Clinical Trials

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Drug Review Steps

1. Preclinical (animal) testing.
2. An investigational new drug application (IND): outlines what the sponsor of a new drug proposes for human testing in clinical trials.
3. Phase 1 studies
4. Phase 2 studies
5. Phase 3 studies
6. Submission of New Drug Application (NDA) is the formal step asking the FDA to consider a drug for marketing approval.
7. FDA reviewers will approve the application or find it either "approvable" or "not approvable."
8. Phase 4 studies

Drug Review

- Before initiation of testing in human beings(clinical trials), pre- clinical or laboratory research is required
- Research involves years of experiments in animal and human cells.
- If this stage of testing is successful, the sponsor then provides this data to the FDA requesting approval to begin testing in humans. This is called an Investigational New Drug (IND) Application
- If IND approved by the FDA, testing in humans begins..

The IND Includes

1. Information on the composition and source of the drug
2. Chemical and manufacturing information
3. All data from animal studies
4. Proposed clinical plans and protocols
5. The names of physicians who will conduct the clinical trials

Clinical Trials

- Testing in humans is begun after sufficient acute and subacute animal toxicity studies have been completed, the chronic safety testing in animals, including carcinogenicity studies, is usually done concurrently with clinical trials
- In each of the three phases of clinical trials, volunteers or patients must be informed of the investigational status of the drug &the possible risks and must be allowed to decline or to participate in the trials

Phase 1

- The effects of the drug as a function of dosage are established in a small number (25-50) of healthy volunteers
- If the drug is expected to have significant toxicity, as is often the case in cancer and AIDS therapy, volunteer patients with the disease are used in phase 1 rather than normal volunteers

Objectives

- Find the maximum tolerated dose
- The study is designed to avoid severe toxicity.
- Determine whether humans and animals show significantly different responses to the drug
- Establish the probable limits of the safe clinical dosage range.

- These trials are nonblind or called open(both the investigators and the subjects know what is being given).
- Many toxicities are detected in this phase.
- Pharmacokinetic measurements of absorption, half-life, and metabolism are often done in phase 1.
- performed in research centers by specially trained clinical Pharmacologists.

Phase 2

- The drug is studied in patients with the target disease to determine its efficacy.
- A modest number of patients (100-200) are studied in detail.
- A single-blind design is often used, with an inert placebo medication and an established active drug (positive control) in addition to the investigational agent.
- Phase 2 trials are usually done in special clinical centers (example , university hospitals).
- A broader range of toxicities may be detected in this phase.

Phase 3

- For further establishing the safety and efficacy.
- The drug is evaluated in much larger numbers of patients with the target disease, sometimes thousands.
- Difficult and expensive because of the large numbers of patients involved and the large collected data which need studies and analyzes .

Phase 3

- Double-blind technique are frequently used.
- Phase 3 trials performed in settings for the ultimate use of the drug.
- The investigators are usually specialists in the disease being treated
- Certain toxic effects, especially those caused by immunologic processes, may first become apparent in phase 3.

New Drug Application (NDA)

- If phase 3 results meet expectations, application is made for permission to market the new agent.
- Marketing approval requires submission of **NDA** to the FDA.
- **NDA** contains all of information gathered during preclinical and clinical data to the drug

- FDA review may vary from months to years leading to approval of the NDA
- For serious diseases, the FDA may permit controlled marketing of a new drug before phase 3 studies are completed,
- For life-threatening diseases, it may permit controlled marketing even before phase 2 studies have been completed

Phase 4

- Phase 4 begins after obtaining the approval of drug for marketing
- This constitutes monitoring the safety of the new drug under actual conditions of use in large numbers of patients.
- Large scale ,multicentre ,controlled trial

- The large sample size required to detect toxicities (for example, several hundred thousand patients may have to be exposed before the first case is observed of a toxicity that occurs with an average incidence of 1 in 10,000)
- Rare drug side effects are not detected before phase 4
- Phase 4 has no fixed duration

Orphan Drugs

Drugs for rare disease-called orphan drugs can be difficult to research, develop, and market.

- Safety and efficacy of drug in small populations must be established, but it is complex process.

Adverse Drug Reactions (ADRs)

An adverse reaction to a drug is a harmful or unintended response.

- ADRs are one of the leading cause of death
- The FDA estimated very large number of adverse events in hospitals, many of them occur as a result of confusing medical information.

- Some adverse reactions, such as overdose, excessive effects, and drug interactions, may occur in anyone.
- Adverse reactions occurring only in susceptible patients include intolerance, idiosyncrasy (frequently genetic in origin), and allergy (usually immunologically mediated).

- During the IND and clinical phase 1-3 trials and before FDA approval, all adverse events must be reported.
- Following FDA approval to market, surveillance, evaluation, and reporting must continue for any adverse events in patients that are related to use of the drug, some time adverse events may cause drug withdrawal from the market.