DRUG DEVELOPMENT PROCESS

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- **MOST OF THE DRUGS ARE UNEXPECTED PLEASANT SURPRISES…**

INTRODUCTION

- Drug development is the process of bringing a new pharmaceutical drug to the market once a lead compound has been identified through the process of drug discovery. It includes pre-clinical research on microorganisms and animals, filing for regulatory status, such as via the United States Food and Drug Administration for an investigational new drug to initiate clinical trials on humans, and may include the step of obtaining regulatory approval with a new drug application to market the drug.

- Modern drug discovery involves the identification of screening hits, medicinal chemistry and optimization of those hits to increase the affinity, selectivity (to reduce the potential of side effects), efficacy/potency, metabolic stability (to increase the half-life), and oral bioavailability.
- Once a compound that fulfils all of these requirements has been identified, it will begin the process of drug development prior to clinical trials.
- One or more of these steps may, but not necessarily, involve computer-aided drug design.
- Modern drug discovery is thus usually a capital-intensive process that involves large investments by pharmaceutical industry corporations as well as national governments (who provide grants and loan guarantees).
- Despite advances in technology and understanding of biological systems, drug discovery is still a lengthy, "expensive, difficult, and inefficient process" with low rate of new therapeutic discovery.

- In 2010, the research and development cost of each new molecular entity was about US$1.8 billion. Drug discovery is done by pharmaceutical companies, with research assistance from universities. The "final product" of drug discovery is a patent on the potential drug.
- The drug requires very expensive Phase I, II and III clinical trials, and most of them fail. Small companies have a critical role, often then selling the rights to larger companies that have the resources to run the clinical trials.
- Discovering drugs that may be a commercial success, or a public health success, involves a complex interaction between investors, industry, academia, patent laws, regulatory exclusivity, marketing and the need to balance secrecy with communication.
- Meanwhile, for disorders whose rarity means that no large commercial success or public health effect can be expected, the orphan drug funding process ensures that people who experience those disorders can have some hope of pharmacotherapeutic advances.

VARIOUS APPROACHES TO DRUG DISCOVERY

INTRODUCTION

- The various approaches to drug discovery include

1. **Pharmacological**
2. **Toxicological**
3. **IND application**
4. **Drug characterization**
5. **Dosage form**

- Broadly, the process of drug development can be divided into pre-clinical and clinical work.
- STEPS 1 and 2 constitute the PRECLINICAL STUDIES.

Pre-clinical

- New chemical entities (NCEs, also known as new molecular entities or NMEs) are compounds that emerge from the process of drug discovery.
- These have promising activity against a particular biological target that is important in disease.
- However, little is known about the safety, toxicity, pharmacokinetics, and metabolism of this NCE in humans. It is the function of drug development to assess all of these parameters prior to human clinical trials.
- A further major objective of drug development is to recommend the dose and schedule for the first use in a human clinical trial ("first-in-man" [FIM] or First Human Dose [FHD]).

- In addition, drug development must establish the physicochemical properties of the NCE: its chemical makeup, stability, and solubility.
- Manufacturers must optimize the process they use to make the chemical so they can scale up from a medicinal chemist producing milligrams, to manufacturing on the kilogram and ton scale.
- They further examine the product for suitability to package as capsules, tablets, aerosol, intramuscular injectable, subcutaneous injectable, or intravenous formulations.
- Together, these processes are known in preclinical development as chemistry, manufacturing, and control (CMC).
- Many aspects of drug development focus on satisfying the regulatory requirements of drug licensing authorities. These generally constitute a number of tests designed to determine the major toxicities of a novel compound prior to first use in humans.
- It is a legal requirement that an assessment of major organ toxicity be performed (effects on the heart and lungs, brain, kidney, liver and digestive system), as well as effects on other parts of the body that might be affected by the drug (e.g., the skin if the new drug is to be delivered through the skin).
- Increasingly, these tests are made using in vitro methods (e.g., with isolated cells), but many tests can only be made by using experimental animals to demonstrate the complex interplay of metabolism and drug exposure on toxicity.

PRECLINICAL TRIALS

- **Preclinical trial** - A laboratory test of a new drug or a new medical device, usually done on animal subjects, to see if the hoped-for treatment really works and if it is safe to test on humans.

PHARMACOLOGICAL APPPROACHES TO DRUG DISCOVERY

- Pharmacology as an academic principle can be loosely defined as the study of effects of chemical substances on living systems.
- This definition is so broad that it encompasses all the aspects of drug discovery, ranging from details of interaction between drug molecule and its target to consequences of placing the drug in the market

Components of pharmacological evaluation

1.Selectivity testing.

2. Pharmacological profiling.

3.Testing in animal models of disease.

4.Safety pharmacology.

SELECTIVITY TESTING

- The selectivity testing mainly involves 2 main stages:

1. **Screening for selectivity**
2. **Binding assays.**

Screening for selectivity

- The selectivity of a compound for a chosen molecular target needs to be assessed because it determines the potency of the drug.
- A selected compound may bind to molecular targets that are related or unrelated to the chosen molecular target thereby causing unwanted side effects.

Binding assays

- The aim of carrying out binding assays is to determine the dissociation constant of the test compound as a measure of affinity to the receptor.
- These assays are generally done with membrane preparations made from intact tissues or receptor expressing cell lines.
- In most cases the assay measures the ability of the test compound to inhibit the binding of a high affinity radioligand which selectively combines with the receptor in question.

PHARMACOLOGICAL PROFILING

- *Pharmacological profiling refers to determining the pharmacodynamic effects of a new compound. Either on:*

1. ***In vitro models:*** *Cell lines or isolated tissues.*
2. ***In vivo models****: Normal animals, animal models of disease*.*

The aim of pharmacological profiling is to answer the following questions:

- Does the molecular and cellular effects measured in screening assays actually give rise to the predicted pharmacological effects in intact tissues and whole animals?
- Does the compound produce effects in intact tissues or whole animals not associated with actions on its principle molecular target?

- Is there a correspondence between potency of the drug at molecular level, tissue level and the whole animal level.
- Do in vivo duration of action match up with the pharmacokinetic properties of the drug.
- What happens if the drug is continuously or repeatedly given to an animal over a course of days or weeks. Does it loose its effectiveness or reveal effects not seen on acute administration and whether there is any rebound after effect when it is stopped.

In vitro profiling

- In vitro profiling involves the studies on isolated tissues.
- This technique is extremely versatile and applicable to studies on smooth muscle* as well as cardiac and striated muscle, secretory epithelia, endocrine glands, brain slices, liver slices.
- In most cases tissue is obtained from a freshly killed or anaesthetized animal and suspended in warmed oxygenated physiological fluid solution.

Advantages

- The concentration-effect relationship can be accurately measured.
- The design of the experiments are highly flexible allowing measurement of:

- Onset and recovery of drug effects.
- Measurements of synergy and antagonism by other compounds.

Disadvantages

- The tissues normally have to be obtained from small laboratory animals, rather than humans or other primates.
- The preparations rarely survive for more than a day, so only short experiments are feasible.

In vivo profiling

- In vivo profiling involves the testing on normal animal models.
- These methods are time consuming and very expensive.
- They can be done on larger animals.
- A particularly important role of in vivo experiments is to evaluate the effects of long term drug administration on intact organism.

SPECIES DIFFERENCES

- It is important to take species differences into account at all stages of pharmacological profiling.
- The same target in different species will generally differ in its pharmacological specificity.
- The growing use of transgenic animal models will undoubtedly lead to an increase in animal experimentation.

Here there involves the use of animal models with the human disease for which the drug has been prepared.

- There tests are done to answer a crucial question to whether the physiological effects result in a therapeutic benefit.
- Despite the range of diversity of animal models from humans these tests will provide a valuable link to the chain of evidence.

TYPES OF ANIMAL MODEL

Animal models of disease can be broadly classified into

1. Acute physiological and pharmacological models
2. Chronic physiological and pharmacological models
3. Genetic models

Acute physiological and pharmacological model

- These models are intended to mimic certain aspects of the clinical disorder. The examples are:
- Seizures induced by electrical stimulation of brain as a model of epilepsy
- The hot plate for analgesic drugs as a model of pain.
- Histamine induced bronchoconstriction as a model of asthma.

Chronic physiological and pharmacological model

- These models involve the use of drugs or physical interventions to induce an ongoing abnormality similar to clinical condition. The examples are:
- The use of alloxan to inhibit insulin secretion as a model of TYPE I diabetes mellitus.
- Self administration of opiates, nicotine or other drugs as a model of drug dependence.

Genetic animals

- These are transgenic animals produced by deletion or over expression of specific genes to show abnormalities resembling the human disease.
- The development of transgenic technology has allowed inbred strains to be produced with the gene abnormality to be present throughout the animals life.
- More recent developments allow more control over timing and location of the transgenic effect.

VALIDITY CRITERIA IN CONTEXT TO ANIMAL TESTING

An animal model produced in a lab can never exactly replicate a spontaneous human disease state so certain validity criteria have been set up, they are:

1. ***Face validity***
2. ***Construct validity***
3. ***Predictive validity***

1. FACE VALIDITY:

This validity refers to the accuracy with which the model reproduces the phenomena(symptoms, clinical signs and pathological changes) characterizing the disease.

2. CONSTRUCT VALIDITY:

This refers to the theoretical rational with which the model is based i.e. the extent to which the etiology of the human disease is reflected in the model.

3. PREDICTIVE VALIDITY:

- This validity refers to the extent to which the effect of manipulations(e.g. drug treatment) in the model is predictive of effects in the human disorder.
- This is the most important of the 3 as it is most directly relevant to the issue of predicting therapeutic efficacy.

SAFETY PHARMACOLOGY

- Safety pharmacology is the evaluation and study of potentially life threatening pharmacological effects of a potential drug which is unrelated to the desired therapeutic effect and therefore may present a hazard.
- These tests are conducted at doses not too much in excess of the intended clinical dose.

- Safety pharmacology seeks to identify unanticipated effects of new drugs on major organ function(i.e. secondary pharmacological effects).
- It is aimed at detecting possible undesirable or dangerous effects of exposure of the drug in therapeutic doses.
- The emphasis is on acute effects produced by single-dose administration rather than effects on chronic exposure as in toxicological studies.

TYPE	PHYSIOLOGIAL SYSTEM	TESTS
CORE BATTERY	*CENTRAL NERVOUS SYSTEM*	Observations on conscious animals
		•Motor activity
		•Behavioral changes
		•Coordination
		•Reflex responses
		•Body temperatures
	CARDIVASCULAR SYSTEM	On anaesthetized animals
		•Blood pressure
		•Heart rate
		•ECG CHANGES
		Tests for delayed ventricular repolarisation
	RESPIRATORY SYSTEM	Anaesthetized and conscious
		•Respiratory rate
		•Tidal volume
		•Arterial oxygen saturation

TYPE	PHYSIOLOGIC SYSTEMS	TESTS
FOLLOW- UP TESTS	*CENTRAL NERVOUS SYSTEM*	•Tests on learning and speech
		•More complex tests for changes in behavior and motor function.
		•Tests for visibility and auditory function
	CARDIOVASCULAR SYSTEM	•cardiac output
		•Ventricular contractility
		•Vascular resistance
		•Regular blood flow
	RESPIRATORY SYSTEM	•Airway resistance and complince
		•Pulmonary arterial pressure
		•Blood gases

TYPE	PHYSIOLOGIC SYSTEM	TESTS
SUPPLEMENTARY TESTS	*RENAL FUNCTION*	•Urine volume, Osmolality, PH, •Proteinuria
		•Blood Urea/Creatinine
		•Fluid/Electrolyte balance
	AUTONOMIC NERVOUS SYSTEM	•C.V.S, Gastrointestinal and respiratory system responses to agonists and stimulation of autonomic nerves.
	GASTROINTESTINAL SYSTEM	•Gastric secretion
		•Gastric PH
		•Intestinal motility
		•Gastrointestinal transit time

Conditions Under Which Safety Pharmacology Studies Are Not Necessary

- Safety pharmacology studies are usually not required for locally applied agents e.g. dermal or ocular, in cases when the pharmacology of the investigational drug is well known, and/or when systemic absorption from the site of application is low.
- Safety pharmacology testing is also not necessary, in the case of a new derivative having similar pharmacokinetics and pharmacodynamics.

TOXICOLOGICAL APPROACHES TO DRUG DISCOVERY

Animal Toxicology:

Acute toxicity:

- Acute toxicity studies should be carried out in at least two species, usually mice and rats using the same route as intended for humans.
- In addition, at least two more route should be used to ensure systemic absorption of the drug, this route may depend on the nature of the drug. Mortality should be looked for up to 72 hours after parentral administration and up to 7 days after oral administration. Symptoms, signs and mode of death should be reported, with appropriate macroscopic and microscopic findings where necessary.
- •LD 50s should be reported preferably with 95 percent confidence limits, if LD 50s cannot be determined, reasons for this should be stated.

Long-term toxicity:

- •Long-term toxicity studies should be carried out in at least two mammalian species, of which one should be a non-rodent.
- •The duration of study will depend on whether the application is for marketing permission or for clinical trial, and in the later case, on the phases of trials.
- •If a species is known to metabolize the drug in the same way as humans, it should be preferred In long-term toxicity studies the drug should be administered 7 days a week by the route intended for clinical use in humans. The number of animals required for these studies, i.e. the minimum number on which data should be available
- •A control group of animals, given the vehicle alone, should always be included, and three other groups should be given graded doses of the drug; the highest dose should produce observable toxicity, the lowest dose should not cause observable toxicity, but should be comparable to the intended therapeutic dose in humans or a multiple of it, example 2.5x to make allowance for the sensitivity of the species; the intermediate dose should cause some symptoms, but not gross toxicity or death, and may be placed logarithmically between the other two doses.

Reproduction studies:

- Reproduction studies need to be carried out only if the new drug is proposed to be studied or used in women of childbearing age. Two species should generally be used, one of them being non-rodent if possible.

A. Fertility studies:

- The drug should be administered to both males and females, beginning a sufficient number of days before mating. In females the medication should be continued after mating and the pregnant one should be treated throughout pregnancy.
- The highest dose used should not affect general health or growth of the animals. The route of administration should be the same as for therapeutic use in humans.
- The control and the treated group should be of similar size and large enough to give at least 20 pregnant animals in the control group of rodents and at least 8 pregnant animals in the control group of non-rodents. Observations should include total examination of the litters from both the groups, including spontaneous abortions, if any.

B. Teratogenicity studies

- The drugs should be administered throughout the period of organogenesis, using three dose levels. One of the doses should cause minimum maternal toxicity and one should be the proposed dose for clinical use in humans or multiple of it. The route of administration should be the same as for human therapeutic use.
- The control and the treated groups should consist of at least 20 pregnant females in case of non-rodents, on each dose used. Observations should include the number of implantation sites, restorations if any; and the number foetuses with their sexes, weights and malformations if any.

C. Prenatal studies

- The drug should be administered throughout the last third of pregnancy and then through lactation and weaning. The control of each treated group should have at least 12 pregnant females and the dose which causes low foetal loss should be continued throughout lactation weaning. Animals should be sacrificed and observations should include macroscopic autopsy and where necessary, histopathology.

D. Local toxicity

- These studies are required when the new drug Is proposed to be used typically in humans. The drug should be applied to an appropriate site to determine local effects in a suitable species such as guinea pigs or rabbits, if the drug is absorbed from the site of applications, appropriate systemic toxicity studies will be required.

- At least three does levels should be used; the highest does should be sub-lethal but cause observable toxicity; the lowest does should be comparable to the intended human therapeutic does or a multiple of it, example 2.5x; to make allowance for the sensitivity of the species; the intermediate does to be placed logarithmically between the other two doses.
- A control group should always be included. The drug should be administered 7 days a week or a fraction of the life span comparable to the fraction of human life span over which the drug is likely to be used therapeutically.
- Observations should include macroscopic changes observed at autopsy and detailed histopathology.

- ***The information is gathered from this pre-clinical testing, as well as information on CMC, and submitted to regulatory authorities (in the US, to the FDA), as an Investigational New Drug application or IND. If the IND is approved, development moves to the clinical phase.***

Clinical phase

Clinical trials involve three or four steps:

- Phase I trials, usually in healthy volunteers, determine safety and dosing.
- Phase II trials are used to get an initial reading of efficacy and further explore safety in small numbers of patients having the disease targeted by the NCE.
- Phase III trials are large, pivotal trials to determine safety and efficacy in sufficiently large numbers of patients with the targeted disease. If safety and efficacy are adequately proved, clinical testing may stop at this step and the NCE advances to the new drug application (NDA) stage.
- Phase IV trials are post-approval trials that are sometimes a condition attached by the FDA, also called post-market surveillance studies.

- The process of defining characteristics of the drug does not stop once an NCE begins human clinical trials. In addition to the tests required to move a novel drug into the clinic for the first time, manufacturers must ensure that any long-term or chronic toxicities are well-defined, including effects on systems not previously monitored (fertility, reproduction, immune system, among others). They must also test the compound for its potential to cause cancer (carcinogenicity testing).
- If a compound emerges from these tests with an acceptable toxicity and safety profile, and the company can further show it has the desired effect in clinical trials, then the NCE portfolio of evidence can be submitted for marketing approval in the various countries where the manufacturer plans to sell it. In the United States, this process is called a "new drug application" or NDA.
- Most NCEs fail during drug development, either because they have unacceptable toxicity or because they simply do not have the intended effect on the targeted disease as shown in clinical trials.

Cost

- The full cost of bringing a new drug (i.e., new chemical entity) to market – from discovery through clinical trials to approval – is complex and controversial. Typically, companies spend tens to hundreds of millions of U.S. dollars. One element of the complexity is that the much publicized final numbers often not only include the out-of-pocket expenses for conducting a series of Phase I-III clinical trials, but also the capital costs of the long period (10 or more years) during which the company must cover out-of-pocket costs for preclinical drug discovery. Additionally, companies often do not report whether a given figure includes the capitalized cost or comprises only out-of-pocket expenses, or both.
- Another element of complexity is that all estimates are based on confidential information controlled by drug companies, released by them voluntarily, leading to inability to verify costs. The numbers are controversial, as drug companies use them to justify the prices of their drugs and various advocates for lower drug prices have challenged them. The controversy is not only between "high" and "low", but also the high numbers may vary considerably for the manifold factors in drug development.

Success rate

- Candidates for a new drug to treat a disease might, theoretically, include from 5,000 to 10,000 chemical compounds.
- On average about 250 of these show sufficient promise for further evaluation using laboratory tests, mice and other test animals. Typically, about ten of these qualify for tests on humans. A study conducted by the Tufts Center for the Study of Drug Development covering the 1980s and 1990s found that only 21.5 percent of drugs that started Phase I trials were eventually approved for marketing. In the time period of 2006 to 2015, the success rate was 9.6%.
- The high failure rates associated with pharmaceutical development are referred to as the "attrition rate" problem.
- Careful decision making during drug development is essential to avoid costly failures. In many cases, intelligent programme and clinical trial design can prevent false negative results. Well-designed, dose-finding studies and comparisons against both a placebo and a gold standard treatment arm play a major role in achieving reliable data.

DRUG CHARACTERIZATION

- Pre-formulation studies will attempt to characterize the drug in a number of respects, they are :

CHARACTER	USE
Spectroscopy	To produce a simple method for analyzing the drug.
Solubility	For identifying the best salt to develop and for producing liquid dosage forms.
Melting point	Which reflects, for example, crystalline solubility.
Assay	development Necessary for drug stability studies and perhaps employing thin layer-or high pressure liquid chromatography.
Stability	In solution and in the solid state.
Microscopy	To determine crystal morphology and particle size
Powder flow & compression properties	Necessary data for capsule & tablet formulation.
Excipient compatibility	To ensure that dosage forms perform correctly.

DOSAGE FORMS

- DOSAGE FORM DESIGN:

At some stage , a decision needs to be made about the dosage form(s) for the delivery of the drug (e.g. a tablet, a capsule or an injection).The factors that determine which dosage form(s)is(are)to be used are many and involve marketing considerations apart from scientific considerations.

TYPES OF DOSAGE FORMS: Now days there are many different dosage forms, including the three examples given above,andt hey all have their relative advantages and disadvantages

DRUG DOSAGE FORMS

Dosage form	Comment
Tablets & capsules	Convenient and commonest dosage forms but likely to be no good if the drug cannot be absorbed in the alimentary tract or if the patient(eg. A child) cannot swallow them.
Injections & infusion	Rapid action but impractical for treating chronic (long term) illnesses.
Pessaries & suppositories	Can deliver the drug to local area where required but have limited general use.
Solution, Suspensions & Elixiris	Useful for children and the elderly but are bulky and less useful if the drug is unpalatable or unstable in the presence of water.
Ointments, Creams, & paints	Use is restricted to topical application.
Aerosols & Dry Powder inhalations	Good for drugs required in the but can be difficult to administer the dose correctly.
Transdermal patches	Convenienent if the dose need to be released over a long period (eg. hormone replacement therapy) but can cause irritation.

- Therapeutic considerations play an important role in deciding the dosage form to formulate. Here are a few examples:

  •A tablet is not suitable dosage form if the drug cannot be absorbed in the alimentary tract - unless, of course, it Is required to treat an ailment in the tract itself (such as a gut infection). Instead of a tablet, an injection might be a suitable alternative. •Even if the drug can be absorbed in the alimentary tract (saying the intestine), as the tablet will still be unsatisfactory if the drug is destroyed in the stomach acid. In such a case the tablet might be enteric coated to prevent drug destruction whilst the tablet is passing through the stomach. By the time the tablet reaches the intestine the coating has dissolved liberating the drug for absorption through the intestinal wall.

- •Drugs which need to act immediately (eg. Bronchodilator drugs for treating asthmatic attacks where the airways suddenly become so constricted that the patient has difficulty in breathing) are best delivered by inhalation directly to the lungs where they can rapidly dilate the airways, rather than being swallowed in a tablet with the consequently delay in action whilst the drug is absorbed and delivered to the lungs.

BIOPHARMACEUTICS

- To be effective, a drug must reach in desired concentration to the part of the body where it is required to act and, ideally, must be maintained at concentration for the appropriate period of time.
- This goal is influenced by the key interactions which takes place between the drug and the body after the drug has been administered. These are:

- Absorption (the way the drug enters the body and reaches the bloodstream).
- Distribution (where the drug goes in the body after it has been absorbed).
- Metabolism (how it is changed by the body - e.g. in the liver).
- Elimination (the route by which it, or its metabolites, leave the body - e.g. in the urine via the kidney).

These processes are referred to as ADME in short. The study of the pharmaceutical factors which affect the fate of the drug after administration is called biopharmaceutics and these factors will need to be evaluated in the development of a new drug.


THANK YOU

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