DRUG DEVELOPMENT AND SAFETY

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OVERVIEW

- Success in modern day pharmacotherapy in disease state treatment affirms the safety and efficacy of prescribed agents
- Drugs can however also be poisonous which can lead to adverse effects which sometimes can lead to eventual death
- This makes drug development and other related safety and evaluating studies very cardinal

DRUG DEVELOPMENT

Generally many countries have many features which include the following;

- Discovery and characterization
- Clinical investigation
- Regulatory approval for marketing the drug

Drug Discovery and characterization

- New drug compounds are synthesized de novo or are isolated from a natural product or a combination of the two like in synthetic drugs
- Synthetic drugs may be patterned after other drugs with known pharmacologic activity
- Their structure may also be designed to bind a particular receptor and based on computer modelling of the drug and receptor

Drug Discovery and characterization Cont'd

- Un certainties surrounding new drug compounds make it imperative for a series of screening to be done to determine their effects
- In some cases, particular pharmacologic activity Some drugs have been discovered by accident after administering the drug for other purposes
- Clonidine's antihypertensive activity was discovered when it was first tested for nasal congestion and then its hypotensive effect led to its use in hypertension

This accidental discovery of the pharmacologic activity of the drug is referred to as **“SERENDIPITY”**

PRE-CLINICAL STUDIES

- These studies involves the thorough investigation of pharmacologic effects of new drugs where they are first administered to animals before humans
- The value of pre-clinical studies is based on the proven correlation between drug toxicity in animals and humans
- The behavior observed Animals treated with new drug molecules is assessed
- The blood samples are analyzed for any tissue damage, metabolic abnormalities and immunologic effects

Pre-clinical studies Cont'd

- Tissues are removed and examined for gross and microscopic pathologic changes
- Extensive toxicity studies in animals conducted to predict the risks that can be associated with administering the drug in health human subjects and patients
- The studies will involve the **short term** and **long term** administration of drugs
- These short term or long term are designed to determine the **acute, sub acute** and **chronic toxicity**
- Furthermore, risks of **teratogenesis, mutagenesis** and **carcinogenesis**
- Offsprings are observed for adverse effects

Functional roles of pre-clinical studies

- Ascertain the harmful or beneficial effects of drugs on vital organ function e.g CVS, renal and respiratory
- Elucidate the drug's mechanism and therapeutic effects on target organs
- Determine the drugs pharmacokinetic properties thereby predicting how the bodies will handle these drugs

Limitations of pre-clinical studies

- Animal studies may not reveal all the adverse effects that humans may eventually suffer due to;

1. Low incidence of particular effect
2. Differences in susceptibility among species

- This means therefore, that some adverse reactions may not be detected until the drug is administered to humans

Pre-clinical running alongside human studies

- Some studies of chronic toxicity of new drugs in animals may require years to be complete
- it is usually possible to begin human studies while animal studies are being completed
- This should however be on the basis that if acute and subacute toxicity studies have not revealed abnormalities in animals

CLINICAL TRIALS

- Clinical trials involve the studies in human subjects

- After the pre-clinical studies , an application is made to the regulatory body for **investigation new drug (IND)**

- This is done before the drug can be distributed for conducting studies in human

- The IND application includes;

I. Complete description of the drug
II. Results of all preclinical studies completed up to that date
III. Description of the design and methods of proposed clinical studies
IV. Qualifications of the investigator

Phase I clinical trials

- This phase seek to determine the pharmacokinetic properties and safety of the IND in healthy human subjects
- Both male and female are involved to ascertain whether gender has any influence on the properties of the IND
- The human subjects undergo a complete history and physical examination, diagnostic imaging studies, chemical and pharmacokinetic analyses of samples of blood and bodily fluids
- The pharmacokinetic analyses provide a basis for estimating doses to be used in the next phase of trials
- The other examinations help to determine the safety profile of the drug in humans

Phase II clinical trials

- These are the first studies conducted in human subjects having a particular disease the IND is targeting and intended to treat

- These studies use a small number of patients to obtain a preliminary assessment of drugs regarding;

I. Efficacy and safety in diseased individuals
II. Dosage range for further clinical trials

Phase III clinical trials

- Conducted to compare the safety and efficacy of IND with that of another drug or treatment approach for the particular disease being targeted by the IND
- Usually involves a larger group of subjects, usually like hundreds or thousands with involving different clinical sites and investigators
- Rigorously designed to prevent investigator bias and involves double blind and placebo control procedures
- In double blind studies, neither the investigator nor the patient knows whether the patient is receiving the IND or not
- Placebo - control designs include a group receiving an identical formulation but with no active ingredients
- It may be unethical in some diseases to use placebos because of the proven benefits of standard drug therapy and so in such cases the new drug is compared to standard drug for treatment of that disease

Phase III trials Cont'd

- Phase III trials often involve crossover studies where patients receive one medication or placebo for a period of time and then switched to another medication or placebo After washout periods
- Statistical analysis are done at various points to help determine whether the IND is sufficiently effective or toxic to justify termination of the trial
- For example, it will be unethical to continue giving a placebo in cases where a statistically significant greater therapeutic effect is demonstrated after 6 months in patients receiving a new drug
- A clinical trial is also stopped if the new drug causes a significant increase in rate of mortality or serious toxicity

THE NEW DRUG APPLICATION APPROVAL

- After Phase III clinical trials have been completed and analyzed, the drug developer may submit a **new drug application (NDA)**
- This usually includes the results of all preclinical and clinical studies as well as the proposed labelling and clinical indications for the drug
- The regulator body will take time to review this application before deciding whether to permit marketing of the drug or not

OFF LABEL INDICATIONS

- Finally the regulator bodies register drugs for clinical use with labels or leaflets clearly showing the indications as proved from the studies
- Some drugs are found to have other clinical uses after the drug has been introduced to the market
- These indications are known as **"off-label"** indications e.g gabapentin was initially approved for partial seizures but was used off label for preventing migraine headaches

POST MARKET SURVEILLANCE

- Post market surveillance is used to monitor drugs' safety on the general patient population after approval for marketing
- It is also referred to as Phase IV
- This depends on voluntary reporting of adverse drug reactions from health care professionals using available forms or web softwares
- Serves a significant role of particularly important for detecting drug reactions that are uncommon and hence unlikely to be found during clinical trials

END