Q. Discuss in detail IND applications?

IND (investigational new drug application)

- The US,FDA **investigational New Drug (IND)** program is the means by which a pharmaceutical company obtains permission to ship an experimental drug across state lines (usually to clinical investigators) before a marketing application for the drug has been approved
- The FDA reviews the IND application for safety to assure that research subjects will not be subjected to unreasonable risk. If the application is cleared, the candidate drug usually enters a Phase 1 clinical trial

Criteria:

- New indication
- Change in the approved route of administration or dosage level
- Change in the approved patient population (e.g. pediatric) or a population at greater or increase of risk (elderly, HIV positive, immunocompromised)
- Significant change in the promotion of an approved drug

Types:

1. Regular IND:
    - An Investigator IND is submitted by a physician who both initiates and conducts an investigation, and under whose immediate direction the investigational drug is administered or dispensed. A physician might submit a research IND to propose studying an unapproved drug, or an approved product for a new indication or in a new patient population.
2. Emergency IND:
    - Emergency Use IND allows the FDA to authorize use of an experimental drug in an emergency situation that does not allow time for submission of an IND.
3. Treatment IND:
    - Treatment IND is submitted for experimental drugs showing promise in clinical testing for serious or immediately life-threatening conditions while the final clinical work is conducted and the FDA review takes place.

When to use IND applications:

1. Drug intended to treat or diagnostic serious or life threatening condition
2. No satisfactory alternative available.
3. Controlled clinical trials in progress under IND or when trials completed & FDA review of request to market as pending
4. Sponsor actively pursuing device marketing approval with FDA
5. Need FDA authorization to use experimental drug in an emergency situation that does not allow time for submission of an IND

6. May be used for patients ineligible per existing study protocol (s), or if approved study protocol does not exist

Categories:

- Commercial
- Research (non-commercial)

IND application contents:

1. Cover sheet/ application form
    - Required for initial IND& all subsequent submissions
    - Provides basIC inFo bout Sponser & submission contents
    - Must be signed & dated
    - obligates sponsei to comply with laws and regulations
2. table of contents
3. Introductory statement
    - drug name , structure, pharmacological class ,development history
4. General investigational plan
    - Summary of studies anticipated in first year
    - Study rationale
5. Investigator brochure
    - Package insert
    - Early version contains more clinical data
    - Later version more heavily weighted with clinical area
6. Protocols
    - Must include at least initial protocol (No subjects , Eligibility requirements)
7. Chemistry , manufacturing and control info
8. pharmacology & toxicology info
9. previous human experience with drug
10. Additional information as required by FDA

- Drug dependency/abuse potential
- Radioactive drugs
- Pediatric drugs

Q. Requirement to conduct clinical trials as per schedual Y

- Participation in the WHO GMP certification scheme
- Coordinating the activities of the State Drugs Control Organizations to achieve uniform administration of the Act; and policy guidance.

Clinical trials Guidelines In India:

The guidelines that govern the conduct of clinical trials in India include:

- Schedule Y (Revised-2005) of Drugs and Cosmetics Act, 1940
- Ethical Guidelines for Biomedical Research on Human Subjects, 2006
- Good Clinical Practices, 2001

SCHEDULE Y (Revised-2005) of Drugs and Cosmetics Act, 1940

[See rules 122A, 122B, 122D, 122DA, 122DAA and 122E]

- **Rule 122 A - Permission to import new drug**
- **Rule 122 B - Permission to manufacture new drug**
- **Rule 122 DA - Definition of Clinical trials**
- **Rule 122 E - Definition of New Drugs***

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The Requirements and guidelines for permission to Import and / or Manufacture of New Drugs for sale or to undertake Clinical Trials

122-DAA Definition of Clinical trial: "Clinical trial" means a systematic study of new drug(s) in human subject(s) to generate data for discovering and / or verifying the clinical, pharmacological (including pharmacodynamic and pharmacokinetic) and /or adverse effects with the objective of determining safety and / or efficacy of the new drug. ".

Application for the permission of carrying out a clinical trial in India is made to the office of DCGI. General recommendations carrying out clinical trials in India as specified in

Schedule Y are as follows:

- The requirements for carrying out clinical trials in India before a new drug is approved for marketing depend upon the status of drug in other countries.
- For new drugs approved outside India, Phase-3 trials are required to be conducted in India before permission to market the drug in India is granted. Prior to conduct of Phase-3 studies in India subjects, Licensing Authority may require pharmacokinetic studies to be undertaken to verify that data generated in India population is in conformity with data already generated abroad.

- For new drug substances discovered in India, clinical trials are required to be carried out in India right from phase-1. For new drugs substances discovered in countries other than India, phase-1 data should be submitted along with the application. After submission of phase-1 data generated outside India to the licensing authority, permission may be granted to repeat phase-1 trials and/or to conduct phase-2 trials and subsequently phase-2 trials concurrently with other global trials for that drug.
- Application for permission to import or manufacture new drugs for sale or to undertake clinical trials shall be made in "Form 44 format.
- If the study drug is intended to be imported for the purposes of examination, test or analysis, the application for import of small quantities of drugs for such purpose should also be made in Form 12.
- For drugs indicated in life threatening / serious diseases or diseases of special relevance to the Indian health scenario, the toxicological and clinical data requirements may be abbreviated, deferred or omitted, as deemed appropriate by the Licensing Authority.
- Laboratories used for generating data for clinical trials should be compliant with Good Laboratory Practices (GCP).

- In case of studies prematurely discontinued for any reason a summary report (in specified format) should be submitted within 3 months.

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- Any unexpected serious adverse event (SAE) occurring during a clinical trial should be communicated promptly (with in 14 calendar days) by sponsor to the licensing authority and to other investigator(s) participating in the study (appendix-
- 9).The investigator has to give an undertaking on GCP compliance as per the format specified in appendix -7.
- The investigator has to report all serious and unexpected adverse events to the sponsor within 24 hours and to the Ethics committee within 7 working days of their occurrence.
- Ethics committee should have written standard operating procedures and should maintain a record of its proceedings. In case an ethics committee revokes its approval accorded to a trial protocol, it must record the reasons for doing so and at once communicate such a decision to the investigator as well as to the licensing authority.
- Geriatric patients should be included in phase-3 clinical trials if the disease intended to be treated is characteristically a disease of aging or when the new drug is likely to the geriatric patient's response compared with that the non-geriatric patient.
- Paediatric subjects are legally unable to provide written informed consent, and are dependent on their patient(s)/legal guardian to assume responsibility for their participation in clinical studies.
- Subsequent to approval of the product, new drugs should be closely monitored for their clinical safety once they are marketed.

- The Periodic Safety Update Reports (PSURs) shall be submitted every six months for the first two years after approval of the drug is granted to the applicant.
- For subsequent two years PSURs need to be submitted annually.
- Licensing authority may extend the total duration of submission of PSURs if it is considered necessary in the interest of public health.
- PSURs due for a period must be submitted within 30 calendar days of the last day of the reporting period.

The global clinical trials are classified into 2 categories on their approval duration:

Category A and Category B

Category A: Clinical trials approved by USA, UK, Switzerland, Australia,

Canada, Germany, South Africa, Japan, and EMEA. DCGI will grant the approved

within2-4 weeks.

Category B: Clinical trials approved by other countries not listed under category

A. Regulatory turnaround time would be approx 8-12 weeks.

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Protocol amendments have been classified into three categories:

1. Those amendments which do not require any information or permission,

a. Administrative and logistic changes

b. Minor protocol amendments and additional safety assessments in case the IEC

2. Those amendments which require being informed but need not wait for permission,

a. Additional investigator sites

b. Amended investigator's brochure, amended ICD

3. Those amendments which require prior permission before implementation of the amendments,

a. Changes of principal investigator

b. Additional patients to be recruited

c. Major changes in the protocol with respect to the study design, dose and treatment options.

Clinical trial on a new drug shall be initiated only after the permission has been granted by the licensing authority under rule

21 (b), and the approval obtained from the respective ethics committee.

Appendices: Provide a study synopsis, copies of the informed consent documents (patient information sheet, informed consent form etc.); CRF and other data collection forms; a summary of relevant pre-clinical safety information and any other documents referenced in the clinical protocol. has already approved these changes.

APPENDIX I

Data to be submitted along with the application to conduct clinical trials / Import / manufacture of new drugs for marketing in the country

1. Introduction

2. Chemical and pharmaceutical information

3. Animal Pharmacology (refer Appendix IV)

4. Animal Toxicology (refer Appendix III)

5. Human / Clinical pharmacology (Phase I)

6. Therapeutic exploratory trials (Phase II)

7. Therapeutic confirmatory trials (Phase III)

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8. Special studies

9. Regulatory status in other countries

10. Prescribing information

11. Samples & testing protocol

APPENDIX I-A

Data required to be submitted by an applicant for grant of permission to import and / or manufacture a new drug already approved in the country.

1. Introduction

2. Chemical and pharmaceutical information

3. Marketing information

4. Special studies conducted with approval of Licensing Authority

Appendix II

Structure, contents and format for clinical study reports

Appendix III

Animal toxicology (non-clinical toxicity studies)

Appendix IV

Animal pharmacology

Appendix V

Informed consent

Appendix VI

Fixed dose combinations (fdcs)

Appendix VII

Undertaking by the investigator

Appendix VIII

Ethics Committee

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Appendix IX

Stability testing of new drugs

Appendix X

Contents of the proposed protocol for conducting clinical trials

Appendix XI

Data Elements for reporting serious adverse events occurring in a clinical trial

Ethical Guidelines for Biomedical Research on Human Subjects, 2006:

The Indian Council of Medical research brought out the 'Policy Statement on Ethical

Considerations involved in Research on Human Subjects' in 1980 and revised these guidelines in 2000 as the 'Ethical guidelines for Biomedical Research on Human subjects'.

This statement of Ethical Guidelines for Biomedical Research on Human Participants shall be known as the ICMR Code and shall consist of the following:-

Q. explain various phases of clinical trials

Clinical trial

- A clinical trial is a research study in human volunteers to answer specific health questions. Carefully conducted clinical trials are the fastest and safest way to find treatments that work in people and ways to improve health. Interventional trials determine whether experimental treatments or new ways of using known therapies are safe and effective under controlled environments. Observational trials address health issues in large groups of people or populations in natural settings.)

Phases:

PHASE 0:

- Its also called as micro-dosing trial
- It involves very limited human exposure and has no therapeutic content
- Exploratory investigational new drug study

Objective:

- Subtherapeutic doses of study drug to a small number of people
- Preliminary data of agents pharmacokinetics and pharmacodynamics
- Does not give data on safety and efficacy
- It helps for determination of 1st dose for phase i trial

Advantages:

- Less chances of adverse effects
- Short duration
- Less no. of volunteers
- Reduced cost of development
- Reduced drug development time

Limitation:

- 6-8 month of study
- Limited number of subject

PHASE I

- Its also called as study of human pharmacology
- First stage of testing in human subjects.

Objective:

- Designed to assess the safety, tolerability of the drug over a wide range of doses
- Study on the drugs PK and PD of properties
- A sequence of single dose is used, the dose range is determined from animal toxicology test

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- These experiments determines the maximum tolerated dose or non toxic effect level

Method:

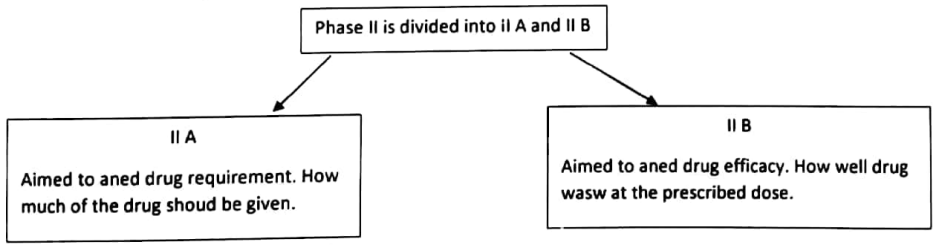
- subjects are 20-80 healthy volunteers.
- The subjects are divided into groups and the experimentation starts with the group assigned to the lowest dose often the dose escalation randomized design is used
- studies are kept under very close observation repeatedly questioned regarding the onset of undesired signs or symptoms
- The volunteers undergo repeated sampling of biological fluids, in order to build the p'kinetic profile of the drug under investigation.
- If the researcher are satisfied with the Safety and tolerability of the first dase, they move to the dose immediately above it, then to the third dose and so on.
- The study ends when either a dose presenting side effects considered unacceptable or the highest dose is reached.

PHASE II

- It is a Therapeutic Exploratory Trial consists of 20-300 Subjects.
- performed on patients affected by the diseas and study.
- Generally the patient selected criteria for phase II are more restrictive compared to phase III, in the sense that subjects with serious or atypical forms of the disease and thosc with concomitant disease or laboratory abnormalities are generally excluded.

objectives:

- Prove that the drug is active on relevani dynamic endpoint..
- select the doses and the frequency of administration for the phase III.
- Objective safety and tolerability data.



Phase II A

- proof of concept studies II A is useful for dealing with an innovative compound.
- Aims to confirm mechanism of action.
- It is based only in "proofs" in vitro and animal models.
- The sample is rigorously selected in that subjects with a "pure" text book like clinical picture are included.
- The chosen dose is the highest that can be administered based on phase I results.
- The proof of concept studies are generally small and complex.

Advantage:

- the drug does not show a sufficient pharmacodynamic action, it is pussibl to discontinue.

PHASE II B (SPECIAL STUDIES)

- Dose finding or dose-ranging studies.
- It includes:
  - studies in elderly patien
  - Studies comparing different races
  - Studies in patient with hepauc and renal insufficiency
  - Studies evaluating interactions between the new drug and other drugs of common use in the disease under study.

PHASE III

- Therapeutic Confirmatory
- phase III are randomized controlled multicenter trials on large patient groups (300-3000) or more depending upon the disease/medical condition studied.
- phase III has two key goals:
  - 1. To demonstrate the therapeutic efficacy of the drug in representative a sample of the population at which the treatment targeted.
  - 2. To demonstrate the safety and tolerability of the drug in a large sample of the population at which the drug is targeted.

PHASE IV

- Methods of post-marketingsurveilance.
  - 1> descriptive study:
    - Case report
    - Case series
  - 2> analytical studies:
    - Case-control
    - Case-cohort
    - Cross-sectional
- Also called as safety surveillance.

Purpose:

- Detect any rare or long –term ADR in large population are large period of time that in not possible in phase 1-3.
- Harmful effects discused by phase IV may result in drug being no longer sold or restricted to certain use.
- Continue CT initiated in phase III.
- Investigate intractions with food, drugs and environmental facts.
- Confirm safty and efficancy in larg population.

Q. different method of post marketing surveillance

- All patients vaccinations and health outcomes are immediately and continuously accessible in automated database allowing optimal detection and analysis are applicable to safety initiatives for other medical products.

Methods of Post Marketing Surveillance (PMS):

The primary objective of post marketing studies is to develop information about drug effects under customary conditions of drug use. Initial clues about a drug's potential effects come from the experimental studies carried out with both animals and humans in the premarketing period. Spontaneous or voluntary reporting (e. g., in letters to the editors of medical journals) is the oldest, and to-date, the most productive source of new in- formation about a drug's possible effects once a drug is marketed. Other types of studies are used to examine in more detail the possible effects of a drug. In general, these other types of studies use either cohort or case-control methods

Thus, four types of studies are generally used to identify drug effects:

1. **Controlled clinical trials,**
2. **Spontaneous or voluntary reporting**
3. **Cohort studies, and**
4. **Case-control studies**

1. Controlled clinical trials:

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PMS studies conducted after the launch of a product is part of Phase IV development of the drug. Some of these studies may be retrospective case-control evaluations. These are done to evaluate rare suspected side effects. For example, when there was a suspicion that use of oral contraceptives may be associated with an increased incidence of thrombophlebitis (clotting of blood in the deep veins) and thromboembolism (blockage of smaller arteries due to detached blood clots) case-control studies were carried out. A group of cases of thromboembolism were compared with age matched controls that were as similar to the cases as possible, but without the disease.

- ❖ To minimize bias through such methods as randomization and " double-blinding"
- ❖ Directly monitor patients for the duration of the study.
- ❖ For evaluating a. thug's efficacy and safety.
- ❖ They are often costly.

2. **Spontaneous or voluntary reporting:** Spontaneous reports are, by definition, submitted voluntarily although under certain circumstances these reports may be encouraged, or "stimulated", by media reports or articles published in medical or scientific publications, or by product lawsuits. In many parts of the world adverse event reports are submitted electronically using a defined message standard by physicians and other health providers & hospitals which may act to alert FDA and pharmaceutical firms to possible adverse effects of drugs.

3. **Cohort studies:** Studies follow a. defined group of patients (the cohort) for a. period of time. Patient's are not randomly assigned, & there is no blinding. If adverse reactions occur. A second group of patients the controls) with the same medical condition, who are not taking the chug and who may be receiving alternative treatment.

   In this method, patients can be directly monitored to ensure they take the drug appropriately, and to observe the drug's effects or monitoring can be less controlled. With less control, a larger cohort can be followed, but bias is thus increased

4. **Case-control studies:** Case-control studies identify patients with the adverse effects to be studied (the cases), and compare them with a. sample (the controls), drawn from the same cohort that gave rise to the cases.

   Controls are matched as closely as possible with the cases, except with regard to the drug's suspected adverse effect, to examine whether exposure to the drug is the cause. Patients with conditions suspected of being associated with a certain drug would have their medical records reviewed or be interviewed concerning the use of that drug. The histories of the controls would also be studied for information about drug use in the general population. By comparing the proportion of drug users among the cases with the proportion of drug users in the general population, it is possible to infer the

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relative frequency with which adverse reactions occur in users of certain drugs as compared with nonusers

References:

1. Borden E. K, The Upjohn Co., "Post-marketing Surveillance of Outpatient Drugs Using a Pharmacy-Based Registry System—Report of Two Studies", presented at the Drug Information Association Workshop, Williamsburg, Va.., December 1981, 10-32.
2. Clarren S. N. et al, "The Evaluabdity Assessment of the Developing Experiment in Post-Marketing Surveillance of Prescription Drugs", (prepared for the Experimental Technology Incentives Program, National Bureau of Standards (Washington D. C. Performance Development Institute, 1981), 10-22.
3. Food and Drug Administration, "Supplementary Report to Contracts and Grants Committee on Medicaid", from the Division of Drug Experience, Bureau of Drugs, 1982, 10-32.
4. Karen Midthun, "Deputy Director Center for Biologics Evaluation and Research", FDA, ICDRA We-Conference Bennie, Switzerland September 15, 2008, 3-20.
5. Phase IV of Drug Development by Dr Viraj Suvarna ,Perspect Clin Res v.1(2); Apr-Jun 2010 PMC314861
6. Post marketing Surveillance of Prescription drug by John H. Gibbons

Q. Explain briefly about ANDA submission

ABBREVIATED NEW DRUG APPLICATION (ANDA)

Introduction:

"ANDA" is the abbreviation for "Abbreviated New Drug Application". It contains data which when submitted to FDA's Center for Drug Evaluation & Research, Office of Generic Drug, provides for the review & ultimate approval of a generic drug product.

Once approved an applicant may manufacture & market the generic drug product provided all issues related to patent protection, safe, effectiveness, low cost alternative to the public. Generic drug applications are termed "abbreviated" because they are generally not required to include preclinical (animal) & clinical (human) data to establish safety & effectiveness. A generic drug product is one that is comparable to an innovator drug product in dosage form, strength, route of administration, quality, performance characteristics & intended use.

All approved products, both innovator & generic, are listed in FDA's Approved Drug Products with Therapeutic Equivalence Evaluations.

Generic applicants must scientifically demonstrate that their product is bioequivalent (i.e. performs in the same manner as the innovator drug). The rate of absorption or bioavailability of the generic drug, is compared to that of the innovator drug.

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The generic version must deliver the same amount of active ingredients into a patient's bloodstream in the same amount as that in the innovator drug. Using bioequivalence as the basis for approving generic copies of the drug products was established by the "Drug Price Competition & Patent Term Restoration Act of 1984", also known as the Waxman-Hatch Act.

At the same time, the branded name companies can apply for up to five additional years longer patent protection for the new medicines they developed to make up for time lost while their products were going through FDA's approval process. Generic drug application reviewers focus on bioequivalence data, chemistry & microbiology data, request for plant inspection, & drug labeling information.

ANDA Requirement:

1. **Signed FDA form 356h.** Provides information regarding the applicants name & address, name of the drug product, the product strength & route of administration, indication of drug master files cited, proposed indications, a statement regarding whether the product is for prescription or over the counter.
2. An **index** should specify volume & page number for each complete & detailed item.
3. **Information on the basis for which the ANDA is being submitted.**

   a) Name of the reference drug, its dosage form & strength.
   b) Information on exclusively for the listed drug.
   c) If a suitability petition is approved a reference to the FDA number that was assigned to that suitability petition.
4. **Condition for use**, including,
   a) A statement regarding the condition for which the drug will be used.
   b) A reference to the annoted labeling for the product & the currently approved labeling for the listed drug product.
5. **A statement that active ingredient is the same as for that of the reference drug. For the combination product this must be shown for both active ingredients**
6. **Route of administration, dosage form & strength**. This should include a statement that the route of administration, dosage form & strength are same as the reference drug.
   Bioequivalence: This should include information to demonstrate that the proposed drug is bioequivalent to the listed drug product.
7. **Labeling**: Include a copy of currently approved labeling for the listed drug as well as the proposed labeling for the drug being provided for in the ANDA. A side by side comparison of two sets of labeling is also necessary.
8. **Chemistry, Manufacturing & Controls:** Describe the composition, manufacture, specifications & analytical procedures for the drug substance & drug product.
9. **Human Pharmacokinetics & Bioavailability**:

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This include information concerning

- The Design
- The Dosing procedure
- The number & frequency of blood & urine collection & Methodology for the assay

10. **Samples:** The sample of the Drug substance & finished product should be provided four individuals units with sufficient quantities in each unit to permit the FDA to perform all the tests included in the specifications at least three times
11. **Analytical method for drug substance & drug product**. This section should consists of the specifications, analytical method, certificates of analysis, method of analysis, method validation & stability indicating data as contained in the chemistry, manufacturing & control part of the application.
12. **Labeling.** 12 specimen of the final printed label & all labeling for the drug product are to be included.
13. **Case report forms & tabulations**. The need for these should be discussed with appropriate personnel of the division of bioequivalence prior to submission of the ANDA.

Patient recruitment and follow up

During the subject enrollment, he/she ensures that all queries are clarified up to the subjects' satisfaction and that the ICF is administered by the Investigator as per the ICH GCP guidelines.

Research Pharmacy, Drug Accountability, and Laboratory Responsibilities

The CRC also have to manage the storage of the study drug - account for study drug received from sponsor, distributed to the patient, returned from the patient and finally back to the sponsor.

They ensure that all laboratory specimens such as blood, urine, tissue etc are properly labeled, packaged and stored before shipment to the central lab. They even coordinate with the central lab on a regular basis for the timely receipt of the reports.

Amendments

They follow up with the sponsor for any amendments in the study protocol or the ICF and ensure that the amended versions are implemented at the site only after the favorable written approval by the IRB.

Post-trial activities

Once the hospital phase of the trial is over, completing the study documentation will become the key focus3. They do a final check

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of the case report forms (CRFs), maintain an archival inventory of records and CRFs in a secure place and coordinate the close out visits.

Q. explain in details NDA submission

New drug application (NDA)

- The NDA application is the vehicle through which drug sponsors, such as biotech and pharmaceutical companies, formally propose that the FDA approve a new pharmaceutical for sale and marketing

Requirement:

Format requirement

A) **No of copies** - Before 1985- 3 copies & now only 2 copies.

1) Archival copy:
- Reference copy for FDA
- Locate information not contained in review copy

2) Review copy:
- Divided in to five or six section containing technical and scientific information separately bound
- It contains copy of cover letter, application form, overall summary, index, specific review section

B) **Assembling the application**

1) Folder
- Color folder
- Name of applicant and name of drug product
- NDA no. if known

2) Paper size and binding
- Page 8.5 – 11 inches
- Bound at left side
- Use both side
- Accurately no.

3) Pagination – page no of both copy should have same

4) Volume size and identification
- Not more than 2 inches thick
- Should have name of applicant, drug and
- NDA no.

5) Packing carton
- Box size 14 -12- 9.5 inches

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Summary requirement

1) **Labeling** : -Proposed label
   - It is also called mini summary
2) **Pharmacological class**
   Intended use
   Potential clinical benefit
3) **Foreign marketing history**
   - List of country who approved same drug
   - List of country who withdrawn same drug

4) **Chemistry, mfg., control**

A) **Drug substance**

-Names:- name, synonym, code designation, brand name, identification no. and chemical name.

-Physical and chemical properties: MP, BP, mol wt., solubility, mol. Formula structural formula, PH, isomer, polymorphs.

-Stability

-Manufacture- Name and method.

B) **Drug product**

-Composition
-Dosage form
-Manufacture
-Closure
-Stability
-Investigational formulation

5) **Nonclinical pharmacology and toxicology summary**

-Pharmacological studies
-Acute toxicity studies
-Multi dose toxicity studies
-Mutagenicity studies
-Reproduction studies
-ADME studies

6) **Human pharmacokinetic summary**
7) **Microbial summary**
   - Microbial spectra
   - Mechanism of action

8) **Clinical data summary and result**

-Clinical pharmacology
-Overview of clinical studies
-Controlled clinical studies
-Uncontrolled clinical studies
-Adverse event
-Clinical laboratory data
-Over dose
-drug abuse

9) **Discussion of benefit to risk relationship and proposed post marketing studies.**
10) **Bioavailability summary**

NDA technical section requirement:

1) **Chemistry, manufacturing, and control**
A) **Drug substance**
B) **Product**
2) **Non clinical pharmacology and toxicology**
3) **Human pharmacokinetics**
4) **Bioavailability section**
5) **Microbiology:**
   -Mechanism of action
   -Pharmacokinetics
   -Antimicrobial activity
   -Enzyme hydrolysis rate
   -Assessment of resistance
   -In vivo animal studies
   -In vitro studies during clinical trial
6) **Clinical data section:**
   - adverse dose- response information
   - drug -drug interaction
   - drug disease interaction

Q. principal of ICH-GCP guideline

Q. explain clinical trial protocol as per ICH-GCP guideline

ICH-GCP guidelines(International Conference on Harmonization)

- ICH-GCP is an International Conference on Harmonization Good Clinical Practice
- the guideline was developed with consideration of the current good clinical practices of the European Union Japan, and the United State as well as those of Australia, Canada, the Nordic countries and the world health organization.
- The ICH was developed in april 1990, hosted by the European Federation of Pharmaceuticals Industries and Association (EFPIA) in Brussels

SPONSORS AND REGIONS of ICH-GCP: Members

- EMEA : The European medicines agency.
- EFPIA : European Federation of Pharmaceutical Industries Association.
- PhRMA : Pharmaceutical Research and Manufactures of America.
- JMHW: Japanese Ministry of Health Welfare
- JPMA: Japanese Pharmaceutical Manufature Association

OBJECTIVE:

- To provide a unified standard for the European Union (EU), japan and the United States to facilitate the mutual acceptance of clinical data by the regulatory authorities in these jurisdictions.
- To identify and then to reduce differences in technical requirements for drug development among regulatory agencies

AIMS:

- Unify registration requirements for new products
- reduce medicinal product development cost more economic use of animal, human and material resources.
- Accelerate medicinal product licensing times: avoid repeat testing in different regions.
- increase patent protection times through reducing delay in licensing times.

Principles:

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. 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 anticipated benefits justify the risks.
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 The available nonclinical and clinical information on an investigational product should be adequate to support the proposed clinical trial
4. Clinical trials should be scientifically sound, and described in a clear, detailed protocol.
5. 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.
6. The medical care given to, and medical decisions made on behalf of subjects should always be the responsibility of a qualified physician or, when appropriate, of a qualified dentist.
7. Each individual involved in conducting a trial should be qualified by education, training, and experience to perform his or her respective task(s).
8. Freely given informed consent should be obtained from every subject prior to clinical trial participation.
9. All clinical trial information should be recorded, handled, and stored in a way that allows its accurate reporting, interpretation and verification.
10. The confidentiality of records that could identify subjects should be protected, respecting the privacy and confidentiality rules in accordance with the applicable regulatory requirement(s).
11. Investigational products should be manufactured, handled, and stored in accordance with applicable good manufacturing practice (GMP). They should be used in accordance with the approved protocol.
12. Systems with procedures that assure the quality of every aspect of the trial should be implemented

Q. Explain Clinical trials and monitoring. Discuss different types of monitoring visits in details (10 M)

Clinical trial:

- a **clinical trial** is any research **study** that prospectively assigns human participants or groups of humans to one or more health-related interventions to evaluate the effects on health outcomes

Monitoring:

- The act of overseeing the progress of a clinical trial, and of ensuring that it is conducted, recorded, and reported in accordance with the protocol, SOPs, GCP, & the applicable regulatory requirements.

Monitoring Report:

- A written report from the monitor to the sponsor after each site visit and other trial-related communication according to the sponsor's SOPs.

Different types of monitoring visits:

1) Site Evaluation/Qualification Visit
2) Site Initiation Visit
3) Site Monitoring Visit
4) Site Close-Out Visit

1) Site Evaluation Visit:

- ICH Guidelines nor FDA regulations specifically require a Site Evaluation Visit.
- ICH does require a pre-trial monitoring report as part of the "Essential Documents" and states that there is a need for on-site monitoring "before, during and after" a trial.
- FDA "Guidelines for the Monitoring of Clinical Investigations" does recommend that a monitor visit the site of the clinical investigation prior to the initiation of the trial.

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2) **Initiation Visit** :

- The purpose of the Site Initiation Visit is to assists the site in its preparation to enroll its first subject & should take place after all required supplies are at the site and just before subject recruitment begins.
- ICH GCP does require a Trial Initiation Monitoring report as part of the "Essential Documents" and the report should be in both the sponsor and site file.
- FDA Guidelines recommend that a monitoring visit should take place "shortly" after the site has enrolled its first few subjects if an SIV was not conducted.

3) **Site Monitoring Visit:**

- ICH 5.1.8.4, Monitor's Responsibilities:
  - Acting as the main line of communication between the sponsor and the investigator.
  - Verifying that the investigator has adequate qualifications and resources throughout the study.
  - Verifying that the investigational product is stored, dispensed and returned properly and that only eligible subjects receive it at the protocol specified dose.
  - Verifying that the investigator follows the approved protocol.
  - Verifying that written informed consent was obtained before each subject's participation in the trial.
  - Ensuring that the investigator receives the current Investigator's Brochure and safety updates.
  - Determining whether all adverse events are appropriately reported within the time periods required by GCP, the protocol, the IRB, the sponsor and the applicable regulatory authorities.

4) **Closing of clinical trial** :

- There are no clear ICH or FDA regulations regarding the close out visit. ICH GCP requires a close-out monitoring report as an Essential Document.
  - The sponsor conducts a close-out visit and signs the monitoring log.
  - The investigator submits a final report to the IRB stating that the site is closed.
  - The sponsor sends the investigator a letter stating that the site is closed.
- Close-Out Visit Activities:
  - Final data review/collection of all outstanding data
  - Return or destruction of all study drug
  - Final review of Regulatory Binder
  - Verification that all biological samples have been submitted
  - Return or destruction of all unused study forms/CRFs
  - Collection of IRB closure report/letter

Q. write note of clinical data managment in clinical trials

Clinical Data Management (CDM)

- **Data management** includes all aspects of data planning, handling, analysis, documentation and storage, and takes place during all stages of a study. The objective is to create a reliable database containing high quality data.

Steps: Components :

1. Planning the data needs of the study
2. Data collection
3. Data entry
4. Data validation and checking
5. Data manipulation
6. Data files backup
7. Data documentation

- Each of these processes requires thought and time; each requires painstaking attention to detail.
- The main element of data management are database files. **Database files** contain text, numerical, images, and other data in machine readable form. Such files should be viewed as part of a database **management systems (DBMs)** which allows for a broad range of data functions, including data entry, checking, updating, documentation, and analysis.

1. Data collection:

- Before analyzing data must collected reviewed coded, computerized, verified, checked, and converted to forms suited or the analyses to be conducted.
- The process must be adequately documented to provide the foundation for analyses interpretation.
- Data collection import baseline data from:
  - Existing systems
  - Import lab results
  - Scan results
  - Other digital data

2. Data management software (data analysis):

- Many DBMSs are Available for personal computer. Options include:
  1) **Spreadsheet** Are to be available for all but the smallest data system, since they are unreliable and easily corrupted.
     E.g. excel. SPSS datasheet (statistical package for the social science)
  2) **Commercially** database program Are expensive. Tend to be large and slow and often **Lack control data entry** facilities.
     E.g. oracle, access.
  3) Especially data entry programs are ideal for data entry and storage.
     E.g. SPSS data entry builder, Epi Data.
- Epi data Repairs to a group of applications used in combination for Creating documented data structures and analyzes of quantitative data.

3. Data entry and validation:

- Data processing errors are errors that a occur After data have been collected.

This is distinct from measurement errors which are differences between the true state of affairs [illegible] appears on the data connection form.

- Errors that are actors during data entry are:
  - Transposition (e.g. 19 becomes 91 during data entry)
  - Copying errors (e.g. 0 (zero) becomes O during data entry)
  - Coding errors (e.g. a racial group gets improperly coded because of changes in the coding scheme)
  - Routing errors (e.g. the interviewer ask the wrong question or asks questions in the wrong order)
  - [illegible] (responses contradictory responses, such as the reporting of a hysterectomy after the respondent has identified himself as male.)
  - Range errors (responses outside of the range of plausible answers, such as a reported age of 290)

Methods **to prevent data entry errors include:**

i. Manual checks during data collection (e.g. checks for comleteness handwriting legibilit)

ii. Renge and consistency checking during data entry (e.g. preventing impossible results such as age greater than 119)

iii. Double entry and validation following data entry.

4. Data backup and storage:

- [illegible] are two kinds of computer users.

i. Those that have lost a major chunk of data.

ii. Those who are going to lose a major chunk of data.

- Data lose can be due to natural disorders human error and computer failure.
- You have worked too hard to collect data and you must not take care of it.
- The most common loss of data among studies is due to lose of data somewhere on the computer.
- The best way to prevent such lose his to know the physical location of your data (Local drive, removable media, network) And to use logical file names. All too often students save files to unknown location (usually the default set up by the program).
- But never fined saved files or have the saved files deleted by the local area network as a part of routine data cleanup
- Always be aware of the location and path folder to which files at are being written.
- It is essential to back-up all data (e.g. data files, code books, software settings, computer programs, word processing documents.)
- Backup system sent all manual or automated copying of files to Removable media (e.g. Floppy disk, zip disks, tape) or to network storage.
- Backup procedures should be truly tested to ensure Archived files remain uncorrupted and can be restored.
- Procedures should be written up so that personnel Unfamiliar with backup and restore methods could follow them from scratch.
- Health researchers must be aware of confidentiality and ethical requirements when working with research files.
- This is especially important when data contain personal identifiers and medical information.

- It is it researchers study to make him or herself of local national and international laws Governing us of health data.

5. Documentation:

- Documentation is a special challenge.
- Documentation should include:
  1. The objectives and methods of study.
  2. Details of events and activities
  3. For each data collection activity a record of the detailed procedures [illegible] accounting of the number of subjects in scope the number selected for data collection and the disposition for all subjects (by category, e.g. Could not count, refusal). This material should have cross references to original sources. (E.g. computer runs) tenable Verification when necessary.
  4. List and descriptions of all interventions applied and materials used (e.g. intervention materials, Training materials).
  5. Documentation on all computerized data and final analyses (Information on databases, variables, computer runs).

Q. write note on pharmaceutical regulations in regard to clinical trial in European union

European union clinical trial Directive

→ The EU directive was first published by the EMEA (European medicine evaluation agency) in 2001

→ Rgulatory in Europe is EMEA, it relies on the results of clinical trials carried out by pharmaceutical company to reach its opinion on the authorisation of medicines, EMEA is a decentralisaal body of the european union with headsquarters in london

→ medicines can be authorized in the european union by using either the centralized authorization procedure or national authorization procedure

→ The purpose of EMEA was to harmonize the initiation and conduct of clinical trials in European union, it was also designed to :-

- protect patients, especially incapacitated and minor patients
- Standardize applications for starting trials
- standardize Ethical committee process

→ The EMEA is a europan agency for the evaluation of medicinal products

→ Committee :

- Committee for medicinal product for human use (cmpH)
- Committee for medicinal products for veterinary use (cmpV)
- Committee for orphan medicinal products (COMP)
- Committee on herbal medicinal products (HMPC)

→ The EU directive applies to all medicinal trials that are interventional, it applies to both commercial and non-commercial trials

→ The directive does not Automatically become effective across european union each country must implement it by passing law enacting them

National authorization procedures:

- Each EU Member State has its own procedures for the authorization, within their own territory, of medicinal products that fall outside the scope of the centralized procedure

- Information about these national procedures can normally be found on the website of the national competent authority in the country concerned.
- The Heads of Agencies website is a useful entry point for such information

- However, there are also two possible routes available to companies for the authorization of such medicinal products in several countries simultaneously:

a. Decentralized procedure:

- Using the decentralized procedure, companies may apply for simultaneous authorization in more than one EU country of medicinal products that have not yet been authorized in any EU country and that do not fall within the mandatory scope of the centralized procedure

b. Mutual-recognition procedure:

- In the mutual-recognition procedure, a medicine is first authorized in one EU Member State, in accordance with the national procedures of that country

2- **Write a note on Centralized procedure and Decentralized Mutual Recognition Procedure in European union. (10 mark)**

Centralized procedure:

- The centralized procedure (also known as the 'Community authorization procedure'). This procedure results in a single marketing authorization (called a 'Community marketing authorization') that is valid across the European Union, as well as in the states Iceland, Liechtenstein and Norway.

- The centralized procedure is compulsory for human medicines that are:
  - Derived from biotechnology processes, such as genetic engineering.
  - Intended for the treatment of HIV/Aids, cancer, diabetes, neurodegenerative disorders or autoimmune diseases and other immune dysfunctions.
  - Officially designated 'orphan medicines' (medicines used for rare diseases).

- For medicines that do not fall within these categories (the 'mandatory scope'), companies have the option of submitting an application for a centralized marketing authorization to the EMEA, as long as the medicine concerned is a significant therapeutic, scientific or technical innovation, or if its authorization would be in the interest of public health.

- Applications through the centralized procedure are submitted directly to the EMEA. Evaluation by the Agency's relevant scientific committee takes up to 210 days, at the end of which the committee adopts an opinion on whether the medicine should be marketed or not. This opinion is then transmitted to the European Commission, which has the ultimate authority for making decisions on

marketing authorizations in the EU. Once a Community marketing authorization has been granted, the marketing-authorization holder can begin to make the medicine available to patients and healthcare professionals in all EU countries.

National authorization procedures:

- Each EU Member State has its own procedures for the authorization, within their own territory, of medicinal products that fall outside the scope of the centralized procedure. Information about these national procedures can normally be found on the website of the national competent authority in the country concerned. there are also two possible routes available to companies for the authorization of such medicinal products in several countries simultaneously:

- **Decentralized procedure:**
  - Using the decentralized procedure, companies may apply for simultaneous authorization in more than one EU country of medicinal products that have not yet been authorized in any EU country and that do not fall within the mandatory scope of the centralized procedure.

- **Mutual-recognition procedure:**
  - In the mutual-recognition procedure, a medicine is first authorized in one EU Member State, in accordance with the national procedures of that country.

- Following this, further marketing authorizations can be sought from other EU countries in a procedure whereby the countries concerned agree to recognize the validity of the original, national marketing authorization.

9. Priority Review, Accelerated Approval, Fast Track

- Speeding the availability of drugs that treat serious diseases are in everyone's interest, especially when the drugs are the first available treatment or if the drug has advantages over existing treatments. The Food and Drug Administration has developed four distinct and successful approaches to making such drugs available as rapidly as possible:
  - Priority Review
  - Breakthrough Therapy
  - Accelerated Approval
  - Fast Track

<u>Accelerated Approval Designation:</u>

- The United States Food and Drug Administration (FDA) initiated the FDA Accelerated Approval Program in 1992 to allow faster approval of drugs for serious conditions that fill an unmet medical need. The faster approval relies on use of surrogate endpoints.
- A surrogate endpoint used for accelerated approval is a marker - a laboratory measurement, radiographic image, physical sign or other measure that is thought to predict clinical benefit, but is not itself a measure of clinical benefit.
- Using surrogate or intermediate clinical endpoints can save valuable time in the drug approval process. For example, instead of having to wait to learn if a drug actually extends survival for cancer patients, the FDA may approve a drug based on evidence that the drug shrinks tumors, because tumor shrinkage is considered *reasonably likely to predict* a real clinical benefit.
  - Drug must treat a serious condition

- Provide significant improvement in safety or effectiveness when compared to drugs currently on the market
- May use surrogate endpoints to demonstrate clinical benefit
- Approval is granted on conditional basis — post-approval trials are necessary
- Earlier and more frequent communication with the FDA during development
- Application is submitted in one package
- Drug is subjected to expedited withdraw

Fast Track Designation:

- The purpose is to get important new drugs to the patient earlier
  - Drug must be intended to treat a serious condition
  - May address an unmet medical need, Filling an unmet medical need is defined as providing a therapy where none exists or providing a therapy which may be potentially better than available therapy.
  - Fast Track designation request can be submitted at any time during drug development process
  - Supporting data can be clinical or nonclinical
  - Earlier and more frequent communication with the FDA during development
  - Rolling review of application , Rolling Review, which means that a drug company can submit completed sections of its Biologic License Application (BLA) or New Drug Application (NDA) for review by FDA, rather than waiting until every section of the NDA is completed before the entire application can be reviewed.
  - Fast Track designation may be withdrawn if drug no longer meets qualifying criteria
- Fast Track designation must be requested by the drug company. The request can be initiated at any time during the drug development process. FDA will review the request and make a decision within sixty days based on whether the drug fills an unmet medical need in a serious condition

Priority Review:

- Drug must treat a serious condition
- Provide significant improvement in safety or effectiveness when compared to drugs currently on the market
- Drug review process is shortened to 6 months
- A Priority Review designation will direct overall attention and resources to the evaluation of applications for drugs that, if approved, would be significant improvements in the safety or effectiveness of the treatment, diagnosis, or prevention of serious conditions when compared to standard applications.

Q. Explain clinical trial audit and inspection with special emphasis on national regulation authorities

AUDIT

- A Systematic and independent examination of trial related activities and documents to determine whether the evaluated trial related activities were conducted and the data were recorded, analyzed and accurately reported according to the Protocol, Sponsor's SOP, Good Clinical Practice and Applicable Regulatory requirement

Qualification of Auditor:

- The sponsor should specify the qualifications of auditors in auditing procedures and should only appoint appropriate individual(s) as auditor(s) based on consideration of his/her education/training, business experience, and ability.
- For example: Knowledge, Skills ,Nature

Responsibilities:

1) Planning of audit:

a. Establishing the Goals of Audits:
- One or more objectives should established for a trial audit based on the importance of the trial with regard to submissions to regulatory authorities
- The most important part of audit planning is to specify the goal(s) of the audit.
- By establishing the goal(s) of an audit, the subjects and methods of the audit will be determined and the consistent conduct of the audit will be ensured.

b. Designing and Updating the Audit Plan
- Planning is essential to systematically, effectively, and efficiently conduct an audit with consideration of resource management in the auditing department
- Audit plans, such as an annual plan, a monthly plan, and a plan specific to each trial or audit, should be established based on:
  - Consideration of the goal,
  - Contents
  - The progress of the targeted trial & other relevant factors.

c. Determining the Subject[s], Timing, and Method[s] of an Audit
- The subject(s) (e.g., a medical institution, CRO system, clinical trial/study report, computerized system validation, and database),
- Timing (e.g., before the start of the trial, during the trial, after the completion of the trial, or periodically)
- Method(s) (e.g., sampling, interview, or tour) of an audit should be determined based on the goal(s) established for the audit.

e. Information in the Audit Plan (irrespective of the type of audit- annual / monthly)

I. The goal of the audit.
II. The subject of the audit.
III. The scope of the audit.
IV. The timing of the audit.
V. The name, title and address of the auditor
VI. The reference documents required.
VII. The person to whom the audit report will be submitted.

2) Conduct of an Audit

- Done by Auditor-according to written plan & procedures
- Involves the examination & evaluation of information obtained through investigation of the Audit trial (SOPs etc) & trial site (facilities & equipment's) as well as interviews with auditee.

a. Explaining the Auditing Procedures
- Auditor should explain auditee in detail about goals & methods of audit- for effective collect of data

b. Conducting an Audit and Collecting Information
- Two types of sponsor's audit
  - Auditing of internal trial-related department(s)
  - Auditing of external establishment(s) involved in the trial concerned, e.g., a medical institution, laboratory, and/or CRO.
- Based upon audit observations collected –auditor will say whether it is in compliance with GCP or not.

c. Confirmation and Evaluation of Audit Observations
- Auditor should discuss the observation made with auditee, so that errors can be confirmed / avoided & can collect if any other information required.
- Auditor should examine whether any violation of protocol / deviation form GCP guidelines.

3) Report the results of an Audit

- Auditor – reports to Sponsor – to make recognize findings & improve.
- To preserve the independence of auditing, the auditor must not be directly involved in the corrective and preventive action (CAPA) process.

a. Preparation of an Audit Report
- Reports will be prepared based upon results of evaluation.
- The contents of an audit report will be as follows:
  - Information that identifies the trial, such as the chemical name or identification code of the investigational drug, the trial title, and the protocol number.
  - The date of issuing the audit report.
  - The subject of the audit.

b. Persons to whom Audit Reports are submitted
- Auditor should submit report to the sponsor.
- A copy of audit report to the Sponsor's auditee
- Auditor should keep in mind about the confidentiality of the reports while handling the data.

4) Corrective and Preventive Actions

- Implementation of CAPA is necessary after audits, to eliminate errors.
- Once audit complete, auditor will should provide CAPA plan to auditee, that will be utilized to remediate issues of non-compliance.

5) Completion of an Audit

- Upon receipt of the preliminary responses to the CAPA from the auditee, the audit is completed.
- CAPA follow-up and subsequent effectiveness verification should be ensured by continued interaction between the auditor and auditee until mutual agreement has been met that the CAPA have been addressed.

6) Audit Certificate:

- The sponsor should attach the audit certificate to a clinical trial/study report of the targeted trial.
- It should contain the following information:
  - Information that identifies the trial, such as the chemical name or identification code of the investigational drug, the trial title, and the protocol number.
  - The date of issuing the audit certificate.
  - The contents of the audit
  - The name, title and address of the auditor
  - The name and workplace address of the auditee.

7) Keeping Audit Record:

- Audit records should be kept according to sponsor's SOPs for record keeping.
- The SOPs should specify the procedures for keeping or destroying audit-related records, as well as the place, subject, and duration of record keeping.

Q. explain procedure of designing of protocol and write importance of CRF

DESIGNING PROTOCOL

1. **Study Summary:**

~~Study summary should include the following~~:

- Protocol title (~~The title on related IRB submissions (e.g., applications for new study, changes in procedure, research progress reports) must match the title of the protocol~~)
- Study phase
- Duration of the study
- Methodology
- Study site
- Approximate number of subjects
- Name, title, address, and telephone number of the PI, Co-PI, sponsors and study coordinators
- Investigator's affiliation

2. **List of Abbreviations:**

Provide a list of abbreviation used in the study protocol.

3. **Background Information/Significance**

- Name and description of the investigational product, and in case of retrospective reviews, justification for the chart and medical record reviews.
- Summary of results from prior clinical studies and clinical data to date. ~~• Human subjects risks and benefits.~~
- Description of the population to be studied.

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- Description and justification for the dosing regimen and treatment period.
- A paragraph stating that the clinical study will be conducted in compliance with the protocol, SOPs and the federal, state and local regulations.
- Citations from the references and data relevant to the study that also provides background for the trial.

4 ➢ **Objectives/Rationale/Research Question**

- Include a detailed description of the primary and secondary objectives and the purpose of the study and clearly state your research hypothesis or your question.
- Discuss the project's feasibility.
- Give details of resources, skills and experience to complete the study.
- Include any pilot study information

5 ➢ **Clinical Study Design:**

- Primary and secondary endpoints, if any, to be measured during the study.
- Include the information that is needed to answer the research question.
- Include the study design e.g. single, double-blind, observational, randomized, retrospective etc. A schematic diagram of the study design would be helpful.
- Include the amount of dosage, dosing regimen of the drug, packaging and labelling of the experimental drug.

- Explain how the study drug will be stored and dispensed.
- Include the expected duration of the study and subject's participation and a description of the sequence and duration of all study periods.
- Include any follow up visits.
- Describe when a subject's participation in the trial may be discontinued.
- Maintenance of randomization codes and confidentiality.
- Describe the potential risks and step s taken to minimize the risks.
- Identify possible benefits of the study.

6 ➢ **Inclusion and Exclusion criteria of the Subjects**

- Include subjects inclusion criteria.
- Include subjects exclusion criteria. Women of childbearing potential may not be routinely excluded from participating in research, however, pregnant women should be excluded unless there is a clear justification to include them.
- Include enrolment of persons of diverse racial and ethnic back grounds to ensure that the benefits of the research study are distributed in an equitable manner.

7 ➢ **Informed consent form process**

- Provide information about the regulatory requirements of the consent form and which languages will be used.
- Include a discussion of additional safeguards taken if potentially vulnerable subjects will be enrolled in the study

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e.g., children, prisoners, cognitively impaired and critically ill subjects.
- Specify Code of Ethics under which consent will be obtained.
- Include a copy of the proposed informed consent along with the protocol.

8 ➢ **Adverse Event Reporting**

- Describe your plan to report any adverse event.
- Anticipated adverse events should be clearly documented.
- Identify the type and duration of follow up and treatment for subjects that experience an adverse event.

9 ➢ **Assessment of Safety and Efficacy**

- Be specific about the efficacy parameters.
- Include the methods and timing for assessing, recording, and analyzing efficacy parameters.
- Specify the safety parameters.
- Record and report properly all the ~~ad verse events and inter~~ current illnesses.

10 ➢ **Treatment of Subjects:**

- List all the treatments to be administered including product's name, dose, route of administration, and the treatment period for subjects.
- Include all medication permitted before and during the clinical trial.

- ~~Include the procedures for monitoring subject compliance.~~

11 ➢ **Data Collection Plan:**

- Define the type of data collection instrument that will be used and list all the variables.
- Specify if computerized databases will be used.
- Identify what software will be used.
- ~~Explain precautionary steps taken to secure the data.~~

12 ➢ **Data Access**

- Inform who will have access to the data and how the data will be used. If data with subject identifiers will be released, specify the person(s) or agency to whom the information will be released and the purpose of the release.
- Address all study related monitoring, audits, and regulatory inspections

13 **Statistical Methods**

- Describe the statistical methods in detail.
- Include the number of subjects you are planning to enroll. For multi-center studies, include the total number of sites expected and the total number of subjects to be enrolled across all sites.
- Provide the rationale for the sample size, the calculations on the power of the trial and the clinical justification.
- Procedure of accounting for missing, unused and spurious data.

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- Procedures for reporting deviations from the original statistical plan.
- Include the selections of subjects to be included in the analyses

(14) ➢ **Conflict of Interest:**

Identify and document clearly any consultative relationship that the principal or co-investigators has with a non-USF entity related to the protocol that might be considered a real or apparent conflict of interest.

(15) ➢ **Publication and Presentation Plans:**

List any meetings or conference you will be presenting the data and the results of your study.

(16) ➢ **Timeline:**

- A short paragraph stating when you plan to start and complete the study.
- Include a description e.g. subjects enrolment within a month, data collection within 6 months etc.

(17) ➢ **References:**

List all the references used in the back ground section at the end of the protocol.

Importance of CRF

(763)

Explain the monitoring visits in initiation, conduction and closing of clinical trial (10 mark)

Monitoring:

- The act of overseeing the progress of a clinical trial, and of ensuring that it is conducted, recorded, and reported in accordance with the protocol, SOPs, GCP, & the applicable regulatory requirements.

Monitoring Report:

- A written report from the monitor to the sponsor after each site visit and other trial-related communication according to the sponsor's SOPs.

Initiation Visit :

- The purpose of the Site Initiation Visit is to assists the site in its preparation to enroll its first subject & should take place after all required supplies are at the site and just before subject recruitment begins.
- ICH GCP does require a Trial Initiation Monitoring report as part of the "Essential Documents" and the report should be in both the sponsor and site file.
- FDA Guidelines recommend that a monitoring visit should take place "shortly" after the site has enrolled its first few subjects if an SIV was not conducted.

Conduction Visit :

- ICH Guidelines nor FDA regulations specifically require a Site Evaluation Visit.
- ICH does require a pre-trial monitoring report as part of the "Essential Documents" and states that there is a need for on-site monitoring "before, during and after" a trial.
- FDA "Guidelines for the Monitoring of Clinical Investigations" does recommend that a monitor visit the site of the clinical investigation prior to the initiation of the trial.

Closing of clinical trial :

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PURPOSE OF INFORMATION TO BE COLLECTED

The data collected through CRF should address two main issues:

1. Study hypothesis.
2. Drug safety.

The CRF should provide the accurate data to achieve the objectives proposed in the study protocol. The honest and complete recording of information in a GCP compliant pattern avoids discrepancy and speeds up drug approval process

FORMATTING CRF

The assessment parameters should be presented in a logical sequence, which ensures careful and accurate completion of CRF is important for quick data processing. A complicated CRF is an invitation to error and misinterpretation at all steps particularly in the hands of a busy investigator. Thus, a good quality CRF ensures complete, credible and reliable data generation

- Ideally multiples assessments done on each patient should appear in the CRF in the same format and sequence as performed, for all visits. This not only helps the investigator to complete all assessments but also assists in database building and quick data entry.
- The various assessments should be separated by white space not to be utilized for writing notes/remarks by the investigator. However, a separate global comments page should be provided with the CRF for his remarks.

- There are no clear ICH or FDA regulations regarding the close out visit. ICH GCP requires a close-out monitoring report as an Essential Document.
  - The sponsor conducts a close-out visit and signs the monitoring log.
  - The investigator submits a final report to the IRB stating that the site is closed.
  - The sponsor sends the investigator a letter stating that the site is closed.
- Close-Out Visit Activities:
  - Final data review/collection of all outstanding data
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  - Final review of Regulatory Binder
  - Verification that all biological samples have been submitted
  - Return or destruction of all unused study forms/CRFs
  - Collection of IRB closure report/letter

Q. Explain Spontaneous Reporting of ADR, Advantage and disadvantage ?

Spontaneous Reporting

→ It's a passive surveillance system in which health professionals are encouraged to report adverse reactions and medication errors which is directly related to regulatory authority

Steps :

① Data acqisition :

→ It's depends largely on the input of information derived from reports submitted by the health professionals who suspected ADR

② Data assessment

→ It involves assessment of pooled data obtained from various sources such as international data base of WHO

③ Data Interpretation

→ It's based on the available data and assessments made a signal related to ADR may be generated

Signal → Reported information on a possible cause relationship between adverse events and a drug

India → Suspected ADR reporting form

UK → yellow card

Australia → Blue card

US → med watch

form FDA 3500 → voluntary reporting

form FDA 3500A → mandatory reporting

Goals:

→ It increase awareness of drug, device and other medical product

→ It helps to make convenient and simple to submit reports of serious ADR, medication errors

→ It clarifieds what should be reported

A good ADR report must include following details:

1. Description of event
2. suspected and therapy details
3. Patient characteristics
4. Documentation of diagnosis
5. patient outcome
6. Relevant therapeutics measures
7. Response to rechallenge
8. Any other relevant information

Advantage:

→ very wide spectrum
→ effective
→ rapid
→ continuous
→ cheap

Disadvantages:

→ no direct information
→ Causal relationship in case reports usually uncertain
→ under reporting and reporting bias
→ no quantitative measurements

level of performance of spontaneous reporting system based on:

1. Reporting rate
2. Reporting distribution
3. Reporting quality
4. Reporting efficacy

Scanned by CamScanner
Scanned by CamScanner

How to report

① Reporting forms:

-> over 100 reporting forms are available
-> pharmacovigillance centres will have developed their own national reporting forms
-> forms should be simple and easy to complete
-> The forms should be printed on a single page and easily folded and sealed The return address should be printed on the ouside with postage pre-paid

② other options for reporting

i) Telephone
ii) E-mail
iii) fax
iv) The internet

what to report

(A) essential data elements

① patient details
② patient medical history of significance example
③ details of medicine
④ Reaction details
⑤ Reporter details
⑥ date of Report

(B) Advice to reporters
(C) follow up when necessary

Who should Report

① physicians
② nurses
③ pharmalist
④ other health workers
⑤ pharmalential companies
⑥ patient

Scanned by CamScanner
Scanned by CamScanner