

Drug synthesis II
Lääkeainesynteetit II

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Drug discovery and development process



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Drug discovery and development is a long and an expensive process

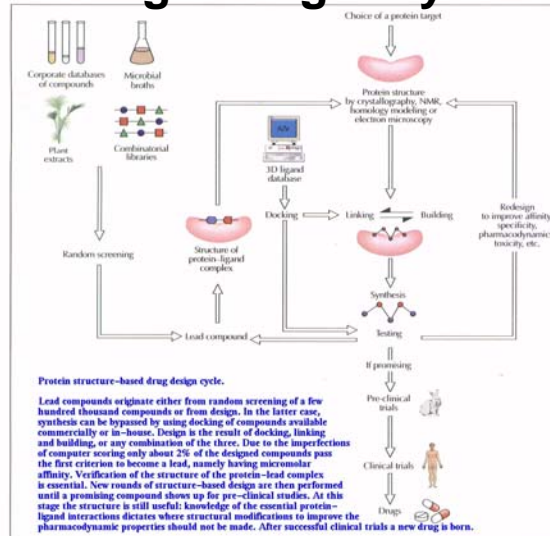
- It takes about 10-15 years to develop one new medicine from the time it is discovered to when it is available for treating patients
- A patent grants 20 years protection to the holder
- The vast majority of molecules fail along the way: for every 5,000-10,000 compounds that enter the research and development (R&D) pipeline, ultimately only one receives approval.
- The estimated cost to bring to market a successful drug (new chemical entity or NCE) is about 1 billion USD. This number includes the cost of the thousands of failures
- High costs consist of R&D costs, extensive clinical testing and safety monitoring.



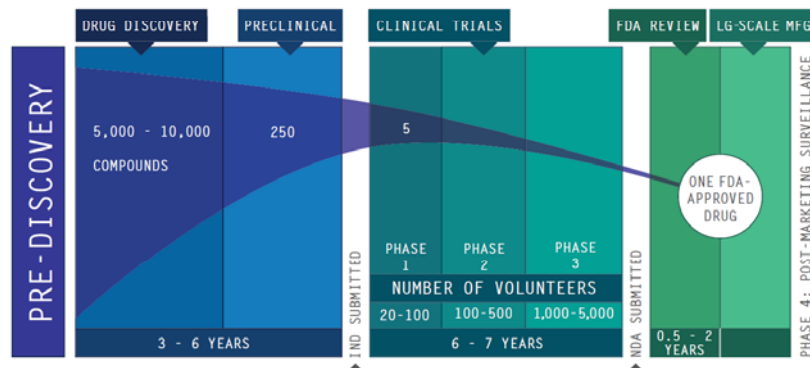
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Structure-based Drug Design Cycle

- Target identification and validation
- Assay development
- Virtual screening (VS)
- High throughput screening (HTS)
- Quantitative structure – activity relationship (QSAR) and refinement of compounds
- Characterization of prospective drugs
- Testing on animals for activity and side effects
- Clinical trials
- FDA approval

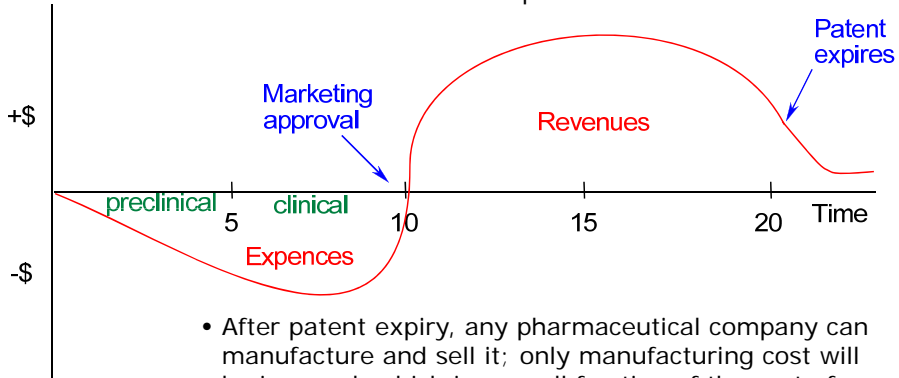


Drug discovery and development process



Expenses and revenues curve for a new drug

- The expenses of a new drug are extremely high and continue to escalate
- it takes about 7 to 10 years and only 3 out of every 20 approved drugs bring in sufficient revenue to cover their developmental costs



- After patent expiry, any pharmaceutical company can manufacture and sell it; only manufacturing cost will be incurred, which is a small fraction of the cost of original testing and development the drug.

Cost of Drug Development

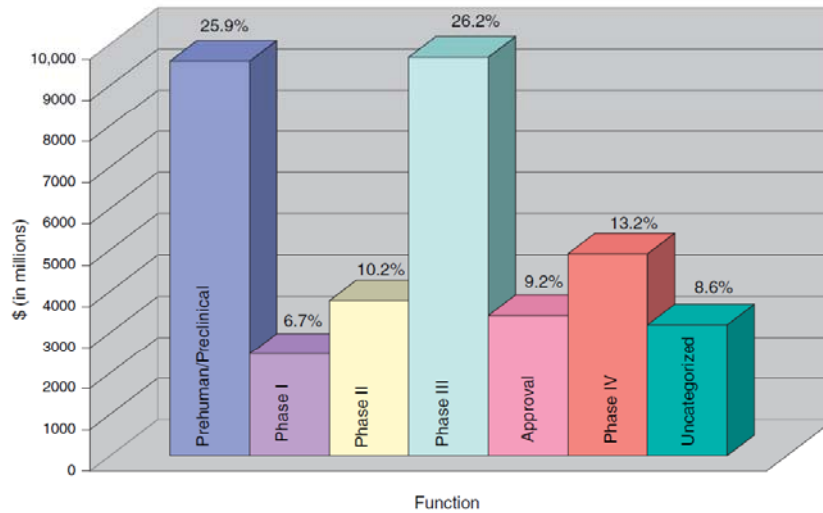


Figure 1.5 ▶ R&D spending by function for PhRMA member companies in 2004. Source: Pharmaceutical Industry Profile 2006, PhRMA.

Cost of Drug Development: The Productivity Gap

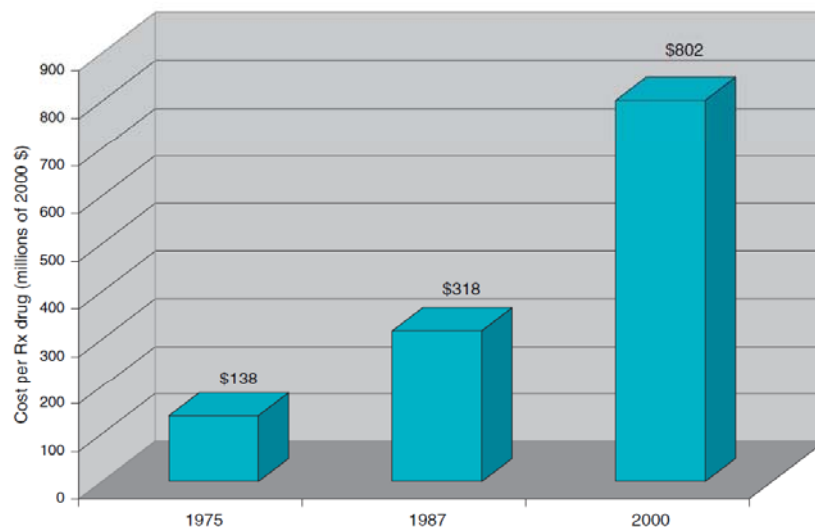
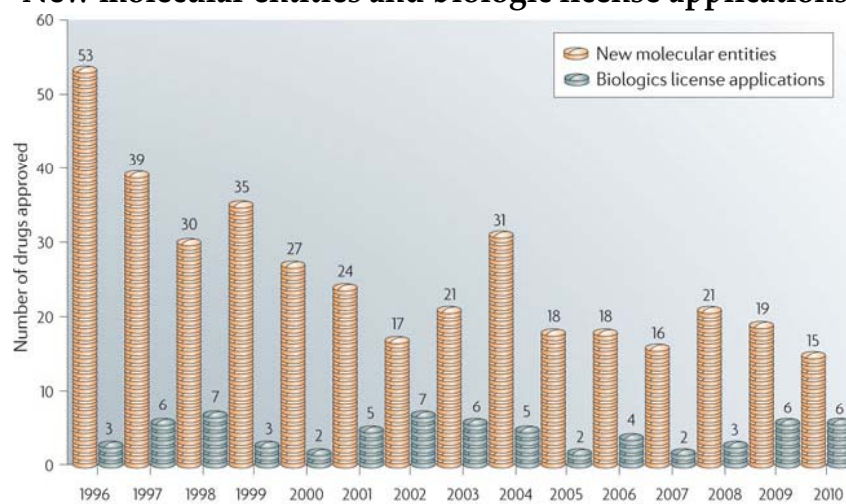


Figure 1.6 ▶ The increasing cost of new drug development. (Source: DiMasi, J.A., et al. The price of innovation: new estimates of drug development costs. *J. Health Econ.* 2003, 22, 151–185.)

New molecular entities and biologic license applications



Nature Reviews | Drug Discovery

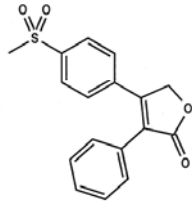


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Nature Reviews Drug Discovery 10, 82-85 (February 2011)

Market Withdrawals

Some drugs have been withdrawn from the market due to unexpected side effects.



- ✓ Rofecoxib (VIOXX) was used to treat rheumatoid arthritis for 5 years, before a clinical trial showed that it was associated with increased risks of heart attack and stroke.
- ✓ Annual profits reached \$1.2 billion (18% overall income)
- ✓ The Merck share price dropped 27% in value in a single day



[List of withdrawn drugs](#)



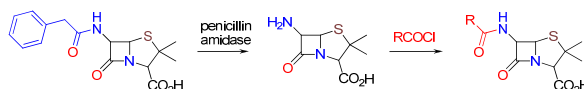
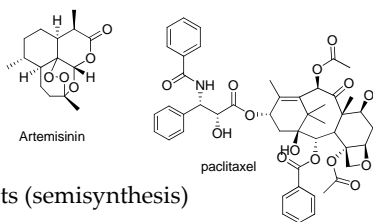
Major Pharma Trends

- Cost to bring a drug to market has risen
- Number of new drugs in clinical trials has fallen
- Number of NDA approvals for NMEs has dropped
- Expensive, high-profile withdrawals have occurred
- Generic competition has increased
- Fewer start-up companies were launched



Finding a lead compound

- Screening of natural products
 - fermentation (antibiotics)
 - plant extracts (anticancer agents)
 - Chemical modification of natural products (semisynthesis)

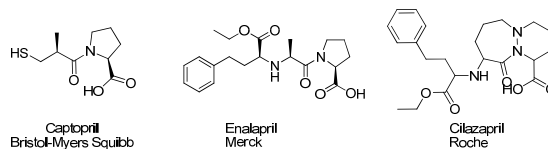


- Screening synthetic compound 'libraries'
 - 75 % of drugs are synthetic chemicals

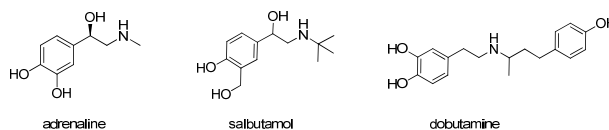


Finding a lead compound

- Chemical modification of existing drugs
 - Captopril and "me too" drugs



- Starting from the natural ligand or modulator compounds
 - Salbutamol and isoprenaline are derived from adrenalin



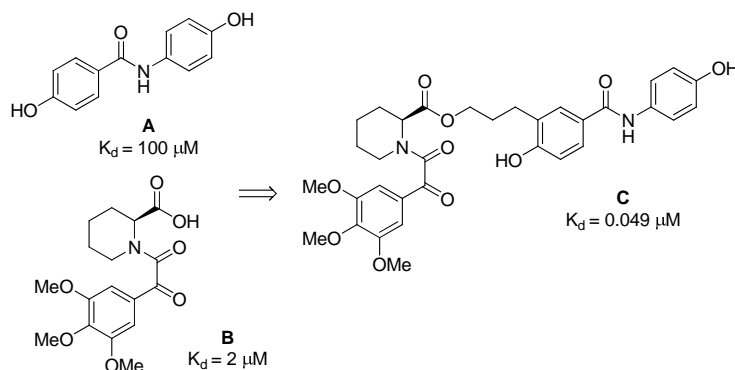
New technologies to find a lead compounds

- Combinatorial and parallel synthesis
 - Compound mixtures or single compounds
 - Solid phase synthesis
- Computer-aided design of lead compounds
- Computerized searching of structural databases
- Fragment-based lead discovery
 - based on identifying small chemical fragments, which may bind only weakly to the biological target, and then growing them or combining them to produce a lead with a higher affinity.



Fragment-based lead discovery

- Design of a ligand C for the FK506 binding protein using NMR spectroscopy. Fragments (A and B) bound to different regions. Structure C with propyl link had higher affinity.



Properties of lead compounds - Lipinski's "Rule of Five"

	If ALL Parameters Are	If ANY Parameter Is
Log P	≤ 5	> 5
H-Bond Donors	≤ 5	> 5
H-Bond Acceptors	≤ 10	> 10
Molecular Weight	≤ 500	> 500
LIPINSKI PREDICTION FOR A COMPOUND	GOOD Absorption or Permeation	POOR Absorption or Permeation

Compound classes that are substrates for biological transporters (antibiotics, antifungals, vitamins and cardiac glycosides) are exceptions to the rule. Reference: [Adv. Drug Delivery Rev., 1997, 23\(1-3\), 3-25.](#)

On-line calculation of drug-relevant properties:

- molinspiration: <http://www.molinspiration.com/>
- OSIRIS Property Explorer: <http://www.organic-chemistry.org/>

Drug names

Chemical name

- 2-[4-(2-methylpropyl)phenyl]propanoic acid

Company code:

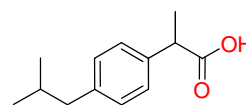
- SR141716 (Rimonabant, Acomplia)

Generic name (when a drug is approved)

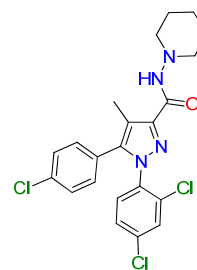
- Ibuprofen
- Rimonabant

Trade-name(s) or Brand name(s)

- Burana (Orion), Brufen retard (Abbott), Ibusal (Orion), Ibuxin (Merckle), Ibumax (Vitabalans), Ibumetin (Nycomed), Ibuprofen-Ratiopharm (Ratiopharm GmbH)
- Acomplia



ibuprofen
Burana®



SR141716A
rimonabant
Acomplia®