COMPUTER AIDED DRUG DESIGN

2. Drug discovery -Issues

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Drug Discovery: a process by which a drug candidate is identified and partially validated for the treatment of a specific disease.

- Mechanism of action
- Target Identification/Validation
- Lead identification/optimisation
- ADME properties
- PK/PD
- Toxicity

Drug discovery process does not include:

- preclinical studies,
- clinical trials,
- regulatory approval,
- Sales and marketing.
- These are all called drug development process.

	Time	M $
•***In silico*** discovery	2-3 years	10
•Preclinical trials – testing on animals toxicity of raw materials	6-12 months	10
•Phase I - safety on human volunteers tolerability, side effects	6-12 months	15
•Phase II - drug efficacy range of concentrations	6-12 months	15
•Phase III - long term effect	3 years	600
•Phase IV - its effect after the drug in the market		

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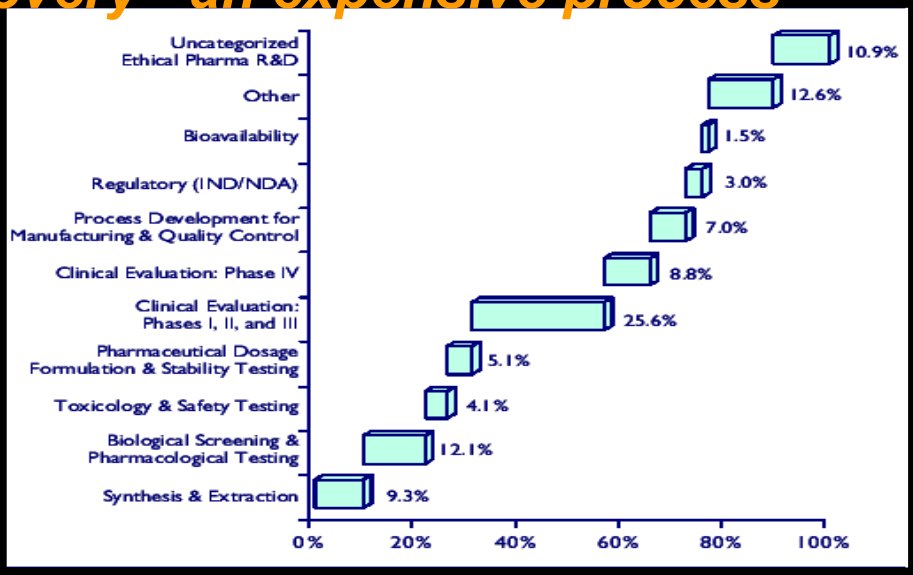
Drug Discovery - an expensive process



Source: Pharmaceutical Research and Manufacturers of America, 2002

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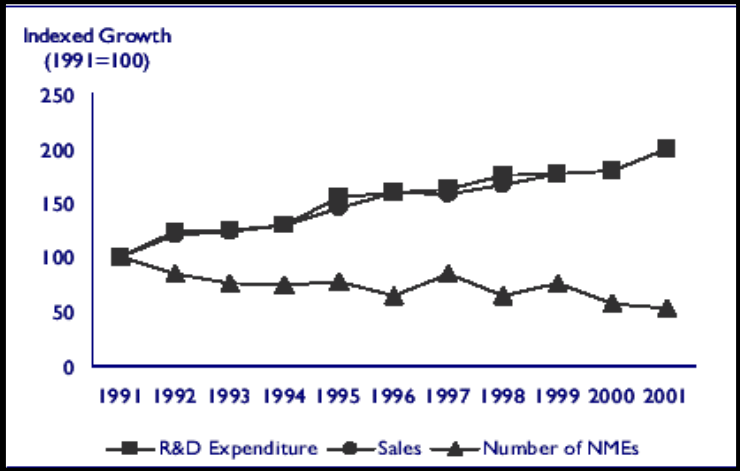
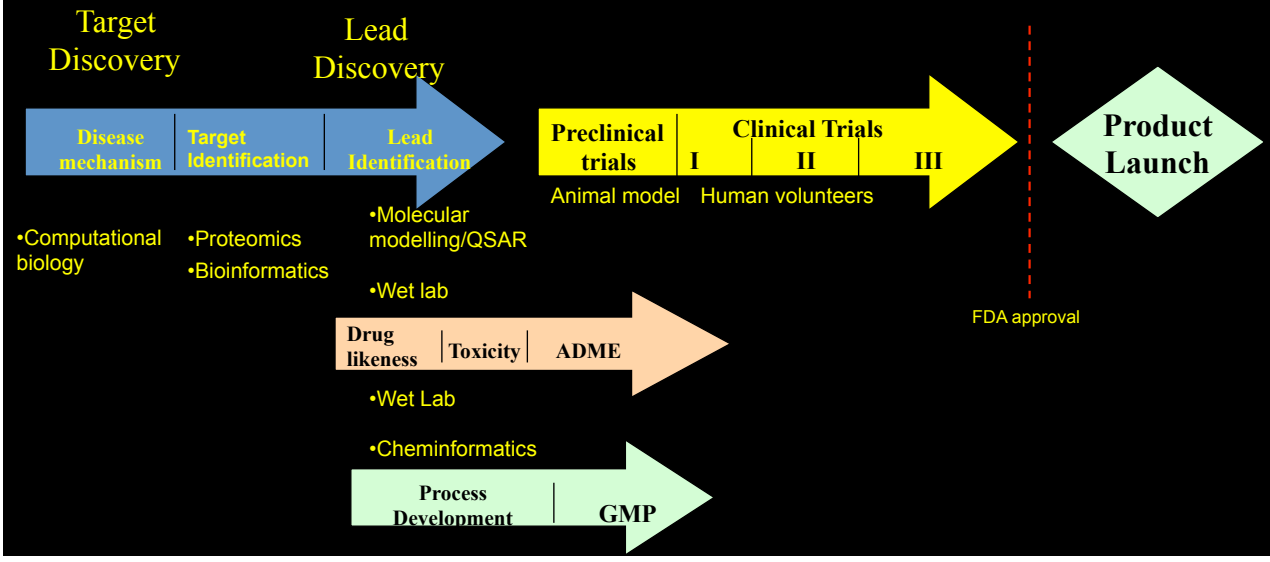
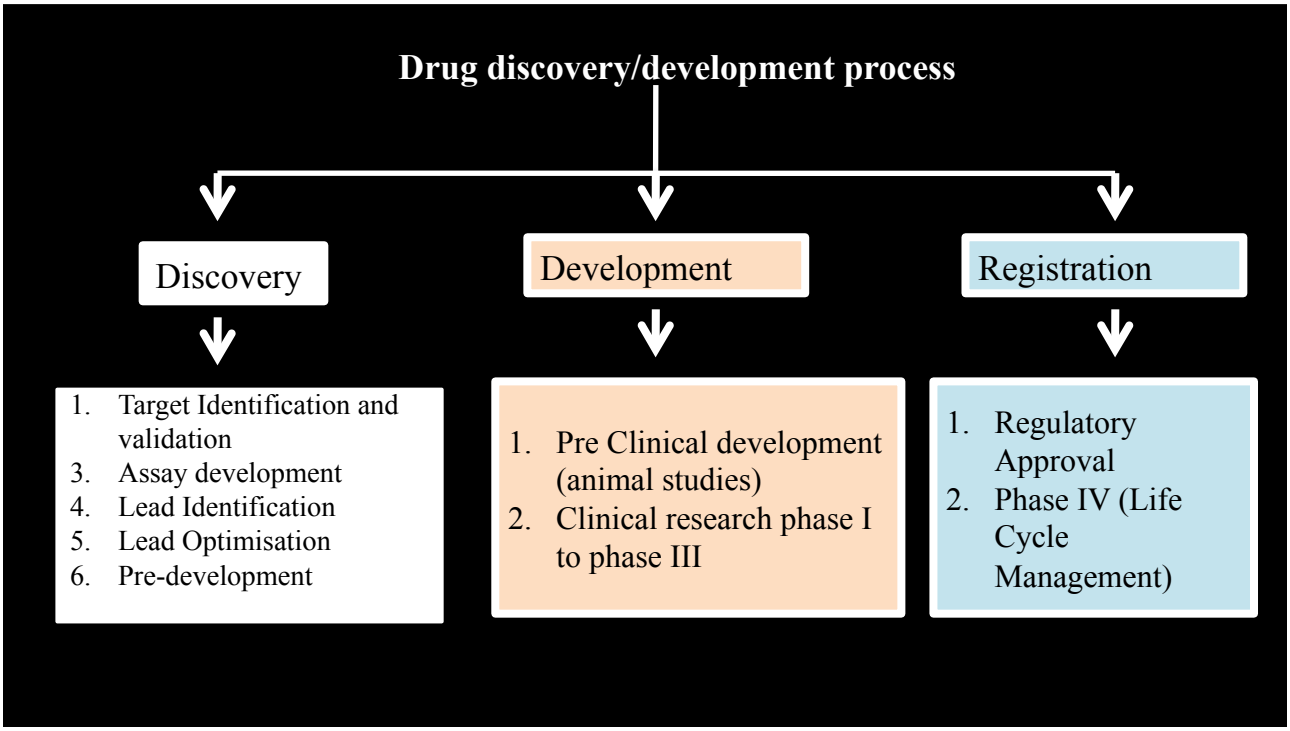
The Drug Discovery Challenge

- The price of R&D is increasing
- Number of new chemical entities is declining



Approx 12-15 years and 1200 million $ to launch one drug molecule in the market





Clinical Trials

- Phase I - Human Pharmacology
- Phase II - Therapeutic Exploratory
- Phase III - Therapeutic Confirmatory
- Phase IV - Post marketing

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Phase I

- **Assess tolerance**
- **Pharmacokinetics and Pharmacodynamics**
- **Explore drug metabolism and drug interactions**
- **Estimate activity**

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Phase II

- **Explore use for targeted indication**
- **Estimate dosage for subsequent studies**
- **Provide basis for confirmatory study design, endpoints, methodologies**

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Phase III

- **Demonstrate/Confirm efficacy**
- **Establish safety profile**
- **Provide an adequate basis for assessing the benefit/risk relationship to support licensing**

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Phase IV

- **Refine relationship of benefit/risk in general or special populations and/ or environments**
- **Identify less common adverse reactions**
- **Refine dosing recommendations**

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Drugs fail

9 out of every 10 new drugs fail in clinical testing. A drug in phase III testing has 32% chance of failure. Only 21% of drugs that enter phase I testing ever make it to market.

Phase I, 50% fail. phase II 30% and phase III 25-50%: overall success rate = 3-8%

The % of drugs failed for neurological diseases is higher.
> 200 candidates failed for Alzheimer's disease in clinical testing.

The drugs have been tested in rats or mice, and they clearly work

Many drugs stop working when tested in people?

suspected toxicity. (for example a liver enzyme showed a slight elevation in one animal.)

One random fluctuation in one of a hundred tests can be enough

Failure of Compounds in Development

- Poor biopharmaceutical properties, 39%
- Lack of efficacy, 29%
- Toxicity, 21%
- Market reasons, 6%