonclinical studies define the relevant efficacy and/or safety characteristics of drugs, biologics, and medical devices. They begin well before a Sponsor's first interaction with the Food and Drug Administration (FDA) and continue throughout product development.

Nonclinical laboratory study means in vivo or in vitro experiments in which test articles are studied prospectively in test systems under laboratory conditions to determine their safety. The term does not include studies utilizing human subjects or clinical studies or field trials in animals.

Information For

Step 1: Discovery and Development.

Step 2: Preclinical Research.

Step 3: Clinical Research.

Step 4: FDA Drug Review.

Step 5: FDA Post-Market Drug Safety Monitoring.[27]

Identification and evaluation of risk including drug drug interactions and drug food interactions

Medicine relations do when a medicine's medium of action is disturbed by the attendant administration of substances similar as foods, potables, or other medicines. The cause is frequently the inhibition of the specific receptors available to the medicine, forcing the medicine motes to bind to othernon-intended targets which results in an array of side-effects. For illustration, consuming both Zolpidem (i.e. Ambien) and alcohol(both depressants) influxes the GABAA receptors, performing in theover-stimulation of sleep-converting chemicals, performing in unconsciousness. The threat of a medicine- medicine commerce increases with the number of medicines used.(1) Over a third(36) of the senior in theU.S. regularly use five or further specifics or supplements, and 15 are at threat of a significant medicine- medicine medicine- food commerce A response between a medicine and a food or libation. Medicine- condition commerce A response that occurs when taking a medicine while having a certain medical condition. For illustration, taking a nasal decongestant if you have high blood pressure may beget an unwanted response.[28]

Types of drug interaction:

Medicine- medicine. A medicine- medicine response is when there is an commerce between two or further tradition medicines..

Medicine- nonprescription treatment. This is a response between a medicine and a nonprescription treatment or two nonprescription treatments.[29]

Drug- food..

Drug- alcohol.

Drug- complaint.

Drug- laboratory.

Design and conduct of observational studies:

On the base of different criteria similar as marketable vacuity, selling of medicines, medium of action, side goods & contraindication of medicine. We select the antidiabetic medicine class as per the Biopharmaceutics Classification System (BCS). The Biopharmaceutics Classification System is a system to separate the medicines on the base of their solubility and permeability and depending on it BCS system is classified into four classes.[30]

Selection of drug class:

On the basis of different criteria such as commercial availability, selling of drugs, mechanism of action, side effects & contraindication of drug. We select the ant diabetic drug class as per the Biopharmaceutics Classification System (BCS). The **Biopharmaceutics Classification System** is a system to differentiate the drugs on the basis of their solubility and permeability and depending on it BCS system is classified into four classes:

- **Class I - high permeability, high solubility**
  - Example: Sitagliptin phosphate, vildagliptin
  - Those compounds are well absorbed and their absorption rate is usually higher than excretion.
- **Class II - high permeability, low solubility**
  - Example: Gliclazide (GLZ) and tolbutamide (TOL)
  - The bioavailability of those products is limited by their salvation rate. A correlation between the *in vivo* bioavailability and the in vitro salvation can be found.
- **Class III - low permeability, high solubility**
  - Example: metformin
  - The absorption is limited by the permeation rate but the drug is solvated very fast. If the formulation does not change the permeability or gastro-intestinal duration time, then class I criteria can be applied.
- **Class IV - low permeability, low solubility**
  - Example: Canagliflozin (CGF) is one of the poorly soluble
  - Those compounds have a poor bioavailability. Usually they are not well absorbed over the intestinal mucosa and a high variability is expected.[31]

From this BCS classification we select the class I & class III for the comparatively study.

Selection of Drug:

By approaching the pharmacy stores, Company representatives and pharmacy companies web portals we select the drugs such as sitagliptin instead of other drug such as metformin because Metformin reduces the absorption of sugar from the stomach, reduces the release of stored sugar from the liver where as Sitagliptin helps to control blood sugar levels by increasing substances in the body that make the pancreas release more insulin. As compared to Metformin, Sitagliptin shows fewer side effects and it has good bioavailability. Sitagliptin has been widely used in the treatment of type 2 diabetes mellitus. Sitagliptin is similar to metformin in reducing HbA1c, decreasing body weight, and improving the function of beta cells, but is inferior to metformin in improving insulin sensitivity. So we select the Sitagliptin drug.

Sitagliptin phosphate:

Sitagliptin is an anti-diabetic drug used to treat type two diabetes. Sitagliptin is used together with diet and exercise to improve blood sugar control in adults with type 2 diabetes mellitus. Sitagliptin is not for treating type 1 diabetes. Sitagliptin is a DPP-4 inhibitor, which is believed to exert its actions in patients with type 2 diabetes by slowing the inactivation of incretion hormones thereby increasing and prolonging the action of these hormones Incretion hormone

MOA:

1. Sitagliptin prolongs the action of GLP-1 (glucagon-like peptide-1) and GIP (glucose-dependent insulin tropic polypeptide).
2. By enhancing active incretion levels, sitagliptin increases insulin production and lowers glucagon secretion from alpha cells, which decreases hepatic glucose overproduction.

Pharmacokinetics properties of sitagliptin:

Pharmacokinetics properties of sitagliptin

Absorption:

The absolute bioavailability of Sitagliptin is roughly 87 because co administration of a high- fat mess with Sitagliptin had no effect on the pharmacokinetics. Sitagliptin may be administered with or without food

Distribution:

The mean volume of distribution at steady state following a single 100 mg Intravenous cure of Sitagliptin to healthy subjects is roughly 198 liters. The bit of Sitagliptin reversibly bound to tube proteins is low(38).

Metabolism

Roughly 79 of Sitagliptin is excreted unchanged in the urine with metabolism being a minor pathway of elimination. Sitagliptin oral dose, roughly 16 of the radioactivity was excreted as metabolites of Sitagliptin; six metabolites were detected at trace situations and aren't anticipated to contribute to the tube DPP- 4 inhibitory exertion of Sitagliptin, in vitro studies indicated that the primary enzyme responsible for the limited metabolism of Sitagliptin was CYP3A4, with donation from CYP2CB

Excretion

Following administration of an oral AC Sitagliptin cure to healthy subjects; roughly 100% of the administered radioactivity was excluded in feces (130) or urine(87%) within one week of dosing. The apparent terminal to Following 100 mg oral cure of Sitagliptin was apprimately12.4 hours and renal concurrence was roughly 350 ml/min. Elimination of Sitagliptin occurs primarily via renal excretion and involves active tubular stashing. Sitagliptin is a substrate for mortal organic anion transporter- 3 hOAT- 3), which may be involved in the renal elimination of Sitagliptin.

Identification of Adverse effects of selected Sitagliptin drug:

- Hypoglycemia (low blood sugar), when sitagliptine phosphate is used with insulin or a sulfonylurea medication such as Glucotrol (glipizide). ...
- Pancreatitis (inflammation in your pancreas). ...
- Bullous pemphigoid (a type of skin reaction that may require treatment in the hospital)
- Sudden kidney failure.
- Hypersensitivity reactions including anaphylaxis, angioedema, rash, urticaria, cutaneous vasculitis, and exfoliative skin conditions including Stevens-Johnson syndrome
- Hepatic enzyme elevations; acute pancreatitis, including fatal and nonfatal hemorrhagic and necrotizing pancreatitis
- Worsening renal function, including acute renal failure (sometimes requiring dialysis)
- Severe and disabling arthralgia
- Tubulointerstitial nephritis
- Constipation, vomiting
- Headache, myalgia, pain in extremity, back pain
- Rhabdomyolysis
- Pruritus
- Mouth ulceration; stomatitis
- Symptoms of heart failure--shortness of breath (even while lying down), swelling in your legs or feet, rapid weight gain.
- low blood sugar;
- headache; or
- Runny or stuffy nose, sore throat.

ADR Monitoring Form:

A. Patient Information
1. Patient initials: MP
2. Age at time of event or date of birth: 56
3. Sex: male
4. Weight: 65
B. Suspected Adverse Reaction
5. Date of reaction started: 01/09/2022
6. Date of recovery: 25/09/2022
7. Describe reaction: Hypersensitivity reactions including anaphylaxis, angioedema, rash, urticaria, cutaneous vasculitis, and exfoliative skin conditions including Stevens-Johnson syndrome.
C. Suspected Medications
8. The details of suspected medication(s) such as:
Drug name (brand or generic name): Sitagliptin Phosphate tablet IP 100mg
Manufacturer: MSD Pharmaceutical Pvt.Ltd.
Batch no/lot no: FHS-22003 expiry date: 12/2025
Dose used: 100 mg route used: oral route
Dates of therapy started: 01/09/2022 date of therapy stopped: 25/09/2022

Indication: angioedema, anaphylaxis
9. Other relevant history: Allergies, smoking, alcohol use.
10. Seriousness of the reaction: Bullous pemphigoid (a type of skin reaction that may require treatment in the hospital), sudden kidney failure, worsening renal function, including acute renal failure (sometimes requiring dialysis
11` Outcomes: The reporter must tick the outcome of the event as:
▪ 'Recovered'- if the patient has recovered from the event
Reporter:
12. Name and Professional address: Ms. Sonali Mali (pharmacist) at post: kavathemahankal.
13 Date of report: 10/12/2022

Hospital visit:

Name of Hospital: Mhetre Hospital, Kavathemahankal
Name of Doctor: Dr. Mrunal Mhetre.
We visited nearest hospital of our area and took detailed information related to ant diabetic drug its uses, adverse drug reaction, side effects, contraindication, MOA etc. by interacting with physicians and nurses for identification of unreported ADR.[32]

Patient Interview:

For understanding and identification of ADR we took interview of patient and ask them question regarding to diabetic disease and there is any ADR of sitagliptin:

Question Asked to Patient:

1. Did you experience any side effect at first?
2. How long have you known that you have diabetes?
3. Do you test your blood sugar levels?
4. Have you had low blood sugars?
5. Have you ever lost consciousness or required assistance to reverse low blood sugar?
6. How often has it occurred? ...
7. Do you ever have HIGH blood sugar levels?
8. Will you gain or loose weight?
9. You know that is there any food or drink need to avoid?
10. When you take medicine at night / morning?

Assessment of ADR by Naranjo scale:

The Naranjo algorithm or adverse drug reaction probability scale or Naranjo scale is a method by which to assess whether there is a casual relationship between an identified untoward clinical event and a drug using a simple questionnaire to assign probability scores. To assess the adverse drug reaction, please answer the following questionnaire and give the pertinent score, that are answered as either Yes, No, or "Do not know". Different point values (-1, 0, +1 or +2) are assigned to each answer.[33]

Questionnaire:

1. Are there previous conclusive reports on this reaction?
2. Did the adverse event appear after the suspected drug was administered?
3. Did the adverse reaction improve when the drug was discontinued or a specific antagonist was administered?
4. Did the adverse reaction reappear when the drug was readministered?
5. Are there alternative causes (other than the drug) that could on their own have caused the reaction?
6. Did the reaction reappear when a placebo was given?
7. Was the drug detected in the blood (or other fluids) in concentrations known to be toxic?
8. Was the reaction more severe when the dose was increased, or less severe when the dose was decreased?
9. Did the patient have a similar reaction to the same or similar drugs in any previous exposure?
10. Was the adverse event confirmed by any objective evidence?

Scoring

1) ≥ 9 = definite ADR
2) 1-4 = possible ADR
3) 0 = doubtful ADR
4) 5-8 = probable ADR

Conclusion:

Pharmacovigilance is the only way to ensure the safety of the drug throughout the life cycle. It is very much crucial as the clinical trials have limitation to detect the rare and very rare ADRs. The knowledge and information available regarding safety of any drug is very much important to take appropriate decision by drug regulators to safe guard public health. Health care professionals are the main reporters of the ADRs. Health care professional mainly include pharmacovigilance For this purpose we visited the nearest hospitals in our area for collecting the more information and monitoring of ADR, side effect by taking patient interview about selected Sitagliptin medicine. From this study we concluded that the selected Sitagliptin medicine shows good result and efficacy to control the blood sugar level and it is widely used throughout the world on the basis of commercial availability and selling of drugs as compared to other drug such as metformin. And it has fewer side effects. Now days it is widely prescribed medicine for diabetic patient.

Reference:

1. The journal of National Library Of Medicine,by author Shanthi N. Pal, Sten Olsson. Page no 1- 3 ; 2014

2.World Health Organisation . *Reporting and learning systems for medication errors: the role of pharmacovigilance centres.* Geneva: WHO Press; 2014.

3. The journal of National Library Of Medicine, Hornbuckle K, Wu H-H, Fung MC. 1999. Evaluation of spontaneous adverse event reports by primary reporter - a 15-year review (1983 to 1997). *Drug Inf J*. 33, 1117-24.

4. The journal of Global Pharmacovigilance by global pharmacovigilance team, December 5 2020.

5. "NIH Clinical Research Trials and You: The Basics". US National Institutes of Health. 3 October 2022. Retrieved 7 November 2022.

6. "Clinical Trials" (PDF). Bill and Melinda Gates Foundation. Retrieved 1 January 2014.

7. Shamoo AE (2008). "The myth of equipoise in phase 1 clinical trials". Medscape Journal of Medicine. 10 (11): 254. PMC 2605120. PMID 1

8. Clinical research". US Food and Drug Administration. 14 October 2016. Retrieved 1 February 2017.

9.Drugs Controller General of India ,Dr.V.G. Somani CENTRAL DRUGS STANDARD CONTROL ORGANIZATION (accessed on 18 Oct 2014) archived 2014.10.23 "Medical Device Rules G.S.R. 78 (E)"

10. A book of Nirali Prakashan,Industrial Pharmacy II , by author Dr.K.P. Sampath Kumar ,Page no 3.10 – 3.12

11.kathie Clark (December 15, 2009). "Updates from the Regulators:FDA". The eCTD summit. Archived from the original on July 16, 2011.

12."Merck KGaA Receives Refuse To File Letter From FDA On Cladribine Tablets New Drug Application". medicalnewstoday.com. Archived from the original on March 5, 2010. Retrieved April 30, 2018.

13. World Health Organization. Guide for writing a Research Protocol for research involving human participation; 2014.

14. Guidelines for writing a research protocol. Pan American Health Organization; 2014.

15..Bowling A. *Research methods in health: Investigating health and health services research.* 4th ed. Maidenhead, England: Open University Press; 2002.

16. Toy A, Santini A, Eaton KA. An introduction to research for primary care clinicians. Part 2: Stage 4. Planning the study. Prim Dent Care. 2011;18(1):16–40. [PubMed]

17.Najafi S. “Importance of Pharmacovigilance and the Role of Healthcare Professionals”. Journal of Pharmacovigilance 6.1 (2018)

18. Parthasarathi G., et al. “Pharmacovigilance Research in India: A Five-Year Literature Review”. Proceedings of the Indian National Science Academy 8 (2018): 225-232

19. Routledge P. “150 years of pharmacovigilance”. The Lancet 351.9110 (2018).

20. Clavel-Arcas, C., R. Chacon, and A. Concha-Eastman. 2004. "Hospital Based Injury Surveillance Systems in Nicaragua and El Salvador, 2001–2002." Paper presented at the Seventh World Conference on Injury Prevention and Safety Promotion, Vienna, June 6–9.

21.Concha-Eastman, A., and A. Villveces. 2001. *Guidelines for the Design, Implementation and Evaluation of Epidemiological Surveillance Systems on Violence and Injuries*. Washington, DC: Pan American Health Organization.

22. Foege W. H., Hogan R. C., Newton L. H. Surveillance Projects for Selected Diseases. International Journal of Epidemiology. 1976;5(1):29–37.

23. Greenland, S. 2004. "Ecologic Inference Problems in the Analysis of Surveillance Data." In *Monitoring the Health of Populations*, ed. R. Brookmeyer and D. F. Stroup, 315–40. New York: Oxford University Press.

24.Lihite, Ratan J.; Lahkar, Mangala (22 September 2015). "An update on the Pharmacovigilance Programme of India". Frontiers in Pharmacology.

25..Kalaiselvan, V; Thota, P; Singh, GN (2016). "Pharmacovigilance Programme of India: Recent developments and future perspectives". Indian Journal of Pharmacology. 48 (6): 624–628..

26.Gupta Y. K. (2010). Pharmacovigilance Programme for India.

27. A text book of Industrial Pharmacy II Pee Vee Publication , Page no. 149-52

28. Hansten PD. (2004) Appendix II: important interactions and their mechanisms, In: Katzung BG. (2004). editor, 09th edn, (2004) Basic and clinical Pharmacology, McGraw hill, Boston pp 1110.

29. Joshi R, Medhi B. Natural product and drugs interactions, its clinical implication in drug therapy management. Saudi Med J 2008. Mar;29(3):333-339 [PubMed]

30. Khan MA., et al. “Assessment of prescribing trend of drugs at outpatient’s chest ward of government tertiary care hospital situated in karachi”. Journal of Bioequivalence and Bioavailability 10.1 (2018).

31.Mehta M (2016). Biopharmaceutics Classification System (BCS): Development, Implementation, and Growth. Wiley. ISBN 978-1-118-47661-1.

32. Mehetre Hospital and Medical Kavathe Mahankal, Dist- Sangli

33. CLINICAL PHARMACOLOGY AND THERAPEUTICS. St. Louis Vol. 30. No. 2, Pages 239-245, August. 1981