Chapter ... 6

DRUG DISCOVERY AND CLINICAL EVAUATION OF NEW DRUGS

♦ LEARNING OBJECTIVES ♦

After completing this unit, reader should be able to:

- ❖ Know Drug discovery and clinical evaluation of new drugs.
- ❖ Know Basic Disciplines of Drug Development.
- ❖ Know Basic Terminology for Pharmacovigilence.

6.1 DRUG DISCOVERY AND CLINICAL EVALUATION OF NEW DRUGS

In medicine, biotechnology and pharmacology, drug discovery is the process by which drugs are discovered and/or designed. The process of drug discovery involves the identification of candidates, synthesis, characterization, screening, and assays for therapeutic efficacy. Once a compound has shown its value in these tests, it will begin the process of drug development prior to clinical trials.

The Drug Discovery Pipeline: Drug discovery is a multi-step, interdisciplinary process that easily can take over a decade to facilitate.

1. **Target identification:** This is the initial phase of the drug discovery pipeline. The identification of specific target, which drive the progression of disease will help full for design and develop drug. Targets can be genes, epigenetic, proteins, RNA, or anything involved in disease pathogenesis.
2. **Lead discovery:** Here, chemical compounds designed to interact with or block specified targets are synthesized and isolated. This step involves combinatorial chemistry, assay development to screen selected compounds, and high throughput screening of them. The assays used to do this can vary dramatically depending on their intended target and function.
3. **Medicinal chemistry:** This phase involves developing a library of compounds and their analogs toward a target, and conducting structure-activity relationship (SAR)

studies which interrogate how the 3D confirmation of the chemical structure in question interacts with its biological target, as well as in silico screening. This phase often involves further synthesis of compounds further optimized toward their intended targets based on the SAR studies and in silico results.

4. ***In-vitro* studies:** *In-vitro* studies investigate drug affinity toward its target and selectivity. Cell culture systems relevant to the disease in question are used, and mechanism of action of the compound is interrogated. Here, the appropriate concentration and duration is often looked at as well, and the lead compounds are then refined.
5. ***In-vivo* studies (pre-clinical):** Once the lead compound(s) have been optimized and characterized to an acceptable level, *in-vivo* studies are undertaken. This involves animal models of the disease in question, often times in mice or rats. This allows researchers to query how the compound works in a systems-biology model rather than 2D cell culture. This accounts for a number of variable such as drug metabolism and clearance, immune response, ability to get into circulation and reach target site, etc. and gives a wealth of information back to the researcher. It also allows for behavioral studies and functional imaging of both the disease in response to the chemical as well as of the chemical itself.
6. **Preclinical Toxicology Testing and IND Application:** Preclinical testing analyzes the bioactivity, safety, and efficacy of the formulated drug product. This testing is critical to a drug's eventual success and, as such, is scrutinized by many regulatory entities. During the preclinical stage of the development process, plans for clinical trials and an Investigative New Drug (IND) application are prepared. Studies taking place during the preclinical stage should be designed to support the clinical studies that will follow.

   The main stages of preclinical toxicology testing are:

   - **Acute Studies:** Acute toxicity studies look at the effects of one or more doses administered over a period of up to 24 hours. The goal is to determine toxic dose levels and observe clinical indications of toxicity. Usually, at least two mammalian species are tested. Data from acute toxicity studies helps to determine doses for repeated dose studies in animals and Phase I studies in humans.
   - **Repeated Dose Studies:** Depending on the duration of the studies, repeated dose studies may be referred to as subacute, subchronic, or chronic. The specific duration should anticipate the length of the clinical trial that will be conducted on the new drug. Again, two species are typically required.
   - **Genetic Toxicity Studies:** These studies assess the likelihood that the drug compound is mutagenic or carcinogenic. Procedures such as the Ames test

(conducted in bacteria) detect genetic changes. DNA damage is assessed in tests using mammalian cells such as the Mouse Micronucleus Test. The Chromosomal Aberration Test and similar procedures detect damage at the chromosomal level.

- **Reproductive Toxicity Studies:** Segment I reproductive toxicity studies look at the effects of the drug on fertility. Segment II and III studies detect effects on embryonic and post-natal development. In general, reproductive toxicity studies must be completed before a drug can be administered to women of child-bearing age.
- **Carcinogenicity Studies:** Carcinogenicity studies are usually needed only for drugs intended for chronic or recurring conditions. They are time consuming and expensive, and must be planned for early in the preclinical testing process.
- **Toxicokinetic Studies:** These are typically similar in design to PK/ADME studies except that they use much higher dose levels. They examine the effects of toxic doses of the drug and help to estimate the clinical margin of safety. There are numerous FDA and ICH guidelines that give a wealth of detail on the different types of preclinical toxicology studies and the appropriate timing for them relative to IND and NDA or BLA

7. **Clinical Trials:** Once thorough studies have been done in the above mentioned steps, if the compound passes the tests required to entire clinical trials in humans, they can then be initiated. There are three phases a drug must pass sequentially: phase 0, phase I, phase II, and phase III clinical trials – each having different endpoint objectives. If a compound shows safety and efficacy and again, meets the specified criteria it may then be considered for FDA approval.

   (a) **Phase 0 clinical trial:** Phase 0 involves exploratory, first-in-human (FIH) trials that are run according to FDA guidelines. Also called human microdose studies, they have single sub-therapeutic doses given to 10 to 15 subjects and yield pharmacokinetic data or help with imaging specific targets without introducing pharmacological effects. Pharmaceutical companies perform Phase 0 studies to decide which of their drug candidates has the best pharmacokinetic parameters in humans.

   (b) **Phase I:** Phase I trials are the first tests of a drug with a small number of healthy human subjects. Patients are generally only used if the mechanism of action of a drug indicates that it will not be tolerated in healthy people – for example, if it induces pronounced hypoglycemia. They are primarily designed to assess the safety and tolerability of a drug, but the pharmacokinetics and, if possible, the pharmacodynamics is also measured.

The typical phase I trial has a single ascending dose (SAD) design, meaning that subjects are dosed in small groups called cohorts. Each member of a cohort might receive a single

dose of the study drug or a placebo. A very low dose is used for the first cohort. The dose is then escalated in the next cohort if safety and tolerability allow. Dose escalation is stopped when maximum tolerability and/or maximum exposure is reached.

Table 6.1: Basic Disciplines of Drug Development

	Preclinical Testing		Clinical Trials: Phase I	Phase II	Phase III		FDA	Phase IV
Years	3.5		1	2	3		2.5	
Test Population	Laboratory and animal studies		20 to 80 healthy volunteers	100 to 300 patient volunteers	1000 to 3000 patient volunteers		Review process / Approval	
Purpose	Assess safety and biological activity	File IND at FDA	Determine safety and dosage	Evaluate effectiveness, look for side effects	Verify effectiveness, monitor adverse reactions from long-term use	File NDA at FDA		Additional Post marketing testing required by FDA
Success Rate	5,000 compounds evaluated		5 enter trails				1 approved	

SAD studies are usually followed by multiple ascending dose (MAD) studies, which have a very similar design, with cohorts and escalating doses. The only difference is that the subjects receive multiple doses of the study drug or placebo.

While safety and tolerability are still important endpoints, the multiple doses setting often allow first investigations of the pharmacodynamic effects in addition to the pharmacokinetics. Depending on the risk potential and the safety and tolerability revealed by the SAD study, many MAD studies may already involve patients rather than healthy individuals. That said, it is important to enroll a relatively healthy patient population with as few complications and concomitant diseases as possible.

Finally, food effect studies are often conducted to investigate the potential impact of food intake on the absorption of the drug. These studies are usually run as a crossover study, with volunteers being given two identical doses of the drug, one after fasting and one after a meal.

(c) **Phase II:** Phase II trials are performed on larger groups of patients and are designed to assess the efficacy of the drug and to continue the phase I safety

assessments. Most importantly, phase II clinical studies help to establish therapeutic doses for the large-scale phase III studies.

Phase II studies are sometimes divided into phases IIA and IIB. Phase IIA is designed to assess dosing requirements whereas phase IIB focuses on drug efficacy. The exact design of phase II studies depends heavily on the compound's mechanism of action. A proof-of-concept study should be included in phase II if it has not already been done during the MAD-study in phase I. In addition, a treatment study with several different doses of the compound in comparison with a placebo and/or an active comparator over treatment duration of 12 to 16 weeks is usually an essential part of the phase II program.

(d) **Phase III:** Phase III investigates the efficacy of a new drug over 6 to 12 months in a large patient population (several hundred patients or more) under conditions that reflect daily clinical life much more closely than the phase I or II trials. These trials are usually done on an outpatient basis with no in-house days and include an active comparator, at least in the case of metabolic diseases, because exposing patients to several months of placebo treatment would not in general be ethical. Because of their size and comparatively long duration, Phase III trials are the most expensive, time-consuming and difficult trials to design and run, especially in therapies for chronic medical conditions. Therefore, drugs that do not show promising results in phase II are often not pursued in phase III. In fact, only 18% of drugs in phase II proceed to phase III. Phase IIIA studies are used for the approval of the drug. The results of these studies are fully included in the submission package to regulatory authorities. Between submission and approval, phase IIIB studies are often performed to obtain additional safety data or to support marketing claims for the drug.

(e) **Phase IV:** Phase IV trials are also known as post-marketing surveillance trials involving safety surveillance (Pharmacovigilance) and ongoing technical support after approval. Phase IV studies may be required by regulatory authorities or may be undertaken by the sponsoring company for competitive purposes or other reasons.

8. **FDA approval and commercialization:** Once a compound is recommended for review, passes review, and is FDA approved it can then be used clinically by physicians nation-wide. The compound or "drug" is then commercially available for purchase and successfully in the clinic to improve patients' lives and outcomes!!

6.2 BASIC TERMINOLOGIES FOR PHARMACOVIGILENCE

- **Adverse Event or Adverse Experience:** Any untoward medical occurrence that may appear during treatment with a pharmaceutical product but which does not necessarily have a causal relationship with the treatment.
- **Adverse Reaction:** A response to a drug which is noxious and unintended, and which occurs at doses normally used in man for the prophylaxis, diagnosis, or therapy of disease, or for the modification of physiological function.

- **Active surveillance system:** The collection of case safety information as a continuous pre-organized process.
- **Bayesian confidence propagation neural network (BCPNN):** A computer architecture that mimics the network of cerebral neurones (neural network) and that uses a logic that determines the disproportionality of relationships between any of the items in the database including complexes of items compared with the background of the remaining or selected items. Changes in the disproportionality can be monitored, as new data are added or different patterns of items selected. Benefit - An estimated gain for an individual or a population. See also: Effectiveness or risk; benefit or harm.
- **Biologicals:** A medical product prepared from biologic material of human, animal or microbiologic origin (such as blood products, vaccines, insulin).
- **Benefit or harm:** Benefit and harm are the positive and negative subjective qualitative experiences of individual patients. These are not usually assessed except in modern quality of life studies or in case reports. Benefit and harm at a societal level may also be considered, but then must include relative effectiveness and risk, the impact of all the outcomes on society and include cost analysis.
- **Case control study:** Study that identifies a group of persons with the unintended drug effect of interest and a suitable comparison group of people without the unintended effect. The relationship of a drug to the drug event is examined by comparing the groups exhibiting and not exhibiting the drug event with regard to how frequently the drug is present.
- **Clinical trial:** A systematic study on pharmaceutical products in human subjects (including patients and other volunteers) in order to discover or verify the effects of and/or identify any adverse reaction to investigational products, and/or to study the absorption, distribution, metabolism and excretion of the products with the objective of ascertaining their efficacy and safety. Clinical trials are generally classified into Phases I to IV. Phase IV trials are studies performed after marketing of the pharmaceutical product. They are carried out on the basis of the product characteristics for which the marketing authorization was granted and are normally in the form of post marketing surveillance.
- **Cohort study:** A study that identifies defined populations and follows them forward in time, examining their rates of disease. A cohort study generally identifies and compares exposed patients to unexposed patients or to patients who receive a different exposure.
- **Complementary or Alternative Medicine:** These terms are used interchangeably with traditional medicine in some countries. They refer to a broad set of healthcare practices that are not part of that country's own tradition and are not integrated into the dominant health care system. They have not usually been tested in specified clinical indications by an objective scientific discipline.
- **Counterfeit Medicine:** A medicine that is deliberately and fraudulently mislabeled with respect to identity and/or content and/or source.
- **Drug or medicine:** Any substance in a pharmaceutical product that is used to modify or explore physiological systems or pathological states for the benefit of the recipient. The term drug or medicinal product is used in a wider sense to include the whole formulated

and registered product, including the presentation and packaging, and the accompanying information.

- **Drug Alerts:** The action of notifying a wider audience than the initial information holder(s) of a suspected association between a drug and an adverse reaction. Note that the term is used in different contexts that can be confusing, for example, an alert may be from a manufacturer to a regulator or from a regulator to the public.
- **Effectiveness or risk:** The balance between the rate of effectiveness of a medicine versus the risk of harm is a quantitative assessment of the merit of a medicine used in routine clinical practice. Comparative information between therapies is most useful. This is more useful than the efficacy and hazard predictions from pre-marketing information that is limited and based on selected subjects.
- **Ethics committee:** An independent body (a review board or an institutional, regional or national committee), constituted of medical professionals and non-medical members whose responsibility is to verify that the safety, integrity and human rights of the subjects participating in a particular clinical trial are protected and to consider the general ethics of the trial, thereby providing public reassurance. Ethics committees should be constituted and operated so that their tasks can be executed free from bias and from any influence of those who are conducting the trial.
- **Generic (multisource pharmaceutical product):** The term 'generic product' has somewhat different meanings in different jurisdictions. Generic products may be marketed either under the non-proprietary approved name or under a new brand (proprietary) name. They are usually intended to be interchangeable with the innovator product, which is usually manufactured without a licence from the innovator company and marketed after the expiry of patent or other exclusivity rights.
- **Herbal medicine:** Includes herbs, herbal materials, herbal preparations and finished herbal products.
- **International Conference on Harmonization (ICH):** The International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use is a project that brings together the regulatory authorities of Europe, Japan and the United States and experts from the pharmaceutical industry in the three regions to discuss scientific and technical aspects of product registration.
- **Lack of efficacy:** Unexpected failure of a drug to produce the intended effect as determined by previous scientific investigation.
- **National pharmacovigilance centre:** A single, governmentally recognized centre (or integrated system) within a country with the clinical and scientific expertise to collect, collate, analyse and give advice on all information related to drug safety.
- **Pharmacoepidemiology:** The study of the use and effects of drugs in large numbers of people. Pharmacovigilance: The science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug-related problem.

- **Prescription event monitoring:** System created to monitor adverse drug events in a population. Prescribers are requested to report all events, regardless of whether they are suspected adverse events, for identified patients receiving a specified drug.
- **Product stewardship:** The demonstrable process by which a business can identify and manage its safety, health and environmental performance as applied to the development, manufacture, marketing, use and disposal of its products (including packaging).
- **Record linkage:** Method of assembling information contained in two or more records, e.g., in different sets of medical charts, and in vital records such as birth and death certificates. This makes it possible to relate significant health events that are remote from one another in time and place.
- **Risk evaluation:** Risk evaluation is the complex process of determining the significance or value of the identified hazards and estimated risks to those concerned with or affected by the process.
- **Risk management:** The making of decisions concerning risks, or action to reduce the consequences or probability of occurrence.
- **Side effect:** Any unintended effect of a pharmaceutical product occurring at a dose normally used in man, which is related to the pharmacological properties of the drug.
- **Signal:** Reported information on a possible causal relationship between an adverse event and a drug, the relationship being unknown or incompletely documented previously. Usually more than a single report is required to generate a signal, depending upon the seriousness of the event and the quality of the information.
- **Spontaneous reporting:** System whereby case reports of adverse drug events are voluntarily submitted from health professionals and pharmaceutical manufacturers to the national regulatory authority.
- **Traditional Medicine:** Traditional medicine is the sum total of the knowledge, skills, and practices based on the theories, beliefs, and experiences indigenous to different cultures, whether explicable or not, used in the maintenance of health as well as in the prevention, diagnosis, improvement or treatment of physical and mental illness. The terms 'complementary medicine' / 'alternative medicine' / 'non-conventional medicine' are used inter-changeably with traditional medicine in some countries.
- **Unexpected Adverse Reaction:** An adverse reaction, the nature or severity of which is not consistent with domestic labeling or market authorization, or expected from characteristics of the drug.

QUESTIONS

1. Define clinical trials.
2. Define the terms acute toxicity and chronic toxicity study.
3. Define clinical trials. Write the phases of clinical trials.
4. Write in detail the new drug development process.

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