New drugs: development & evaluation

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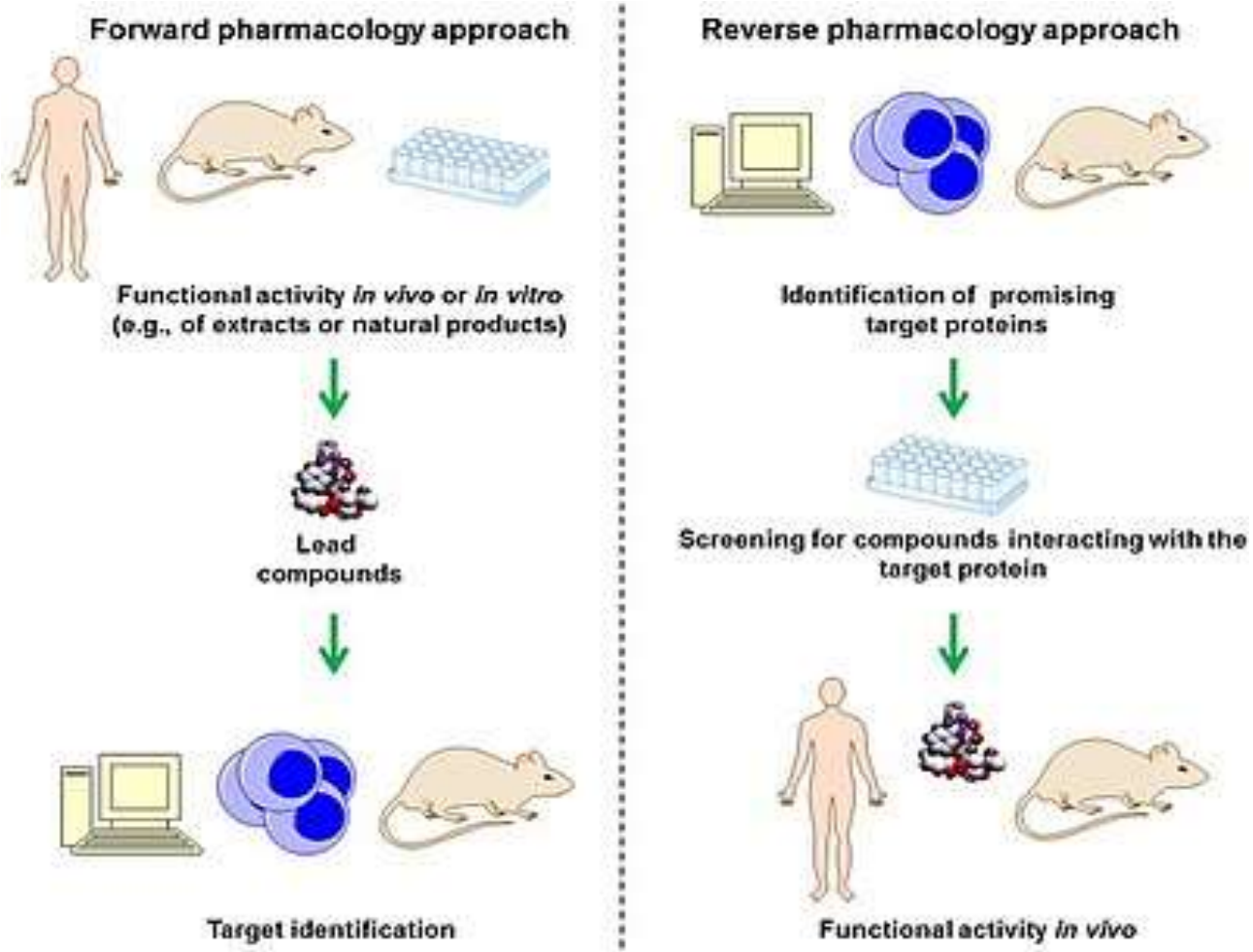
Scientific methods of drug discovery



•Developing new, innovative drugs takes time – a very long time and a lot of money (2 billion dollars).

• On average, the journey from discovery to market takes 12 years, however, in newer areas of medicine, like gene therapy, it can take up to 30 years.

• 1 in 5000 new compounds are approved as pharmaceutical drugs by regulatory agencies like the Food and Drug Administration (FDA) in the US or the European Medicines Agency (EMA) in the EU.

Phases of a "typical" project, aimed at producing a marketable drug for a specific clinical need

 DRUG DISCOVERY	 PRECLINICAL DEVELOPMENT	 CLINICAL DEVELOPMENT			 REGULATORY APPROVAL	 PHASE IV
• Target selection • Search for the lead compound • Optimization of the lead compound • Assessment of pharmacological characteristics	• Pharmacokinetics • Short-term toxicology • Formulation • Large-scale synthesis	Phase I Pharmacokinetics, tolerability, side effects in healthy volunteers	Phase II Small-scale trials in patients to assess efficacy and dose. Long-term toxicology studies	Phase III Large-scale controlled clinical trials	Comprehensive data is submitted and reviewed by regulatory authorities	Post-marketing surveillance
2-5 years	**1-5 years**	**5-7 years**			**1-2 years**	
100 projects	20 compounds	10	5	2	1.2	1
Candidate drug						
Compound in development						
				Referral to the Health Registration Committee		
				Drug approved for marketing		

This table only shows the activities in each phase, but the details of each vary greatly according to the type of drug being developed

Drug development

•**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.

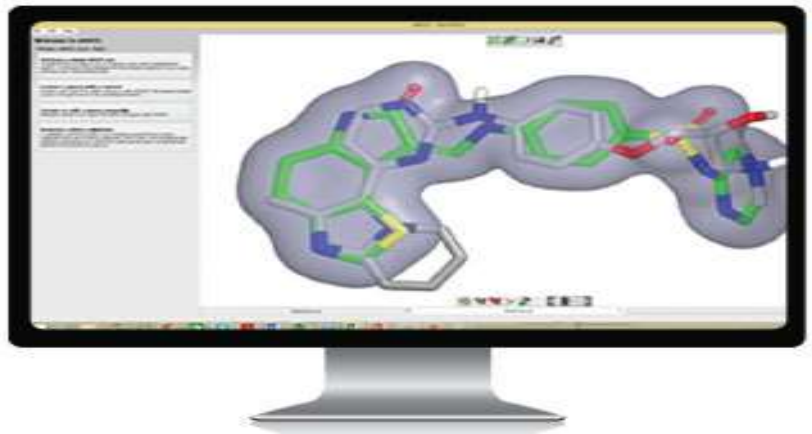
1. Drug Discovery

•The discovery stage starts with research and development in a labs.

• Researchers identify target molecules – such as genes, proteins or enzymes that plays a significant role in a disease.

•This is followed by so-called *in silico* – computational – testing performed on hundreds – sometimes thousands – of chemical or biological compounds (hits) to evaluate their effects on the disease.

•Leads: chemical or biological compounds with increased activity at a chosen target (potency) and reduced activity against unrelated targets (specificity)



•**Lead optimization:**

•to identify one or two drug candidates suitable for further investigation by:

•High-throughput screening (HTS) is one of the newest techniques used in drug design applied by robots, detectors and software .

2. Preclinical research

•The discovery phase is followed by a pre-clinical research phase, where the lead compounds are tested both *in vitro* and *in vivo* – experimental models (cell cultures and animal studies).

•Once fully characterized, the most promising compounds become lead candidates.

•The most important aspect of preclinical research is the safety tests to ensure that the candidate is not toxic before it can go through clinical studies in humans.

•The discovery phase and the preclinical phase can take 4-7 years.
•After completion of the preclinical tests, developers will apply for permission to proceed with clinical – in-human – studies.
• This is done either through an *Investigational New Drug (IND)* application in the US or a *Clinical Trial Application* (*CTA*) in the EU.
•The respective regulator authority then examines all available data and decides whether to approve the clinical studies.

3. Clinical development

- **Phase I – safety**
- Following regulatory approval and approval from ethics committees, the first clinical study, a phase I study – which constitutes the first study in humans, is initiated.
- Here, the candidate is generally tested on 20 to 80 healthy volunteers with the aim of determining whether the candidate behaves in the same way in the human body as the preclinical studies have indicated.

•The safety profile – or toxicity – of the substance is again the main focus, but this time in humans.
•In phase I: a safe dose, how the drug is absorbed, and how long it is active in the body are tested.
• For safety reasons, phase I clinical trials tend to exclude women of childbearing age.
•A phase I study takes up to one year to perform

- **Phase II – Proof-of-Concept**
- With positive safety results from phase I, drug developers can apply for permission to take the next clinical development step – phase II.
- In this phase, the candidate is most often evaluated in 100 to 300 patients diagnosed with the disease that the candidate is intended to treat.
- Efficacy and safety are tested: minimum and maximum dosages of the drug are determined for use in the next phase of development.
- Phase II typically takes up to two years.

- **Phase III – regulatory evidence**
- In the case of positive safety and efficacy data from phase II, the next step is phase III.
- This is the last step in the evaluation of a drug before requesting market approval from pharmaceutical regulators.
- The number of patients enrolled in a phase III study is usually at least 1000 – this ensures that enough data is obtained to show that the drug is safe for humans and has the intended clinical efficacy.

•In the phase III study: researchers document and report any side effects experienced by patients.
• The patients need to be exposed to the drug for long periods of time in order to make sure those side effects are properly assessed.
•Any side effects noted at this stage are listed in the package leaflet of the final product.
•Phase III takes an average 1-4 years.

Market approval & launch

- **the drug registration process**
- With good results from phases I-III, an application for market approval is submitted, called *New Drug Application* (NDA)*/*Biologics License Application* (BLA) in the US and *Marketing Authorization Application* (MAA) in the EU.
- These can include hundreds of thousands of pages of documentation summarizing all collected data from the discovery phase onwards, and where the principal investigator argues for approval with the FDA and/or EMA

•Preparing the application documentation can take several months, followed by about 6-10 months for the authorities to process the application.

•**Market launch**

•If the regulatory authorities approve an application, the candidate – or medicine as it is now called – is ready for market launch.

•At this point, price negotiations begin between the principal and the potential buyers (government agencies or insurance companies, depending on the healthcare system).

• The price negotiation process can differ greatly from country to country.

Phase IV studies – monitoring marketing and safety

•In some cases, regulatory authorities require follow-up phase IV studies after a drug has received market approval.
• This is done by collecting data from clinical practice: real care units that treat patients.
•The aim is to increase pharmacovigilance.
•Phase IV studies evaluate whether the drug is interacts with other substances, any additional side effects.
•This is especially important for: drugs for complex medical conditions, drugs for the treatment of pregnant women.

•Additionally, phase IV studies may be relevant for drugs that will treat rare conditions, which had a limited number of patients in phases I-III.

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Thank you