Drug design and development

Stages:

1) Identify target disease
2) Identify drug target
3) Establish testing procedures
4) Find a lead compound
5) Structure Activity Relationships (SAR)
6) Identify a pharmacophore
7) Drug design - optimising target interactions
8) Drug design - optimising pharmacokinetic properties
9) Toxicological and safety tests
10) Chemical development and production
11) Patenting and regulatory affairs
12) Clinical trials

1

What do you think?

- Have you ever had to take a medicine to treat an illness?
- Have you ever wondered how researchers determine if the medicines you take are safe or not?

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The Drug Development Process

Step 1: Discovery and Development

Step 2: Preclinical Research

Step 3: Clinical Research

Step 4: FDA Review

Step 5: FDA Post-Market Safety Monitoring

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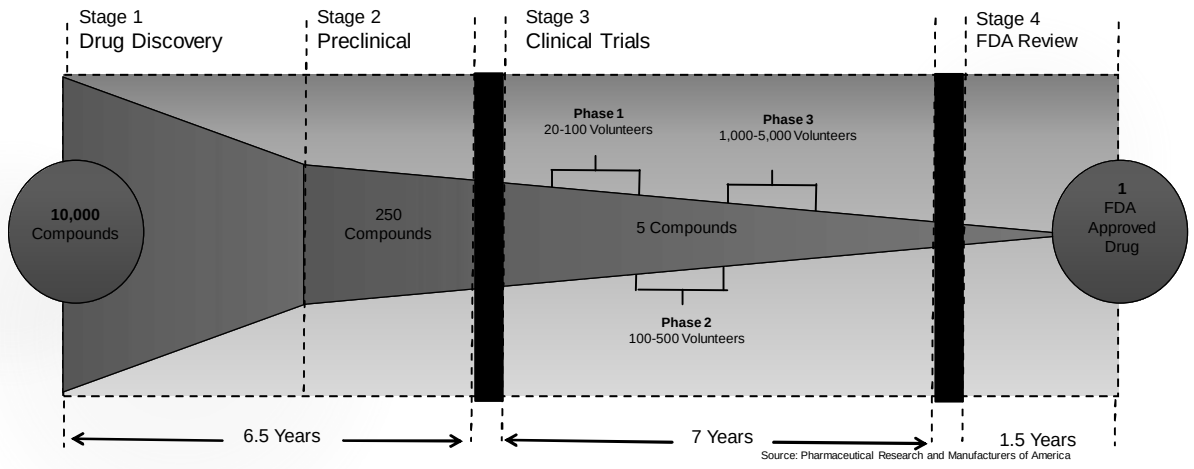
A Slow and Costly Process



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What is Pre-Clinical Studies?

- In drug development, pre-clinical studies OR non-clinical studies , is a stage of research that begins before clinical trials (testing in humans), and during which important testing and drug safety data is collected.
- The main goals of pre-clinical studies are to determine a product's ultimate safety profile . Products may include new medical devices, drugs , gene therapy solutions , etc.

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Objective of Pre-Clinical Studies:

- Pre-Clinical Trials and Clinical Trials are the processes by which scientists test drugs and devices to see if they are SAFE and EFFECTIVE.

Means, a laboratory test of a new drug or a new medical device , usually done on animal subjects, animal pharmacology/toxicology testing , to see if the treatment really works and if it is safe to test on humans

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Review: Steps to New Drug Discovery Pre-Clinical Trials

Get idea for drug target

↓

Develop a bioassay

↓

Screen chemical compounds in assay

↓

Establish effective and toxic amounts

↓

File for approval as an Investigational New Drug (IND) (leads to clinical trials)

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➢ Steps in Doing a Pre-Clinical Trial:

<u>Step One:</u> Get an idea for a drug **target.**

- Drugs usually act on either cellular or genetic chemicals in the body, **targets**, which are believed to be associated with disease.
- Scientists use a variety of techniques to identify and isolate individual targets to learn more about their functions and how they influence disease.
- Compounds are then identified that have various interactions with the drug targets that might be helpful in treatment of a specific disease.

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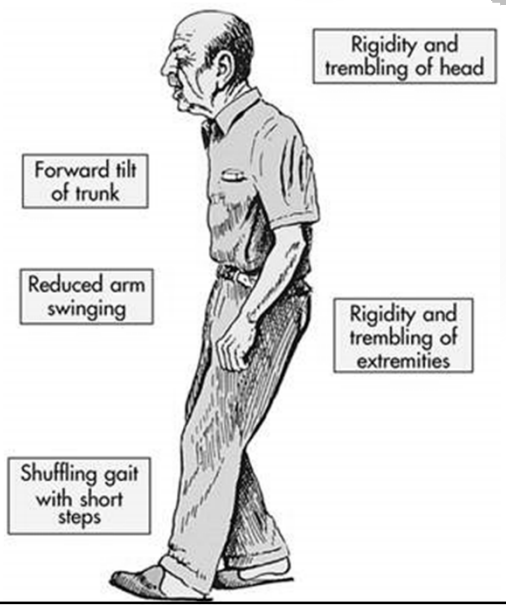
Finding the Right Target Is Not Easy

Parkinson's Disease Example:

Parkinson's disease:
a disease which causes deterioration of the central nervous system over a period of time. This disease often impairs the patient's movement, speech, and other functions.



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How is Parkinson's treated? Where should the focus be?

- Tremors or shaking occurs when cells in one part of brain die. These cells communicate using a chemical called dopamine.
- Drugs that replace dopamine work only for a few years.
- Other Parkinson's symptoms (depression, sleep disorder, digestive problems, loss of brain function) have other causes.
- Another sign of Parkinson's disease: many cells have deposits of a protein, synuclein.
  - Four drug companies are developing drugs to counter synuclein, even though nobody knows if it is a cause or a consequence of Parkinson's.
  - Synuclein could be like a tombstone—a marker, not a cause of cell death.

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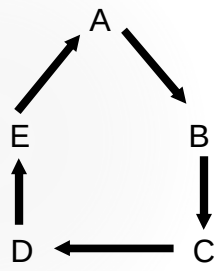
- Drugs **target** specific points in biochemical pathways
- Biochemical pathways are series of chemical reactions occurring within a cell. In each pathway, a principal chemical is modified by chemical reactions.
- Examples of different types of biochemical pathways:



A → B → C → D → E

Any step in the pathway, for example from A to B, or B to C, might be a target for the right drug.

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➢ Steps in Doing a Pre-Clinical Trial:

<u>Step Two</u>: Develop a **Bioassay**

A Bioassay is a "live" system that can be used to measure drug effect.

- It may be a culture of cells or organs or a whole animal.

For example:

- Zebra-fish embryos - you can see effects of drugs on bone density, blood vessel growth and many other systems of the zebra-fish.

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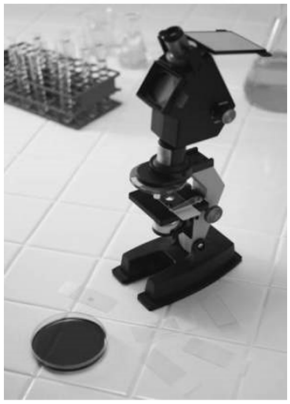
➢ Steps in Doing a Pre-Clinical Trial:

Step Three: Screen the drug in the Bioassay.



- This is the actual test of the drug on the chosen bioassay.
- This will determine if the drug is **SAFE** and if it is **EFFECTIVE** in the bioassay (BEFORE it is ever tested on humans!)

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➢ Steps in Doing a Pre-Clinical Trial

Step Four: Establish what dosage amount of the drug is **safe** and what dosage amount of the drug is **toxic**.

- Most drugs have a toxic level or an amount at which the drug will become harmful instead of helpful.

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➢ Steps in Doing a Pre-Clinical Trial

Step Five: Application is made to the Food and Drug Administration (FDA) as an Investigational New Drug (IND).

IND must show how the drug:

- **Is manufactured.**
- **Appears (color, solubility, melting point, particle size, moisture content).**
- **Formulated (pills, liquid, etc. + inactive ingredients).**
- **Will be analyzed for purity, concentration, stability.**
- **Will be tested for safety (this will be the basis for allowing first use in humans).**

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In these studies, safety of compound in at least two animal species, mostly mouse/rat and dog by oral and parenteral routes. Various types of tests are performed.

They are a lot of tests to be performed:

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1. **Screening Test: These are simple and rapidly performed tests to indicate presence OR absence of a particular pharmacodynamic activity. For example, analgesic OR hypoglycemic activity.**

2. **Tests on isolated organs, bacterial cultures: These also are preliminary tests to detect specific activity, such as anti-histaminic, anti- secretory , vasodilator, antibacterial, etc.**

3. **Tests on animal models of human disease: Animal models used such as kindled seizures in rats, genetically hypersensitive rats, experimental tuberculosis in mouse, etc.**

4. **General observational test: Drug is injected in tripling doses to small groups of mice which are observed for overt (hidden) effects. Preliminary clues are drawn from the profile of effect observed.**

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Preclinical studies involves:

1. **Toxicity testing**
2. **Drug metabolism studies**
3. **Pharmacology**
4. **Formulation, Stability tests, Delivery Methods**

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1.Toxicity testing

Test for carcinogenisity: *in vitro tests on* genetically engineered cell cultures and/or *in vivo testing* on transgenic mice to examine any effects on cell reproduction and to identify potential carcinogens.
Any signs of carcinogenicity would prevent the drug being taken any further studies.

Test for acute toxicity: administering sufficiently large doses *in vivo to produce a toxic* effect or death over a short period of time.

Further studies on acute toxicity then take place over a period of months, where the drug is administered to laboratory animals at a dose level expected to cause toxicity but not death.

Finally, long-term toxicology tests are carried out over a period of years at lower dose levels to test the drug for chronic toxic effects, carcinogenicity, special toxicology, mutagenicity, and reproduction abnormalities.

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LD 50 : Value measuring drug toxicity which is the lethal dose required to kill 50% of a group of animals.

ED 50: dose required to produce the desired effect in 50% of test animals.

Therapeutic ratio or therapeutic index : The ratio of **LD 50** to **ED 50**

A therapeutic ratio of 10 indicates an LD 50 :ED 50 ratio of 10:1. This means that a 10-fold increase in the ED 50 dose would result in a 50% death rate.

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2. Drug metabolism studies

- Find out what metabolites are formed from any new drug.
- The structure and stereochemistry of each metabolite.
- Biological activity of metabolite have to be tested .

Ideally, any metabolites that are formed should be inactive and quickly excreted

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In order to carry out such studies, it is necessary to synthesize the drug with an isotopic label, such as deuterium (2 H or D), carbon-13 (13 C), tritium (3 H or T), or carbon-14 (14 C).

In vitro drug metabolism studies can also be carried out using perfused liver systems, liver microsomal fractions, or pure enzymes. Many of the individual cytochrome P450 enzymes that are so important in drug metabolism are now commercially available.

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3. Pharmacology, formulation, and stability tests

Pharmacological tests involves the study of:

- Drug activity at targets other than the intended one.
- Drug's mechanism of action.
- The dose–response relationship.
- Drug's duration of action.

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Formulation studies involves:

- Developing a preparation of the drug which is both stable and acceptable to the patient.
- Testing drug compatibility with other tablet excepients.
- Characterization of a drug's physical, chemical, and mechanical properties in order to choose what other ingredients should be used in the preparation.
- Particle size, salt forms, crystal polymorphism, solvates, pH, and solubility, as all of these can influence bioavailability.
- **Drug load**: the ratio of the active drug to the total contents of the dose. A low drug load may cause homogeneity problems. A high drug load may pose flow problems or require large capsules if the compound has a low bulk density.

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***Stability studies involves**:*

- Effect of temperature, humidity, ultraviolet light, or visible light.
- Degradation products.
- Unwanted interactions between the preparation and the container.

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PATENTING AND REGULATORY AFFAIRS

REGULATORY AFFAIRS

- **Drug must be approved by regulatory bodies**
- **Food and Drugs Administration (FDA)**
- **European Agency for the Evaluation of Medicinal Products (EMEA)**
- **Proper record keeping is essential**
- **GLP - Good Laboratory Practice**
- **GMP - Good Manufacturing Practice**
- **GCP - Good Clinical Practice**

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Patenting and regulatory affairs

Patents

Exclusive rights to sell and manufacture its products for a reasonable period of time, and at a price which will not only recoup its costs, but that will generate sufficient profits for further research

In order to gain a patent,
1- submit or file the patent (what the new pharmaceutical is, what use it is intended for, and how it can be synthesized. This is no straightforward task).

2- The patent authorities decide whether the claims are novel and whether they satisfy the necessary requirements for that patent body.

It is important that a patent is filled as soon as possible.

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- **Patents in most countries run for 20 years after the date of filing. The protection period starts from the time of filing, not from when the drug comes onto the market.**

Chiral switching : The issue of chiral switching relates mostly to racemic drugs that have been on the market for several years and are approaching the end of their patent life.
By switching to the pure enantiomer, companies can argue that it is a new invention and take out a new patent.

However, they have to prove that the pure enantiomer is an improvement on the original racemate and that they could not reasonably have been expected to know that when the racemate was originally patented.

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Regulatory affairs:

a) The regulatory process

Before clinical trials can begin, the company has to submit the results of its scientific and preclinical studies to the relevant regulatory authority.

- **Food and Drug Administration (FDA) in the USA**
- **Agency for the Evaluation of Medicinal Products (EMEA) in Europe**

1- Investigational Exemption to a New Drug Application (IND)

Confidential document submitted to the regulatory affair. The IND should contain information regarding the chemistry, manufacture, and quality control of the drug, as well as information on its pharmacology, pharmacokinetics, and toxicology).

2-The regulatory affair. assesses this information and then decides whether clinical trials can begin.

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3- Any adverse results must be reported to the regulatory affair, who will discuss with the company whether the trials should be stopped.

4-If the clinical trials proceed smoothly, the company applies to the regulatory authority for marketing approval. This involves:

Submission of a **New Drug Application (NDA) to the FDA** in USA
Or Marketing Authorization Application (MAA) in Europe.

An NDA or MAA is typically 400–700 volumes in size, with each volume containing 400 pages! ! ! ! ! ! ! ! !

5- Once an NDA is approved, any modifications to a drug's manufacturing synthesis or analysis must be approved.

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b) Fast-tracking and orphan drugs

Fast-tracking : drug reach the market as quickly as possible, smaller number of phase II and phase III clinical trials before the drug is put forward for approval.
FT is carried out for drugs that show promise for diseases where no current therapy exists and for drugs that show distinct advantages over existing ones in the treatment of life-threatening diseases as cancer.

Orphan drugs: are drugs that are effective against relatively rare medical problems. In the USA, an orphan drug is defined as one that is used for less than 200,000 people.

Because there is a smaller market for such drugs, pharmaceutical companies may be less likely to reap huge financial benefits and may decide not to develop and market an orphan drug.

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c) Good laboratory, manufacturing, and clinical practice

Good Laboratory Practice (GLP) and Good Manufacturing Practice (GMP) are scientific codes of practice for a pharmaceutical company's laboratories and production plants.

They detail the scientific standards that are necessary, and the company must prove to regulatorybodies that it is adhering to these standards.

Investigators involved in clinical research must demonstrate that they can carry out the work according to **Good Clinical Practice (GCP) regulations.**

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d) Analysis of cost versus benefits

A medicine that is successfully licensed and reaches the market has one other hurdle to negotiate—a cost versus benefit analysis carried out by individual government authorities.

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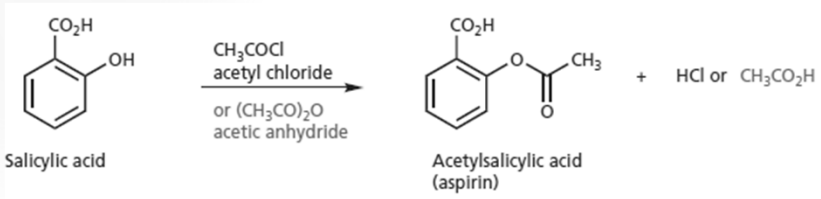
Chemical and process development

Chemical development

Once a compound goes forward for preclinical tests, it is necessary to start the development of a large-scale synthesis as soon as possible.

During chemical development, the conditions for each reaction in the synthetic route are studied closely and modified in order to get the best yields, purity, less cost and safety.

It is not necessary to scale up the synthetic route used by the research laboratories



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Stages in chemical development

1- kilogram of drug is required for short-term toxicology and stability tests, analytical research, and pharmaceutical development.(original synthetic route)

2- 10 kg for long-term toxicology tests, as well as for formulation studies. Some of the material may also be used for phase I clinical trials.

3-100 kg is prepared for phase II and phase III clinical trials.

The **specifications of** the fi nal product are defined and determine the various analytical tests and purity standards required.

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Process development

Process development aims to ensure that :

1-The number of reactions in the synthetic route is as small as possible

2- All the individual stages in the process are integrated with each other, such that the full synthesis runs smoothly and efficiently on a production scale.

3-Reduce the number of operations to a minimum.

4-Environmental and safety issues are extremely important.

5-Keeping costs low is a high priority and it is more economic to run the process such that a small number of large batches are produced rather than a large number of small batches.

6- Safety

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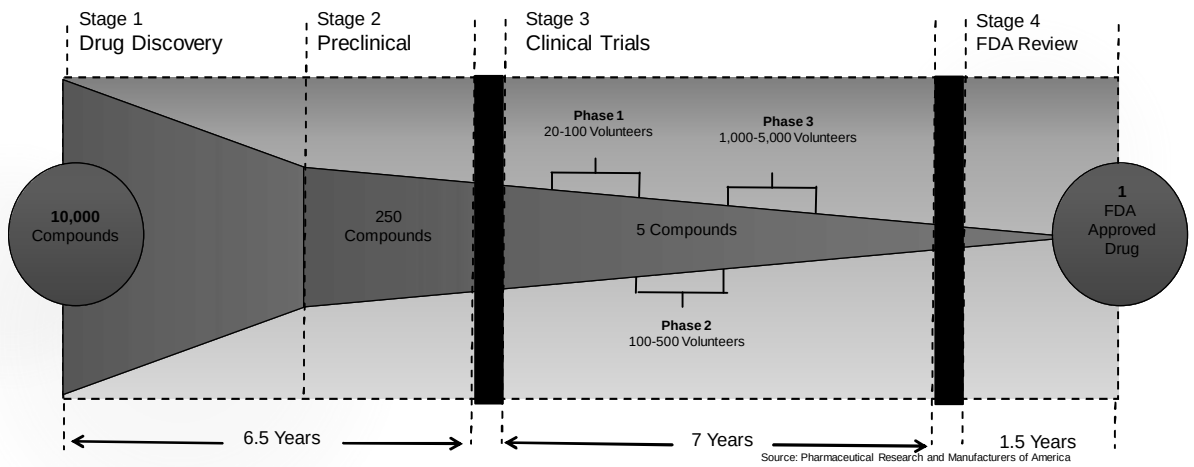
A Slow and Costly Process



Preclinical Development

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Phase 0

- **Sometimes a phase 0 trial is conducted before a phase I trial.**
- **Phase 0 trials use a very small dose of a drug to study the effects in a small group of people (about 10–15).**
- **These trials are used to gather information about how the drug is used by and affects the human body.**
- **Researchers may need blood tests or biopsies of the tumor. The removal of cells or tissues for examination under a microscope.**
- **Phase 0 studies are not used to gather information about the safety of the drug or its effectiveness in treating cancer.**
- **People who take part in phase 0 studies usually have advanced disease and do not have an effective, known treatment option.**

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Phase I trials

- First introduction of IND (investigational new drug) in humans
  - Usually only healthy adult volunteers (no patients)
  - Purpose is to investigate metabolic and pharmacological actions of the compound in humans
  - Use dose-ranging (increasing dosages) to determine what side effects may occur
  - Usually 20 – 80 subjects in the trial

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Phase II trials

- Early controlled trials in a patient population, with limited scope, to obtain preliminary data on efficacy
- Further indication of side effects, this time in patients
- about 200-400 subjects

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Phase III trials

- **expanded trials in a much larger sample of patients**
- **more information about drug efficacy and safety**
- **information about benefit : risk ratio**
- **obtain some information to determine what should be included in the labelling of the marketed drug**
- **several hundred to several thousand patient subjects (usually multi-centre studies and very expensive)**

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Phase IV trials

- not always performed
- may be required to explore possible side effects in more detail or give a better indication of efficacy
- may involve a different type of patient (different age range, different male:female ratio)
- may investigate potential efficacy in a different therapeutic area
- number of subjects is variable depending upon the reason for the study

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Ethical issues

- In phases I–III of clinical trials, the permission of the patient is mandatory.
- Ethical problems:

Unconscious patients, mentally ill patients and children.

Most licensed drugs have been licensed for adults, it means that around 40% of medicines given to children have never actually been tested on that age group.

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