Pharmacology

Mid Material – Lecture 2

Drug discovery and development

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Drugs from bench to bedside

Drug discovery

- **Drug discovery** is the process through which potential new medicines are identified. It involves a wide range of scientific disciplines, including biology, chemistry and pharmacology.
- For example: the discovery of the factor that induced **Mydriasis** from the plant **Atropa Belladonna** by isolating & analysing different chemicals of that plant.

Drug Development

- The process of developing a new drug that effectively targets a specific weakness in a cell. This process involves specific pre-clinical development and testing, followed by trials in humans to determine the efficacy of the drug.
- **The trial starts on**: 1-cells and tissues(preclinical) 2- animals like rats (preclinical) 3-on humans(clinical), and after it passed all of these stages we can get to marketing.
- The development of new drugs is very complex, costly and risky.
- **Complex** because we have multivariant stages.
- **Costly**; a company can spend millions over the development of one drug
- **Risky** if we don't know much about the medicine, it can present a risk on the patients'/healthy volunteers' life.

Pharmacovigilance

- The science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other possible drug-related problems
- This stage happens *after* the release of the drug to the market; the company keeps on tracing the rare drug's side effects that shows after a big number of people use it.
- Will be discussed later during the semester.

Investigational Drug Success

- Discovery/Screening: 5000-10,000
- Enter Preclinical Testing: 250
- Enter Clinical Testing: 5
- Approved by Regulatory Bodies: 1
- Elimination for drugs before entering the preclinical testing trials due to reasons for example: finding a reactive group in a drug that may cause *toxicity*, or due to its *large size* that may stop it from being absorbed
- Drugs may cause test-animals' death, toxicity, undesirable side effects, or have less-than-expected efficacy in the preclinical testing trials, so only a small number successfully passes to the Clinical testing trials (trial on Humans).
- Reductine is a drug used for weight reduction, before it was released it passed all the trials and was approved to be released to the market, but then they discovered it had lethal side-effects & caused a stroke to the patients and therefore the benefit wasn't worth the risk so it was pulled out of the market.

Drug Discovery & Development

1. Starts with prediction=an idea & hypothesis

- Awareness of the beneficial effects of plants and animal products (natural sources)
- Chemical identification of a wide variety of natural mediators and the possibility of modifying them chemically
- Avoid chemicals with highly reactive groups (toxic)

2. Design and synthesis of useful drugs or substances through simple techniques or with the help of advanced technology.

- **Plant** → fractionation, chromatographic experiments → identification of the active ingredients → isolation → purification → good drug (recently most drugs of plant source could be synthesized).
- **Animal** → isolation of a substance (insulin)
  Simple peptides → a.a sequencing machine
  Complex proteins → recombinant DNA technology
- **Receptology studies:**
  Allowed synthesis of huge number of agonists and antagonists

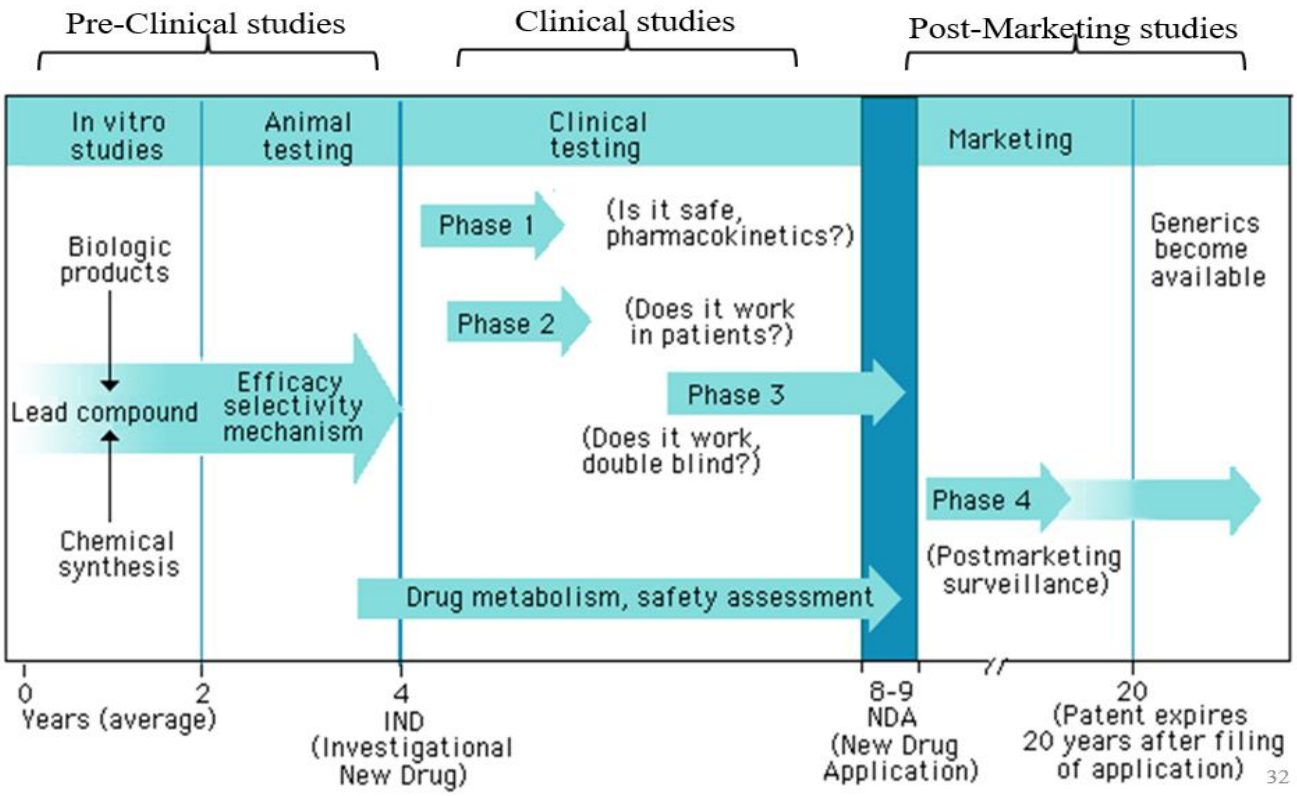
Rational drug design

- This implies the ability to predict the chemical structure of drug molecule on basis of 3-dimensional structure of its receptor, employing at present suitable computer programs. Only few drugs in clinical use at present were developed in this rational way.
- Most drugs were in the past developed through random testing of chemicals, or modified molecules of known drugs that are known to have some other pharmacological effect.
- However, as more would become known about detailed structure of receptors, rational drug design with aid of computers will become more feasible.

Facts about development of drugs

- Enormous and increasing costs, with estimates from $150 million to $900 million, are involved in the research and development of a single new drug that reaches the marketplace.
- Only 3 of 10 marketed drugs return their research and development (R&D) investments.
- At the same time, the incentives to succeed in drug development can be equally enormous.
- The global market for pharmaceuticals in 2006 is estimated at about $640 billion.
- From 1996 to 2012 under the trade name Lipitor, atorvastatin became the world's best-selling medication of all time, with more than $125 billion in sales over approximately 14.5 years.
- Lipitor alone "provided up to a quarter of Pfizer Inc.'s annual revenue for years."
- Pfizer's patent on atorvastatin expired in November 2011.
- *Patent*: **pharmaceutical patent** or **drug patent** is a patent for an *invention* in the chemical or pharmaceuticals industry, which doesn't allow other companies to manufacture or sell that drug for some time (usually 20 years) since the start of the development, and then after that time period is over any company would be able to make that drug.
- **Lipitor** is from the *statin* family. It wasn't the first statin drug to be released but it was more developed and advanced than the older ones.
- ***Statins*** are a class of drugs often prescribed by doctors to help *lower* cholesterol levels in the blood by inhibiting **HMG-CoA reductases** in the liver.

Drug development steps and timeline



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Pre-clinical Testing

- **Determine pharmacokinetic parameters**
  - ✓ Absorption, distribution, metabolism…etc

- **Determine pharmacodynamics (MOA)**

- **Assessment of drug toxicity=safety**
  - ✓ **Acute toxicity** studies
    Determination of LD_{50}; Margin of safety…etc
  - ✓ **Sub-acute and chronic toxicity** studies.
  - ✓ **Repeated dose studies**.
- The most important thing to test in the pre-clinical is the safety of the drug.
- Testing the blood toxicity in the pre-clinical:
- **1-Acute:** giving the animals one high dose of the drug.
- **2-Sub-acute:** giving them a smaller dosage 3-5 times.
- **3-Chronic:** gives them a dosage that we usually give to humans but on a long period of time like 6 months so we can know what accumulate and the toxicity of the drug

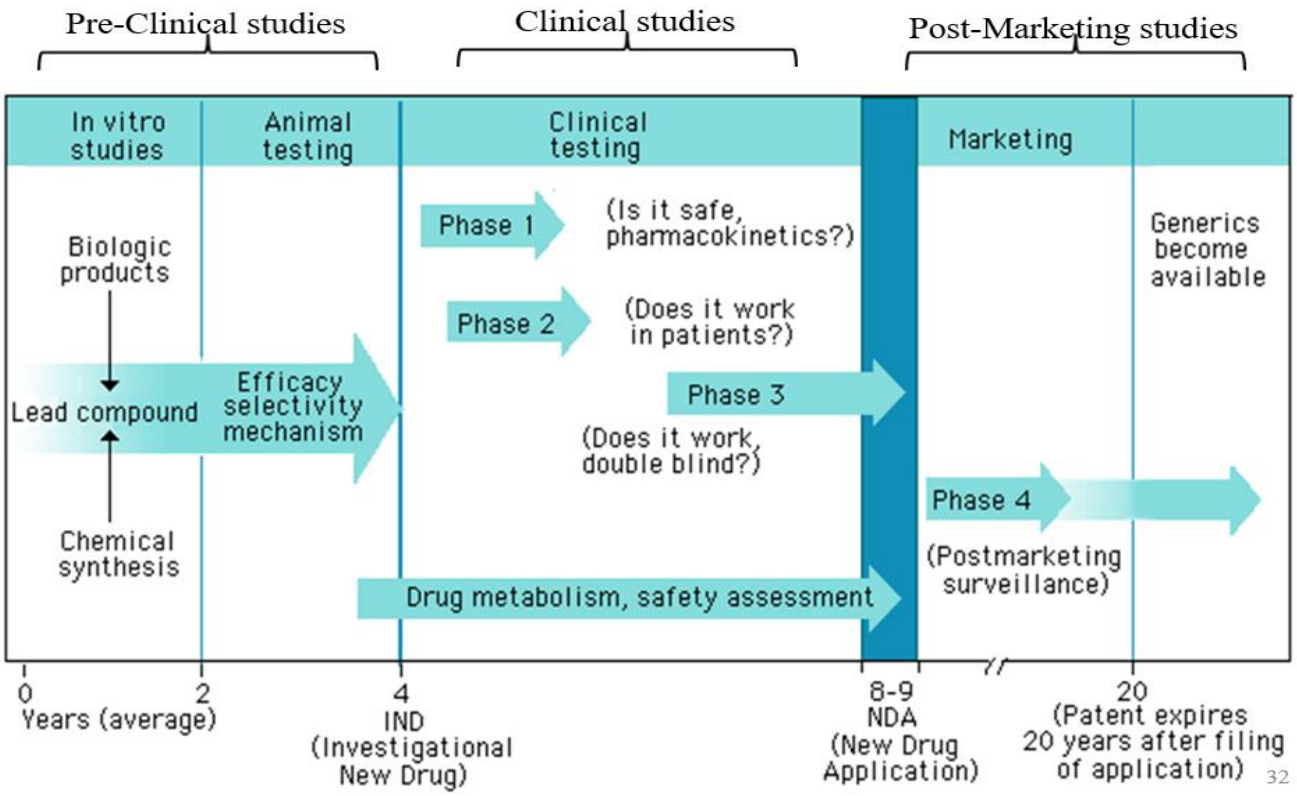
Pre-clinical safety and toxicity testing

- To correctly define the limiting toxicities of drugs and the therapeutic index comparing benefits and risks of a new drug.
- The most essential part of the new drug development process.

Parameters measured during pre-clinical phase

- **"No-adverse effect" dose**: the maximum dose at which a specified toxic effect is not seen
- **The minimum lethal dose:** the smallest dose that is observed to kill any experimental animal, even if one.
- **The Median lethal dose (LD50):** the dose that kills approximately 50% of the animals...
- These doses are used to calculate the initial dose to be tried in humans, usually taken as one hundredth to one tenth of the no-adverse effect dose in animals.
- Presently, the LD50 is estimated from the smallest number of animals possible.
- **Example**:
- We have 100 mice to test a new drug X
- At 11 mg: all mice developed acute renal failure and died
- At 10 mg: all mice developed acute renal failure and died
- At 9 mg: 89 mice developed ARF and died
- At 8 mg: 64 mice developed ARF and died
- At 7 mg: 50 mice developed ARF and died
- At 6 mg: 43 mice developed ARF and died
- At 5 mg: 30 mice developed ARF and only one died
- At 4 mg: 15 mice developed ARF but no one died
- At 3 mg: none of the mice developed ARF nor died
- At 2 mg: none of the mice developed ARF nor died
    - Please determine the no adverse effect dose for the ARF, the minimum lethal dose and the LD50 for drug X
- **Solution:**
- No-adverse effect: 3 mg
- Minimum lethal dose: 5 mg
- LD50: 7 mg

Drug development steps and timeline



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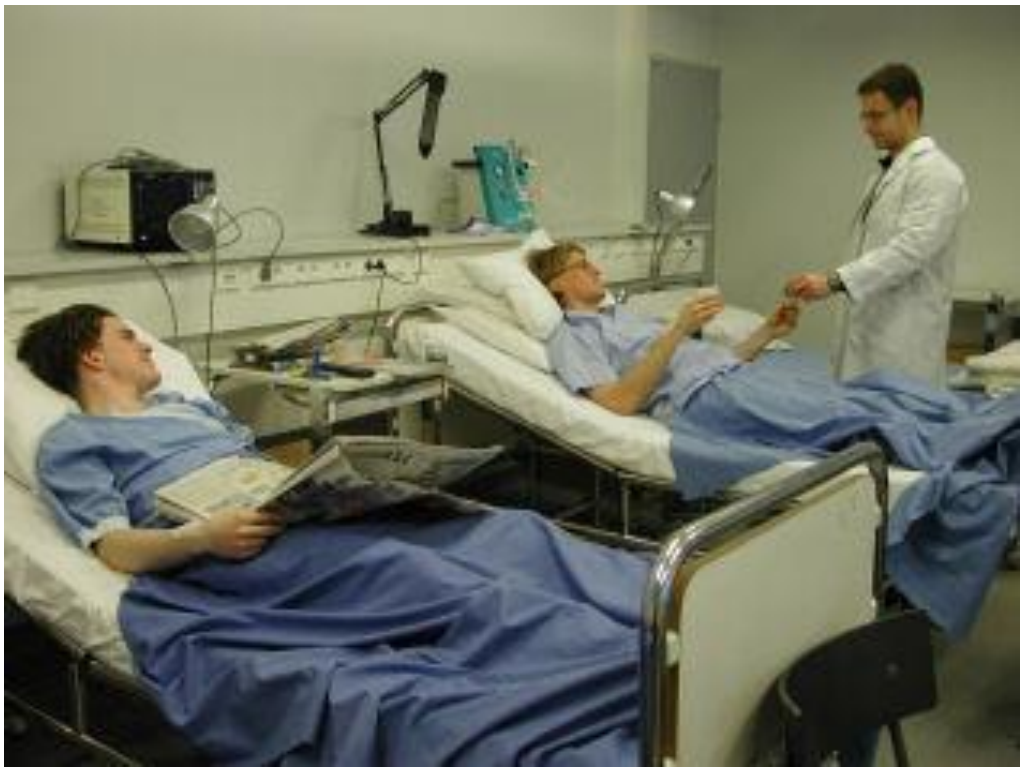
Clinical Trials



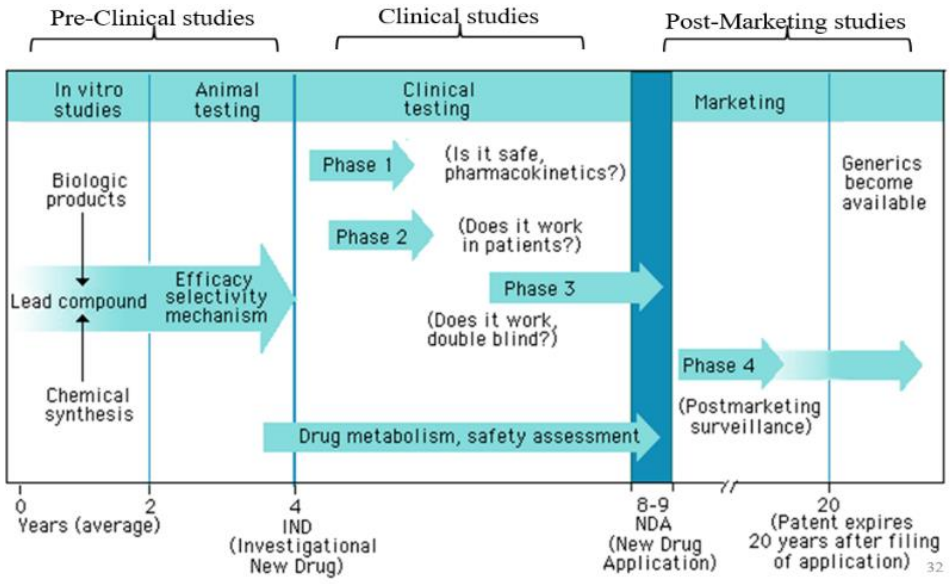
Ethics of the use of drugs in humans

- Full detailed protocol has to be approved by the ethical committee, the institutional review board (IRB)
- All subjects should sign an informed agreement form
- All subjects should be insured for life and damage

Clinical Trials

- Once a drug is judged ready to be studied in humans, a **Notice of Claimed Investigational Exemption for a New Drug (IND)** must be filed with the FDA
- The IND must be available at the site of the experiment.
- **IND contains:**
  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 and credentials of physicians who will conduct the clinical trials, and
  6. a compilation of the key data relevant to study the drug in man made available to investigators and their institutional review boards.

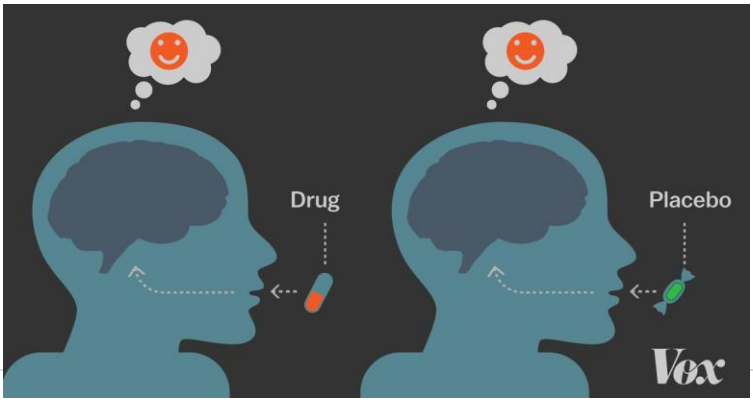
Drug development steps and timeline



Clinical Trials

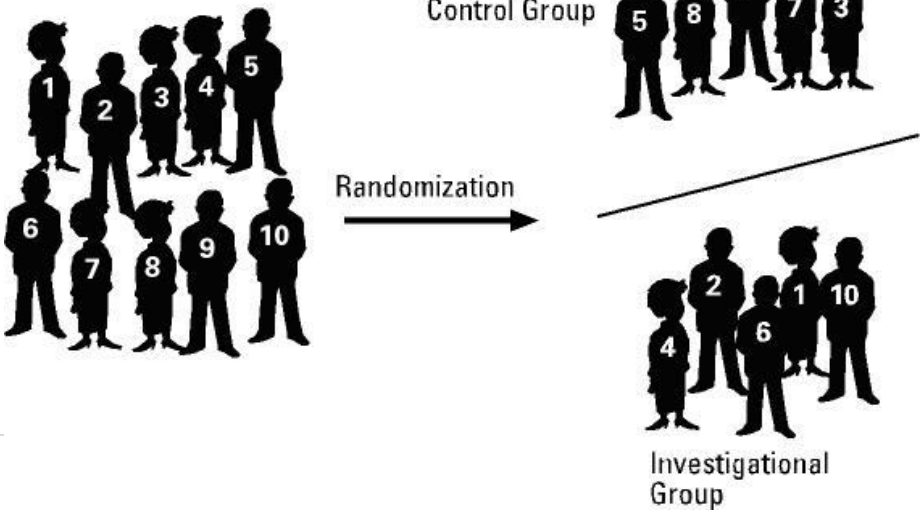
- **Phase 1:**

– observes the **effect** of drug as a function of dosage
– *small* number of healthy volunteers (25-50) with age of 20-40s, because the drug has only been tested on animals.
– **Goal**: find maximum tolerated dose & avoid severe toxicity.
– Detect safety (Many predictable toxicities are detected in this phase).
– 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.
– Pharmacokinetic measurements of absorption, half-life, and metabolism are often done in phase 1.
– We *can't* study the **efficacy** of the drug in phase 1 because it is only tested on *healthy people*.
– Done in research centers by trained clinical pharmacologists
– These trials are **nonblind or "open";** that is, both the investigators and the subjects know what is being given, and they get informed if it's the drug or it's the placebo (placebo effect) and they need to report the side effects and every little single detail they have even if they think it is *trivial* or *unrelated* to the drug
– A **placebo** is a substance or treatment which is designed to have no therapeutic value.
– **Placebo effect:** a beneficial effect produced by a placebo drug or treatment, which cannot be attributed to the properties of the placebo itself, and must therefore be due to the patient's belief in that treatment.



- **Phase II:**
  - Drug studied in patients with the target disease to determine **efficacy,** (In this stage we experiment the drug on patients (unhealthy people) but they should *only* have the illness that the drug was designed for).
  - Number of *patients* is 100-200
  - Detects broader range of toxicities
  - Done in special clinical centers (eg, university hospitals) i.e. Supervised by doctors
  - Single-blind design with a **placebo & positive control**
  - ***Single-blind***; means that the investigator knows what the patients are getting while the patient doesn't know if he's getting the real drug or the placebo (won't have any real physical effects on the patient).
  - In advanced stages, we use the ***double-blinded technique*** in which neither the patient nor the investigator knows who is getting the drug and the placebo but *a third party* distributes the groups and that *raises the accuracy* and removes any *bias* behavior.
  - Another helpful technique we use beside the placebo is ***positive control***.
  - A positive control is a part of good experimental design. A positive control receives a treatment with a *known* response (old drug that we know its effect), so that this *positive* response can be compared to the *unknown* response of the treatment (a new drug that we are developing).
  - For example: when testing a new drug for diabetes, the positive-control group are given Glucophage (Metformin) for comparison purposes.

Fig. 3 **A double-blind placebo-controlled clinical trial for CAM therapies.**



- **Phase III:**

- *Larger* number of patients (e.g. Thousands)
- In phase 3 the volunteers must have the illness that the drug was designed for but it's *acceptable* if they suffer from other illnesses.
- Conducted to minimize errors caused by placebo effects, variable cause of the disease etc.
- Further study of safety & efficacy (*Safety* is studied in all phases while the *efficacy* starts from phase 2).
- Double-blind & crossover techniques
- ***cross over:*** switching the drugs so the patients that took the placebo over a period of time will be given the drug, and the patients that were using the drug get the placebo.
- Investigators are **specialists** in disease being treated.
- If results meet expectations: application is made for permission to market the agent (NDA-new drug application)
- Food and Drug administration (FDA) review of New Drug application (NDA) may take up to 3 years
- For serious diseases, the FDA may permit extensive but controlled marketing of a new drug before **phase 3** studies are completed;
- For life threatening disease, it may permit controlled marketing even before **phase 2** studies have been completed;
- In some cases, we might skip phases 1 & 2, such as when a disease suddenly becomes an epidemic.
- Some drugs like *anticancer* and *antiviral* are cytotoxic (toxic/lethal to living cells) so we don't try it on healthy volunteers and we skip phase 1 to phase 2 because it can be harmful to healthy humans.
- Once approval to market the drug has been obtained, phase 4 begins…

- **Phase IV:**
  - Constitutes monitoring the safety of the new drug under actual conditions of use in large numbers of patients.
  - Has no fixed duration.
  - Some rare toxicities are revealed (low incidence)
  - **Efficacy studies**; by following up with patients who have used the drug.
  - Features averages & statistics.

- **Phase 0:**
  - Phase 0 or first-in-human trials is a *recent* phase approved in accordance with the United States FDA's 2006 Guidelines
  - Phase 0 trials are also known as human microdosing studies and are designed to speed up the development of promising drugs by establishing very early on whether the drug or agent behaves in human subjects as was expected from preclinical studies
  - Distinctive features of Phase 0 trials include the administration of single subtherapeutic doses of the study drug to a small number of subjects (10 to 15) to gather preliminary data on the agent's pharmacokinetics and pharmacodynamics.
  - A Phase 0 study gives no data on safety or efficacy, being by definition a dose too low to cause any therapeutic effect.
  - Drug development companies carry out Phase 0 studies to rank drug candidates in order to decide which has the best pharmacokinetic parameters in humans to take forward into further development
  - Phase 0 studies enable go/no-go decisions to be based on relevant human models instead of relying on sometimes inconsistent animal data
  - Questions have been raised by experts about whether Phase 0 trials are useful, ethically acceptable, feasible, speed up the drug development process or save money, and whether there is room for improvement

- *After all these clinical drug trials the drug is usually approved by national or International regulatory authorities and is licensed for General prescribing.*

Generic Drug

- Generic drug: a drug product that is produced by any pharmaceutical company after the patent of the originator drug is expired.

- All of these drugs have the same chemical formula but they can differ in price, taste and some may have less side effects.
- Also, some may be film-coated and others not.

Test Yourself

Overdose midterm selected questions:

1. In which drug discovery phase the acute toxicity level is determined?
   a) Phase I
   b) Phase II
   c) Phase II
   d) Preclinical testing

   Answer: D

Vagus midterm selected questions:

2. Regarding the drug development process, which one of the following combinations is correct?

   Answer: Phase III+ involves crossover techniques

3. " phase 0 " or " first in human " trials were approved by the FDA in 2006. which one of the following statements is correct regarding these trials during drug development process?

   Answer: these studies enable go / no go decisions to be based on relevant human models instead of relying on sometimes inconsistent animals' data.

4. During drug development process and before testing drugs on human, a full detailed protocol has to be approved by the ethical committee. which of the following is considered as an ethical committee?
   Answer: IRB (institutional review board)