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REVIEW ON CLINICAL RESEARCH AND PHARMACOVIGILANCE

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Abstract: The term "clinical research" refers to the entire bibliography of a drug/device/biologic, in fact any test article from its inception in the lab to its introduction to the consumer market and beyond. Once the promising candidate or the molecule is identified in the lab, it is subjected to pre-clinical studies or animal studies where different aspects of the test article (including its safety toxicity if applicable and efficacy, if possible at this early stage) are studied.

Pharmacovigilance (PV) plays a key role in the healthcare system through assessment, monitoring and discovery of interactions amongst drugs and their effects in human. Pharmaceutical and biotechnological medicines are designed to cure, prevent or treat diseases; however, there are also risks particularly adverse drug reactions (ADRs) can cause serious harm to patients. Thus, for safety 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. Pharmacogenetics and pharmacogenomics are an indispensable part of the clinical research. Variation in the human genome is a cause of variable response to drugs and susceptibility to diseases are determined, which is important for early drug discovery to PV.

***Keywords*- Food-drug interaction, Cytochrome P450, Drug, Chelation**

I. INTRODUCTION

Module 1

Clinical research

is a branch of healthcare science that determines the safety and effectiveness (efficacy) of medications, devices, diagnostic products and treatment regimens intended for human use. These may be used for prevention, treatment, diagnosis or for relieving symptoms of a disease. Clinical research is different from clinical practice. In clinical practice established treatments are used, while in clinical research evidence is collected to establish a treatment.

The term "clinical research" refers to the entire bibliography of a drug/device/biologic, in fact any test article from its inception in the lab to its introduction to the consumer market and beyond. Once the promising candidate or the molecule is identified in the lab, it is subjected to pre-clinical studies or animal studies where different aspects of the test article (including its safety toxicity if applicable and efficacy, if possible at this early stage) are studied.[1][2][3]

In the United States, when a test article is unapproved or not yet cleared by the Food and Drug Administration (FDA), or when an approved or cleared test article is used in a way that may significantly increase the risks (or decreases the acceptability of the risks), the data obtained from the pre-clinical studies or other supporting evidence, case studies of off label use, etc. are submitted in support of an Investigational New Drug (IND) application[4] to the FDA for review prior to conducting studies that involve even one human and a test article if the results are intended to be submitted to or held for inspection by the FDA at any time in the future (in the case of an already approved test article, if intended to submit or hold for inspection by the FDA in support of a change in labeling or advertising). Where devices are concerned the submission to the FDA would be for an Investigational Device Exemption (IDE) application if the device is a significant risk device or is not in some way exempt from prior submission to the FDA.

Clinical research is often conducted at academic medical centers and affiliated research study sites. These centers and sites provide the prestige of the academic institution as well as access to larger metropolitan areas, providing a larger pool of medical participants. These academic medical centers often have their internal Institutional Review Boards that oversee the ethical conduct of medical research.[5]

PHASE 0

Distinctive features of Phase 0 trials include the administration of single subtherapeutic doses of the study drug to a small number of subjects (10 to 15) to gather preliminary data on the agent's pharmacokinetics (what the body does to the drugs).[4]

A Phase 0 study gives no data on safety or efficacy, being by definition a dose too low to cause any therapeutic effect. Drug development companies carry out Phase 0 studies to rank drug candidates in order to decide which has the best pharmacokinetic parameters in humans to take forward into further development. They enable go/no-go decisions to be based on relevant human models instead of relying on sometimes inconsistent animal data

PHASE 1

Phase I trials were formerly referred to as "first-in-man studies" but the field generally moved to phrase "first-in-humans" in the 1990s; [6] these trials are the first stage of testing in human subjects.[7] They are designed to test the safety, side effects, best dose, and formulation method for the drug.[8] Phase I trials are not randomized, and thus are vulnerable to selection bias.[9]

Normally, a small group of 20–100 healthy volunteers will be recruited.[2] [7] these trials are often conducted in a clinical trial clinic, where the subject can be observed by full-time staff. These clinical trial clinics are often run by contract research organization (CROs) who conduct these studies on behalf of pharmaceutical companies or other research investigators. The subject who receives the drug is usually observed until several half-lives of the drug have passed. This phase is designed to assess the safety (pharmacovigilance), tolerability, pharmacokinetics, and pharmacodynamics of a drug. Phase I trials 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 a compound is too poisonous to administer. The tested range of doses will usually be a fraction of the dose that caused harm in animal testing.

PHASE 2

Once a dose or range of doses is determined, the next goal is to evaluate whether the drug has any biological activity or effect.[11] Phase II trials are performed on larger groups (50–300) and are designed to assess how well the drug works, as well as to continue Phase I safety assessments in a larger group of volunteers and patients. Genetic testing is common, particularly when there is evidence of variation in metabolic rate.[11] When the development process for a new drug fails, this usually occurs during Phase II trials when the drug is discovered not to work as planned, or to have toxic effects.drug is discovered not to work as planned, or to have toxic effects.

Summary of clinical trial phases

Phase	Primary goal	Dose	Patient monitor	Typical number of participants	Success rate[2]	Notes
Preclinical	Testing of drug in non-human subjects to gather efficacy, toxicity and pharmacokinetic information	Unrestricted	Scientific researcher	No human subjects, *in vitro* and *in vivo* only		Includes testing in model organisms. Human immortalized cell lines and other human tissues may also be used.
Phase 0	Pharmacokinetics; particularly oral bioavailability and half-life of the drug	Small, subtherapeutic	Clinical researcher	10 people		Often skipped for Phase I.
Phase I	Dose-ranging on healthy volunteers for safety	Often subtherapeutic, but with ascending doses	Clinical researcher	20–100 normal healthy volunteers (or cancer patients for cancer drugs)	Approx. 70%	Determines whether drug is safe to check for efficacy.
Phase II	Testing of drug on participants to assess efficacy and side effects	Therapeutic dose	Clinical researcher	100–300 participants with a specific disease	Approx. 33%	Determines whether drug can have any efficacy; at this point, the drug is not presumed to have any therapeutic effect
Phase III	Testing of drug on participants to assess efficacy, effectiveness and safety	Therapeutic dose	Clinical researcher and personal physician	300–3,000 people with a specific disease	25–30%	Determines a drug's therapeutic effect; at this point, the drug is presumed to have some effect
Phase IV	Post marketing surveillance in public	Therapeutic dose	Personal physician	Anyone seeking treatment from a physician	N/A	Monitor long-term effects

This phase is designed to assess the effectiveness of the new intervention and, thereby, its value in clinical practice.[11] Phase III studies are randomized controlled multicenter trials on large patient groups (300–3,000 or more depending upon the disease/medical condition studied) and are aimed at being the definitive assessment of how effective the drug is, in comparison with current 'gold standard' treatment. Because of their size and comparatively long duration,

PHASE 3

While not required in all cases, it is typically expected that there be at least two successful Phase III trials, demonstrating a drug's safety and efficacy, in order to obtain approval from the appropriate regulatory agencies such as FDA (US), or the EMA (European Union).

A Phase IV trial is also known as a postmarketing surveillance trial or drug monitoring trial to assure long-term safety and effectiveness of the drug, vaccine, device or diagnostic test.[1] Phase IV trials involve the safety surveillance (pharmacovigilance) and ongoing technical support of a drug after it receives regulatory approval to be sold.[7] Phase IV studies may be required by regulatory authorities or may be undertaken by the sponsoring company for competitive (finding a new market for the drug) or other reasons (for example, the drug may not have been tested for interactions with other drugs, or on certain population groups such as pregnant women, who are unlikely to subject themselves to trials). The safety surveillance is designed to detect any rare or long-term adverse effects over a much larger patient population and longer time period than was possible during the Phase I-III clinical trials. Harmful effects discovered by Phase IV trials may result in a drug being withdrawn from the market or restricted to certain uses; examples include cerivastatin (brand names Baycol and Lipobay), troglitazone (Rezulin) and rofecoxib (Vioxx)

1.1 FUNCTIONS OF DCGI

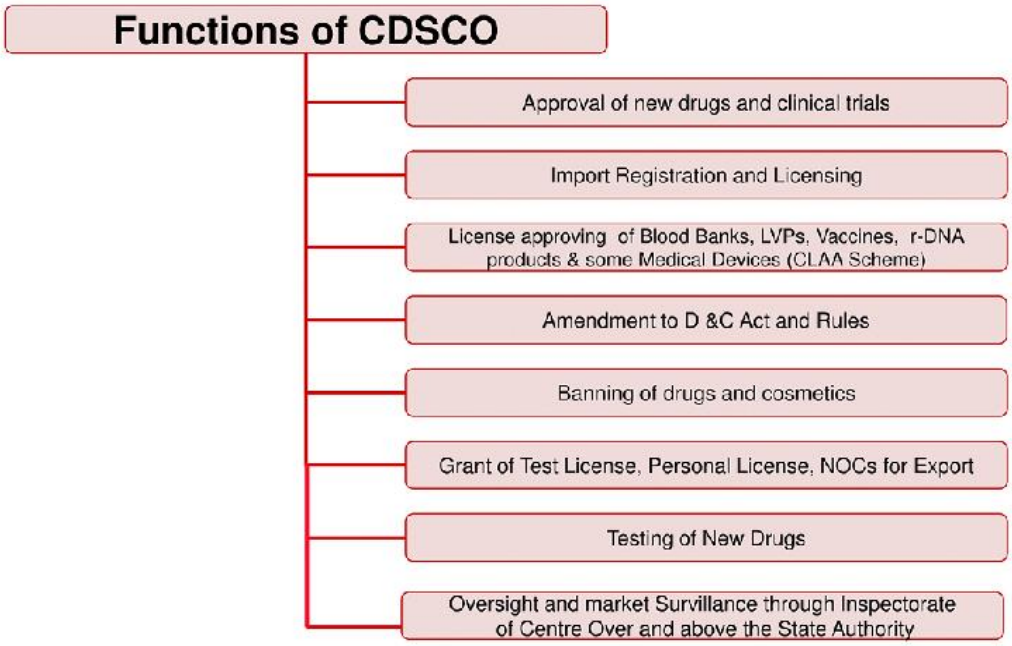
DCGI lays down the standard and quality of manufacturing, selling, import and distribution of drugs in India.

- Preparation and maintenance of national reference standard.
- To bring about the uniformity in the enforcement of the Drugs and Cosmetics Act.
- Training of Drug Analysts deputed by State Drug Control Laboratories and other Institutions
- Analysis of Cosmetics received as survey samples from CDSCO (central drug standard control organisation)

Functions of CDSCO

Under the Drug and Cosmetics Act, the regulation of manufacture, sale and distribution of Drugs is primarily the concern of the State authorities while the Central Authorities are responsible for approval of New Drugs, Clinical Trials in the country, laying down the standards for Drugs, control over the quality of imported Drugs, coordination of the activities of State Drug Control Organizations and providing expert advice with a view of bring about the uniformity in the enforcement of the Drugs and Cosmetics Act.

Drug Controller General of India is responsible for approval of licenses of specified categories of Drugs such as blood and blood products, I. V. Fluids, Vaccine and Sera. Central Drugs Standard Control Organization Head quarter is located at FDA Bhawan, Kotla Road, New Delhi 110002 and functions under the Directorate General of Health Services General of Health Services. General of Health Services General of Health Services.



1.3 TYPESOF REGULATORY APPLICATION

A)INVESTIGATIONAL NEW DRUG APPLICATION

The United States Food and Drug Administration's **Investigational New Drug (IND)** program is the means by which a pharmaceutical company obtains permission to start human clinical trials and to ship an experimental drug across state lines (usually to clinical investigators) before a marketing application for the drug has been approved. Regulations are primarily at 21 CFR 312. Similar procedures are followed in the European Union, Japan, and Canada.

Application

The IND application may be divided into the following categories:

1. **Preclinical testing** consists of animal pharmacology and toxicology studies to assess whether the drug is safe for testing in humans. Also included are any previous experience with the drug in humans (often foreign use).
2. **Manufacturing Information** includes composition, manufacturer, and stability of, and the controls used for, manufacturing the drug. Used to ensure that the company can adequately produce and supply consistent batches of the drug.

3. **Investigator information** on the qualifications of clinical investigators, that is, the professionals (generally physicians) who oversee the administration of the experimental drug to the study subjects. Used to assess whether the investigators are qualified to fulfill their clinical trial duties.
4. Clinical trial protocols are the centerpiece of the IND. Detailed protocols for proposed clinical studies to assess whether the initial-phase trials will expose the subjects to unnecessary risks.
5. Other commitments are commitments to obtain informed consent from the research subjects, to obtain review of the study by an institutional review board (IRB), and to adhere to the investigational new drug regulations.

An IND must also include an Investigator's Brochure intended to educate the trial investigators of the significant facts about the trial drug they need to know to conduct their clinical trial with the least hazard to the subjects or patients.

B) NEW DRUG APPLICATIO0N

The Food and Drug Administration's (FDA) **New Drug Application** (**NDA**) is the vehicle in the United States through which drug sponsors formally propose that the FDA approve a new pharmaceutical for sale and marketing.[1][2] Some 30% or less of initial drug candidates proceed through the entire multi-year process of drug development, concluding with an approved NDA, if successful.[1]

The goals of the NDA are to provide enough information to permit FDA reviewers to establish the complete history of the candidate drug.[3] Among facts needed for the application are:[2]

- Patent and manufacturing information
- Drug safety and specific effectiveness for its proposed use(s) when used as directed
- Reports on the design, compliance, and conclusions of completed clinical trials by the Institutional Review Board
- Drug susceptibility to abuse
- Proposed labeling (package insert) and directions for use

C) ABBREVIATED NEW DRUG APPLICATION

An **Abbreviated New Drug Application** (**ANDA**) is an application for a U.S. generic drug approval for an existing licensed medication or approved drug.

The ANDA is submitted to FDA's Center for Drug Evaluation and Research, Office of Generic Drugs, which provides for the review and ultimate approval of a generic drug product. Once approved, an applicant may manufacture and market the generic drug product to provide a safe, effective, low cost alternative to the American public. Electronic submissions of ANDAs have grown by 70% since November 2008.[1] The Section IV challenge has been credited with suppressing new drug innovation.[2]

A generic drug product is one that is comparable to a patented drug product in dosage form, strength, route of administration, quality, performance characteristics and intended use. All approved products, both innovator and generic, are listed in FDA's Approved Drug Products with Therapeutic Equivalence Evaluations (Orange Book).

Generic drug applications are termed "abbreviated" because (in comparison with a New Drug Application) they are generally not required to include preclinical (animal and in vitro) and clinical (human) trial data to establish safety and effectiveness. Instead, generic applicants must scientifically demonstrate that their product is bioequivalent (i.e., performs in the same manner as the innovator drug). One way scientists demonstrate bioequivalence is to measure the time it takes the generic drug to reach the bloodstream in 24 to 36 healthy volunteers. This gives them the rate of absorption, or bioavailability,

MODULE 2

2.1THE PRINCIPLES OF ICH GCP

2.1 Clinical trials should be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, and that are consistent with GCP and the applicable regulatory requirement(s).

2.2 Before a trial is initiated, foreseeable risks and inconveniences should be weighed against the anticipated benefit for the individual trial subject and society. A trial should be initiated and continued only if the anticipated benefits justify the risks.

2.3 The rights, safety, and well-being of the trial subjects are the most important considerations and should prevail over interests of science and society.

2.4 The available nonclinical and clinical information on an investigational product should be adequate to support the proposed clinical trial.

2.5 Clinical trials should be scientifically sound, and described in a clear, detailed protocol.

2.6 A trial should be conducted in compliance with the protocol that has received prior institutional review board (IRB)/independent ethics committee (IEC) approval/favourable opinion. .

ICH HARMONISED GUIDELINE INTEGRATED ADDENDUM TO ICH E6(R1): GUIDELINE FOR GOOD CLINICAL PRACTICE E6(R2) Current Step 4 version dated 9 November 2016.

2.2 NEW 2.1."ICH-Good Clinical Practice":

A) Objectives:

1. To provide an overview of the history of Good Clinical Practice (International Conference on Harmonisation).
2. To emphasize the importance of ICH GCP compliance when conducting clinical trials.
3. To discuss key aspects of GCP such as patient recruitment, consent and data privacy.
4. To recognize the implications of non-compliance.
5. To review positive and negative case studies.

B) Scope:

The objective of this Guideline is to outline the mission and the organization of a sponsor's auditing department and the principles for planning, performing and reporting audits, all of which should be considered when the auditor who belongs to the sponsor performs an audit a clinical trial performed by the sponsor.

2.2:"New Drug and Clinical Trial Rules 2019

A) Objectives:

These rules shall apply to clinical trials, bioavailability or bioequivalence (BA/BE) studies of new drugs and regulation of ethical committees approving them. The primary objectives of the new rules are:

Promotion of research and development in India.

Faster accessibility to new drugs.

Predictability and transparency in approval process.

Improvement data credibility and accuracy.

B) Scope: These rules shall apply toNDs, INDs for human use, CT,BA,BE and regulation of ethics committee relating to CT,BA/BE study and biomedical health research.Definition of new drugs has been modified to incorporate novel drug delivery system (NDDS), living modifies organism, monoclonal antibody, stem cell, gene therapeutic products,xenografts, etc.

2.2. Protocol Designing for clinical trials:

Trial Design: The scientific integrity of the trial and the credibility of the data from the trial depend substantially on the trial design. A description of the trial design should include:

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

- A description of the trial treatment(s) and the dosage and dosage regimen of the investigational product(s). Also include a description of the dosage form, packaging, and labeling of the investigational product(s).
- The expected duration of subject participation, and a description of the sequence and duration of all trial periods, including follow-up, if any.
- A description of the "stopping rules" or "discontinuation criteria" for individual subjects, parts of trial, and entire trial.
- Accountability procedures for the investigational product(s), including the placebo(s) and comparator(s), if any.
- Maintenance of trial treatment randomization codes and procedures for breaking codes.

2.3 Clinical Trial Protocol Development

The NIH provides many resources for protocol development to assist investigators in writing and developing clinical research protocols that are in compliance with regulatory/GCP requirements. Some NIH institutes have a mandatory requirement for using their protocol template.

For more information on protocol resources at UCSF and for a video with information about protocol development

Sample Protocol Templates and Resources:

- UCSF Protocol Template
- MOP Template
- UCSF Descriptive Study Protocol Template - The protocol template is a tool to help facilitate the development of protocols for retrospective chart reviews.

Protocol development assistance covering a wide-range of therapeutic areas is available. .

EU Clinical Trials Application Process (Initial Application)

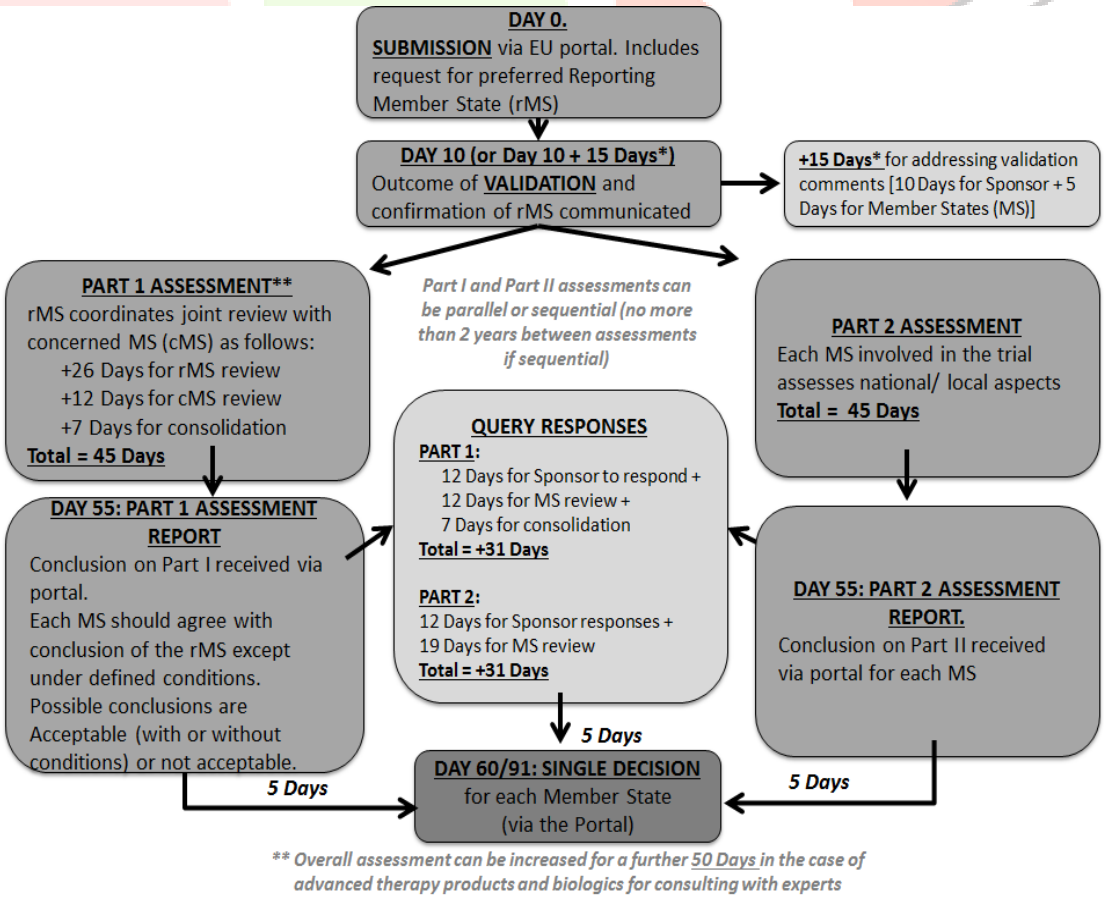


Table 2. EU Clinical Trials Application Process Timelines

	VALIDATION	ASSESSMENT	OUTCOME	TOTAL DURATION
	Submission Date to Validation Date	Validation Date to Reporting Date	Reporting Date to Notification Date	Submission Date to Notification Date
Initial CT Application	10-25	45-76 (+ 50 days for advanced therapies or biologics)	5	60- 106 (+50)
Addition of a MS	Not Applicable			52-83
Substantial Modification	6-21	38-69	5	49-95

NOTE: Some member states may work to shorter timelines for mono-state applications, and indeed the UK and Belgium have suggested this would be the case for applications they receive for Phase I CTs.

MODULE 3

CONCEPT OF PHARMACOVIGILANCE

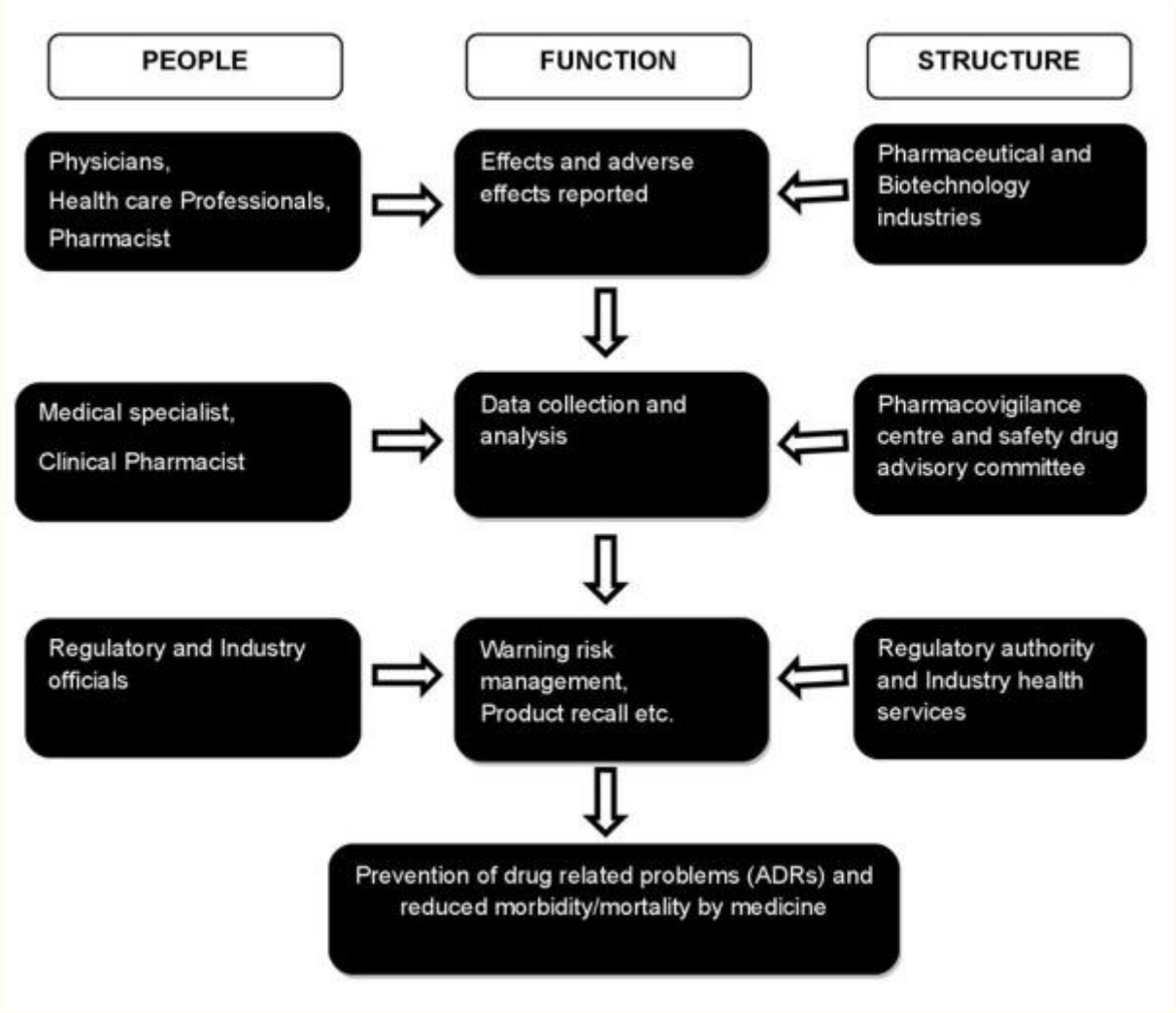
Pharmacovigilance (PV) plays a key role in the healthcare system through assessment, monitoring and discovery of interactions amongst drugs and their effects in human. Pharmaceutical and biotechnological medicines are designed to cure, prevent or treat diseases; however, there are also risks particularly adverse drug reactions (ADRs) can cause serious harm to patients. Thus, for safety 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. Pharmacogenetics and pharmacogenomics are an indispensable part of the clinical research. Variation in the human genome is a cause of variable response to drugs and susceptibility to diseases are determined, which is important for early drug discovery to PV.

3.1.2 OBJECTIVES

Pharmacovigilance (PV) was officially introduced in December 1961 with the publication of a letter (case report) in the Lancet by W. McBride, the Australian doctor who first suspected a causal link between serious fetal deformities (phocomelia) and thalidomide, a drug used during pregnancy: Thalidomide was used as an antiemetic and sedative agent in pregnant women . In 1968, the World Health Organization (WHO) promoted the “Programmed for International Drug Monitoring”, a pilot project aimed to centralize world data on adverse drug reactions (ADRs). In particular, the main aim of the “WHO Programme” was to identify the earliest possible PV signals. The term PV was proposed in the mid-70s by a French group of pharmacologists and toxicologists to define the activities promoting “The assessment of the risks of side effects potentially associated with drug treatment”.

PV is the science of collecting, monitoring, researching, assessing and evaluating information from healthcare providers and patients on the adverse effects of medications, biological products, blood products, herbals, vaccines, medical device, traditional and complementary medicines with a view to identifying new information about hazards associated with products and preventing harm to patients. The challenge of maximizing drug safety and maintaining public confidence has become increasingly complex. Pharmaceutical and biotechnology companies must not only monitor, but also proactively estimate and manage drug risk throughout a product’s lifecycle, from development to post-market [3].

3.1.3. SCOPE OF PV



A typical pharmacovigilance setup

3.1.4 Vaccines and biological medicines

Vaccines and biological medicines require modified systems of safety monitoring. They are often administered to healthy children. This applies particularly to vaccines used within a national immunization program. In many countries, those exposed to a particular vaccine represent the entire birth cohort and therefore a sizeable part of the entire population. People's expectations of safety are high, and they are reluctant to countenance even a small risk of adverse events. Concerns regarding vaccine safety, real or imagined, may result in loss of confidence in the entire vaccine programs. This can result in poor compliance and a consequent resurgence in morbidity and mortality of vaccine-preventable disease.

3.2Costituttional objectives of PvPI

PHARMACOVIGILANCE PROGRAMME OF INDIA

The **Pharmacovigilance Programme of India** (**PvPI**) is an Indian government organization which identifies and responds to drug safety problems.Its activities include receiving reports of adverse drug events and taking necessary action to remedy problems. The Central Drugs Standard Control Organisation established the program in July 2010 with All India Institute of Medical Sciences, New Delhi as the **National Coordination Centre**, which later shifted to Indian Pharmacopoeia Commission in Ghaziabad on 15 April 2011.

History

Many developed countries set up their pharmacovigilance programs following the Thalidomide scandal in the 1960s.[1] India set up its program in the 1980s.[2] This general concept of drug safety monitoring went through different forms, but the Central Drugs Standard Control Organisation established the present Pharmacovigilance Program of India in 2010.[2] Now the program is well integrated with government legislation, a regulator as leader, and a research center as part of the Indian Pharmacopoeia Commission.[2]

3.3List of national adverse drug monitoring centre and their function

Lists of National Adverse Drug Monitoring Centers (AMCs):

1. Department of Pharmacology, All India Institute of Medical Sciences, New Delhi.
2. Department of Pharmacology, Therapeutics & Toxicology, Govt. Medical College, Bakshi Nagar, Jammu.
3. Department of Pharmacology, PGIMER, Chandigarh.
4. Department of Pharmacology, R.G. Kar Medical College, Kolkata.
5. Department of Pharmacology, Lady Hardinge Medical College, New Delhi
6. Department of Clinical Pharmacology, Seth GS Medical College & KEM Hospital, Parel, Mumbai .
7. Department of Clinical & Experimental Pharmacology, School of Tropical Medicine, Chittaranjan Avenue, Kolkata .
8. Department of Pharmacology, JIPMER, Pondicherry.
9. Department of Clinical Pharmacy, JSS Medical College Hospital, Karnataka.
10. Department of Pharmacology, Medical College, Guwahati. Assam.
11. Institute of Pharmacology, Madras Medical College, Chennai.
12. Department of Pharmacology, SAIMS Medical College, Indore-Ujjain.
13. Department of Pharmacology, GSVM Medical College, Swaroop Nagar, Kanpur, U.P.
14. Department of Pharmacology, Pandit Bhagwat Dayal Sharma, Post Graduate Institute of Medical Sciences, Rohtak, Haryana.
15. Department of Pharmacology, Dayanand Medical College and Hospital, Ludhiana, Punjab.
16. Department of Clinical Pharmacology, Sher-i-Kashmir Institute of Medical Sciences, Srinagar, J&K.
17. Himalayan Institute of Medical Sciences, Dehradun, Uttrakhand.
18. Department of Pharmacology, Santosh Medical University, Santosh Nagar, Ghaziabad.
19. Department of Pharmacology, SMS Medical College , Jaipur.
20. Department of Clinical Pharmacology, Christian Medical College,Vellore, Tamil Nadu.

Function:

1. To boost the care and safety of the patient with respect to the consumption of medicines, medical devices and other healthcare interventions;
2. To improve the public health and safety, while using medicines;
3. To detect problems of medicine usage, reduce risks and communicate the observations in a disciplined way;
4. To contribute to the evaluation of benefit, hazard, effectiveness and dangers of medicines, directing to the curbing of harm and maximization of beneficial effects;
5. To embolden the safe, effective (i.e., cost-effective) and rational applications of medicines;
6. To enhance the understanding, education and the scientific and clinical tutelage in PV and its fruitful communication to the people.

MODULE 4

4. INTERNATIONAL CONFERENCE ON HARMONISATION(ICH) E2e Guidlines

1.1 Objectives of the Guideline The purpose of this document is to recommend international standards for, and promote harmonisation of, the nonclinical safety studies recommended to support human clinical trials of a given scope and duration and marketing authorization. Harmonisation of the guidance for nonclinical safety studies will help to define the current recommendations and reduce the likelihood that substantial differences will exist between regions. This guidance should facilitate the timely conduct of clinical trials, reduce the use of animals in accordance with the 3R (reduce/refine/replace) principles and reduce the use of other drug development resources. This should promote safe and ethical development and availability of new pharmaceuticals. 1.2 Background The recommendations of this revised guidance further harmonize the nonclinical safety studies to support the various stages of clinical development among the regions of Europe, USA, and Japan. The present guideline represents the consensus that exists regarding the scope and duration of nonclinical safety studies to support the conduct of human clinical trials and marketing authorization for pharmaceuticals. 1.3 Scope of the Guideline The nonclinical safety study recommendations for the marketing approval of a pharmaceutical usually include safety pharmacology studies, repeated dose toxicity studies, toxicokinetic and nonclinical pharmacokinetic studies, reproduction toxicity studies, genotoxicity studies and, for drugs that have special cause for concern or are intended for a long duration of use, an assessment of carcinogenic potential. Other nonclinical studies including phototoxicity studies, immunotoxicity studies, juvenile animal toxicity studies, and abuse potential studies should be conducted on a case-by-case basis as appropriate. These types of studies and their relation to the conduct of human clinical trials are presented in this guideline. This guideline applies to the situations usually encountered during the conventional development of pharmaceuticals and should be viewed as providing general guidance for drug development. Animal safety studies and human clinical trials should be planned and designed to represent an approach that is scientifically and ethically appropriate for the pharmaceutical under development. It is generally recognized that the types of safety studies conducted in the evaluation of biotechnology-derived products (as defined in Ref. 1) are varied and should be determined in accordance with the ICH guideline for biotechnology-derived products. The present ICH guideline (M3) can provide general insight for biotechnology-derived products only with regard to timing of nonclinical studies relative to clinical development stage.

4.1Elements of the non-clinical and clinical safety specifications

Non clinical safety specification:

Within the Specification, this section should present non-clinical safety findings that have not been adequately addressed by clinical data, for example: • Toxicity (including repeat-dose toxicity, reproductive/developmental toxicity, nephrotoxicity, hepatotoxicity, genotoxicity, carcinogenicity etc.); • General pharmacology (cardiovascular, including QT interval prolongation; nervous system; etc.); • Drug interactions; • Other toxicity-related information or data. If the product is intended for use in special populations, consideration should be given to whether specific non-clinical data needs exist.

Clinical Safety Specifications:

A.Limitations of the Human Safety Database:Limitations of the safety database (e.g., related to the size of the study population, study inclusion/exclusion criteria) should be considered, and the implications of such limitations with respect to predicting the safety of the product in the marketplace should be explicitly discussed.

B.Populations not Studied in the Pre-Approval Phase:The Specification should discuss which populations have not been studied or have only been studied to a limited degree in the pre-approval phase. The implications of this with respect to predicting the safety of the product in the marketplace should be explicitly discussed.

c. Adverse Events (AEs) / Adverse Drug Reactions (ADRs): This section should list the important identified and potential risks that require further characterisation or evaluation. Specific references should be made to guide a reviewer to where clinical safety data are presented.

d. Epidemiology: The epidemiology of the indication(s) should be discussed. This discussion should include incidence, prevalence, mortality and relevant co-morbidity, and should take into account whenever possible stratification by age, sex, and racial and/or ethnic origin.

4.2Identification and evaluation of risks inclunding drug drug interation and drug food interaction:

Identified risks that require further evaluation More detailed information should be included on the most important identified AEs/ADRs, which would include those that are serious or frequent and that also might have an impact on the balance of benefits and risks of the product. This information should include evidence bearing on a causal relationship, severity, seriousness, frequency, reversibility and at-risk groups, if available. Risk factors and potential mechanisms should be discussed. These AEs/ADRs should usually call for further evaluation as part of the Pharmacovigilance Plan (e.g., frequency in normal conditions of use, severity, outcome, at-risk groups, etc.). Potential risks that require further evaluation Important potential risks should be described in this section. The evidence that led to the conclusion that there was a potential risk should be presented. It is anticipated that for any important potential risk, there should be further evaluation to characterise the association. Pharmacovigilance Planning 5 d. Identified and Potential Interactions, Including Food-Drug and DrugDrug Interactions Identified and potential pharmacokinetic and pharmacodynamic interactions should be discussed. For each, the evidence supporting the interaction and possible mechanism should be summarised, and the potential health risks posed for the different indications and in the different populations should be discussed.

4.2.1 Drug drug interaction

Background: Drug-drug interactions (DDIs) are ubiquitous, harmful and a leading cause of morbidity and mortality. With an aging population, growth in polypharmacy, widespread use of supplements, and the rising opioid abuse epidemic, primary care physicians (PCPs) are increasingly challenged with identifying and preventing DDIs. We set out to evaluate current clinical practices related to identifying and treating DDIs and to determine if opportunities to increase prevention of DDIs and their adverse events could be identified.

Introduction

Drug-drug interactions (DDIs) are ubiquitous, costly and a leading cause of morbidity and mortality worldwide. In the United States alone, DDIs contribute to 20% of all adverse drug events which cause nearly 770,000 deaths and result in $30 billion to $180 billion in healthcare expenditures and four hospitalizations per 1,000 people annually

An aging population, polypharmacy treatment, supplements use and drug abuse will only make this problem worse. Today the average patient over 65 is on four medications and, by 2020, 18% of the US population will be over 65. Polypharmacy, defined as concomitant use of five or more medications, is associated with an 80% risk of experiencing a DDI. Today, in the US, approximately 36% of adults can be categorized as polypharmacy patients. The risk of potentially life-threatening drug interactions extends beyond just prescription medications as well. Dietary and herbal supplement use is both common and rapidly rising throughout the US .Concurrent use of supplements with just one prescription medication is associated with a 1 in 25 risk of a DDI .

4.2.2Food-Drug Interactions

The effect of drug on a person may be different than expected because that drug interacts with another drug the person is taking (drug-drug interaction), food, beverages, dietary supplements the person is consuming (drug-nutrient/food interaction) or another disease the person has (drug-disease interaction). A drug interaction is a situation in which a substance affects the activity of a

drug, i.e. the effects are increased or decreased, or they produce a new effect that neither produces on its own. These interactions may occur out of accidental misuse or due to lack of knowledge about the active ingredients involved in the relevant substances. Regarding food-drug interactions physicians and pharmacists recognize that some foods and drugs, when taken simultaneously, can alter the body's ability to utilize a particular food or drug, or cause serious side effects. Clinically significant drug interactions, which pose potential harm to the patient, may result from changes in pharmaceutical, pharmacokinetic, or pharmacodynamic properties. Some may be taken advantage of, to the benefit of patients, but more commonly drug interactions result in adverse drug events. Therefore it is advisable for patients to follow the physician and doctors instructions to obtain maximum benefits with least food-drug interactions. The literature survey was conducted by extracting data from different review and original articles on general or specific drug interactions with food. This review gives information about various interactions between different foods and drugs and will help physicians and pharmacists prescribe drugs cautiously with only suitable food supplement to get maximum benefit for the patient.

Medicines can treat and cure many health problems. However, they must be taken properly to ensure that they are safe and effective. Medications should be extremely specific in their effects, have the same predictable effect for all patients, never be affected by concomitant food or other medications, exhibit linear potency, be totally non-toxic in any dosage and require only a single dose to affect a permanent cure. However, this ideal drug is still to be discovered.

Many medicines have powerful ingredients that interact with the human body in different ways. Diet and lifestyle can sometimes have a significant impact on drugs. A drug interaction is a situation in which a substance affects the activity of a drug, i.e. the effects are increased or decreased, or they produce a new effect that neither produces on its own. Typically, interactions between drugs come to mind (drug-drug interaction). However, interactions may also exist between drugs and foods (drug-food interactions), as well as drugs and herbs (drug-herb interactions).

CONCLUSION

A large number of drugs are introduced every year. Food-drug interactions can produce negative effects in safety and efficacy of drug therapy, as well in the nutritional status of the patient. Generally speaking, drug interactions are to be avoided, due to the possibility of poor or unexpected outcomes. Like food, drugs taken by mouth must be absorbed through the lining of the stomach or the small intestine. Consequently, the presence of food in the digestive tract may reduce absorption of a drug. Often, such interactions can be avoided by taking the drug 1 hour before or 2 hours after eating. Like drugs, foods are not tested as comprehensively so they may interact with prescription or over-the-counter drugs. The authors would suggest patients to tell their doctors and pharmacists about their food intake and dietary supplements

4.3DESIGN AND CONDUCT OF OBSERVATIONAL STUDIES

Observational study designs, also called epidemiologic study designs, are often retrospective and are used to assess potential causation in exposure-outcome relationships and therefore influence preventive methods. Observational study designs include ecological designs, cross sectional, case-control, case-crossover, retrospective and prospective cohorts. An important subset of observational studies is diagnostic study designs, which evaluate the accuracy of diagnostic procedures and tests as compared to other diagnostic measures. These include diagnostic accuracy designs, diagnostic cohort designs, and diagnostic randomized controlled trials.

Study design plays an important role in the quality, execution, and interpretation of biomedical and public health research. Each study design has their own inherent strengths and weaknesses, and there can be a general hierarchy in study designs, however,

Observational and interventional studies

Within primary research there are observational studies and interventional studies. Observational studies, also called epidemiological studies, are those where the investigator is not acting upon study participants, but instead observing natural relationships between factors and outcomes. Diagnostic studies are classified as observational studies, but are a unique category and will be discussed independently. Interventional studies, also called experimental studies, are those where the researcher intercedes as part of the study design. Additionally, study designs may be classified by the role that time plays in the data collection, either retrospective or prospective. Retrospective studies are those where data are collected from the past, either through records created at that time or by asking participants to remember their exposures or outcomes. Retrospective studies cannot demonstrate temporality as easily and are more prone to different biases, particularly recall bias. Prospective studies follow participants forward through time, collecting data in the process. Prospective studies are less prone to some types of bias and can more easily demonstrate that the exposure preceded the disease, thereby more strongly suggesting causation.

MODULE 5: ASSESMENT OF ADR BY NARANJO SCALE

The Naranjo Algorithm, or Adverse Drug Reaction Probability Scale, is a method by which to assess whether there is a causal relationship between an identified untoward clinical event and a drug using a simple questionnaire to assign probability scores.

The Adverse Drug Reaction (ADR) Probability Scale was developed in 1991 by Naranjo and coworkers from the University of Toronto and is often referred to as the Naranjo Scale. This scale was developed to help standardize assessment of causality for all adverse drug reactions and was not designed specifically for drug induced liver injury. The scale was also designed for use in controlled trials and registration studies of new medications, rather than in routine clinical practice.

The ADR Probability Scale consists of 10 questions that are answered as either Yes, No, or “Do not know”. Different point values (-1, 0, +1 or +2) are assigned to each answer. A simplified version of the 10 questions is provided below:

- Are there previous conclusive reports of this reaction?
- Did the adverse event appear after the drug was given?
- Did the adverse reaction improve when the drug was discontinued or a specific antagonist was given?
- Did the adverse reaction reappear upon readministering the drug?
- Were there other possible causes for the reaction?
- Did the adverse reaction reappear upon administration of placebo?
- Was the drug detected in the blood or other fluids in toxic concentrations?
- Was the reaction worsened upon increasing the dose? Or, was the reaction lessened upon decreasing the dose?
- Did the patient have a similar reaction to the drug or a related agent in the past?
- Was the adverse event confirmed by any other objective evidence?

Probability Scale is easier to apply, but has less sensitivity and specificity in assigning causality to cases of drug induced liver injury.

Narjo Algorithm-ADR Probablity Scale

5.1 Naranjo Algorithm - ADR Probability Scale

Score	Interpretation of Scores
Total Score ≥9	**Definite**. The reaction (1) followed a reasonable temporal sequence after a drug or in which a toxic drug level had been established in body fluids or tissues, (2) followed a recognized response to the suspected drug, and (3) was confirmed by improvement on withdrawing the drug and reappeared on reexposure.
Total Score 5 to 8	**Probable**. The reaction (1) followed a reasonable temporal sequence after a drug, (2) followed a recognized response to the suspected drug, (3) was confirmed by withdrawal but not by exposure to the drug, and (4) could not be reasonably explained by the known characteristics of the patient's clinical state.
Total Score 1 to 4	**Possible**. The reaction (1) followed a temporal sequence after a drug, (2) possibly followed a recognized pattern to the suspected drug, and (3) could be explained by characteristics of the patient's disease.
Total Score ≤0	**Doubtful**. The reaction was likely related to factors other than a drug.

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