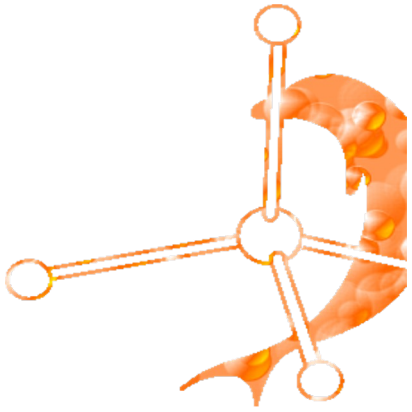
B. Samuelsson

Medivir AB, Huddinge (Sweden)

ISCHIA PORTO (NAPOLI), ITALY
HOTEL CONTINENTAL TERME
SEPTEMBER 18-23, 2004



IASOC 2004
Round table discussion

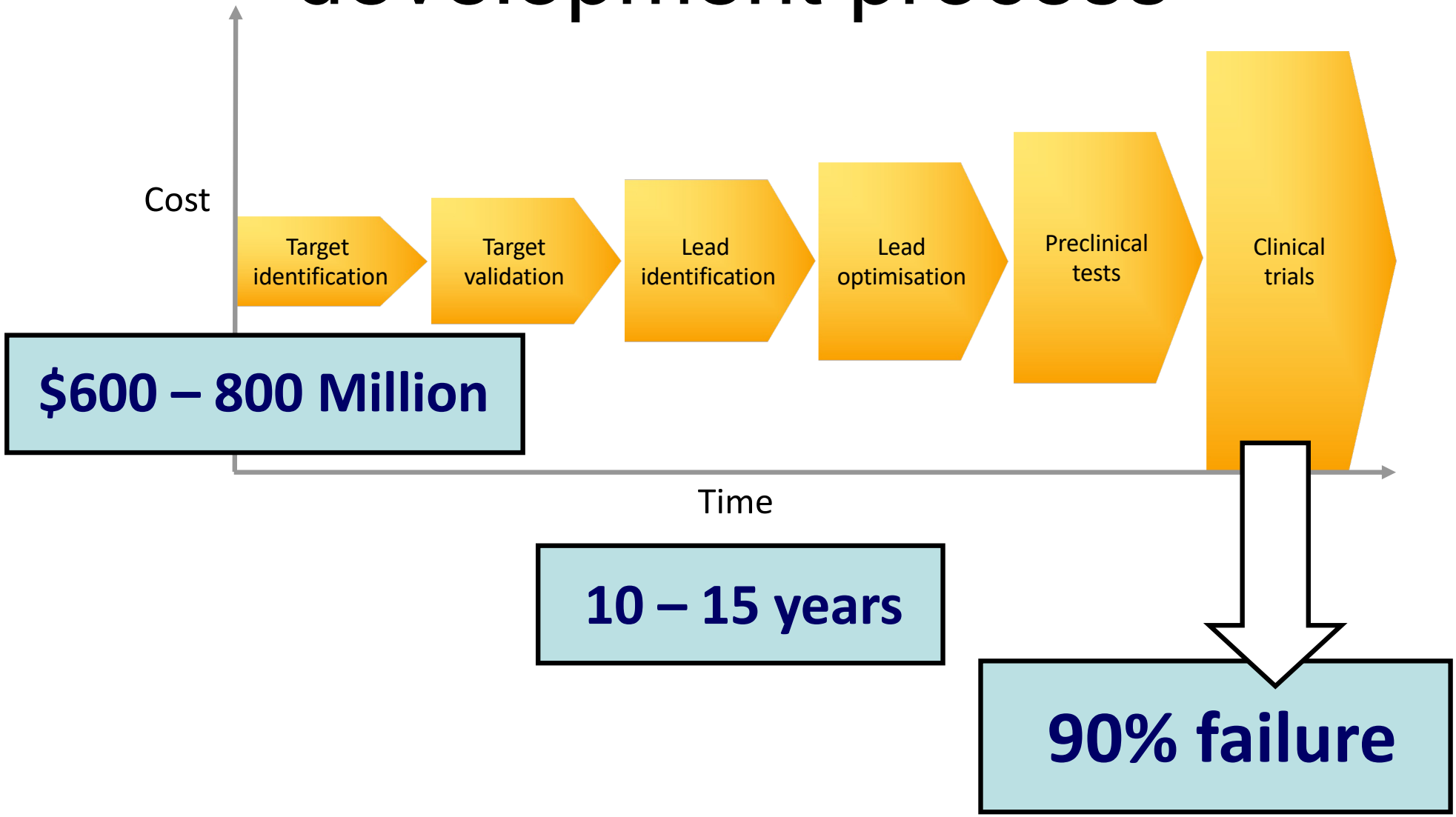
"The Impact of Organic Synthesis on Drug Discovery"

Bertil Samuelsson
IASOC 2004

Discussion Items

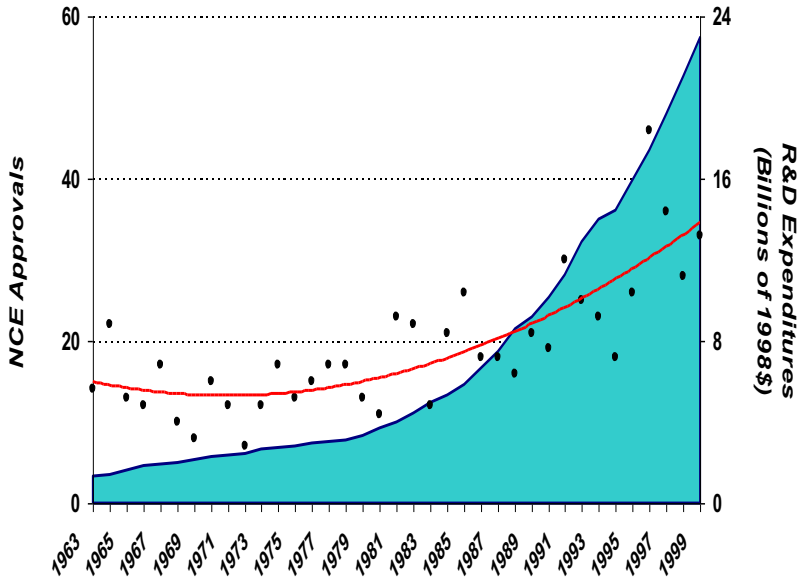
- How can/should organic synthesis contribute to discovery programs in Pharma
  - Process chemistry
  - Development candidate
- What can/should academic organic synthesis/medicinal chemistry labs contribute to discovery programs
  - Process chemistry
  - Development candidate

The drug discovery & development process



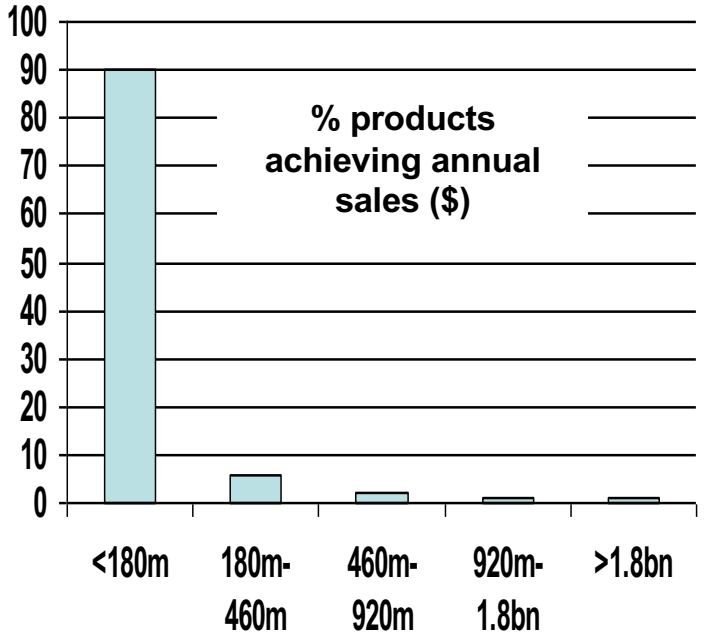
Economic Pressure for Change

Declining Productivity

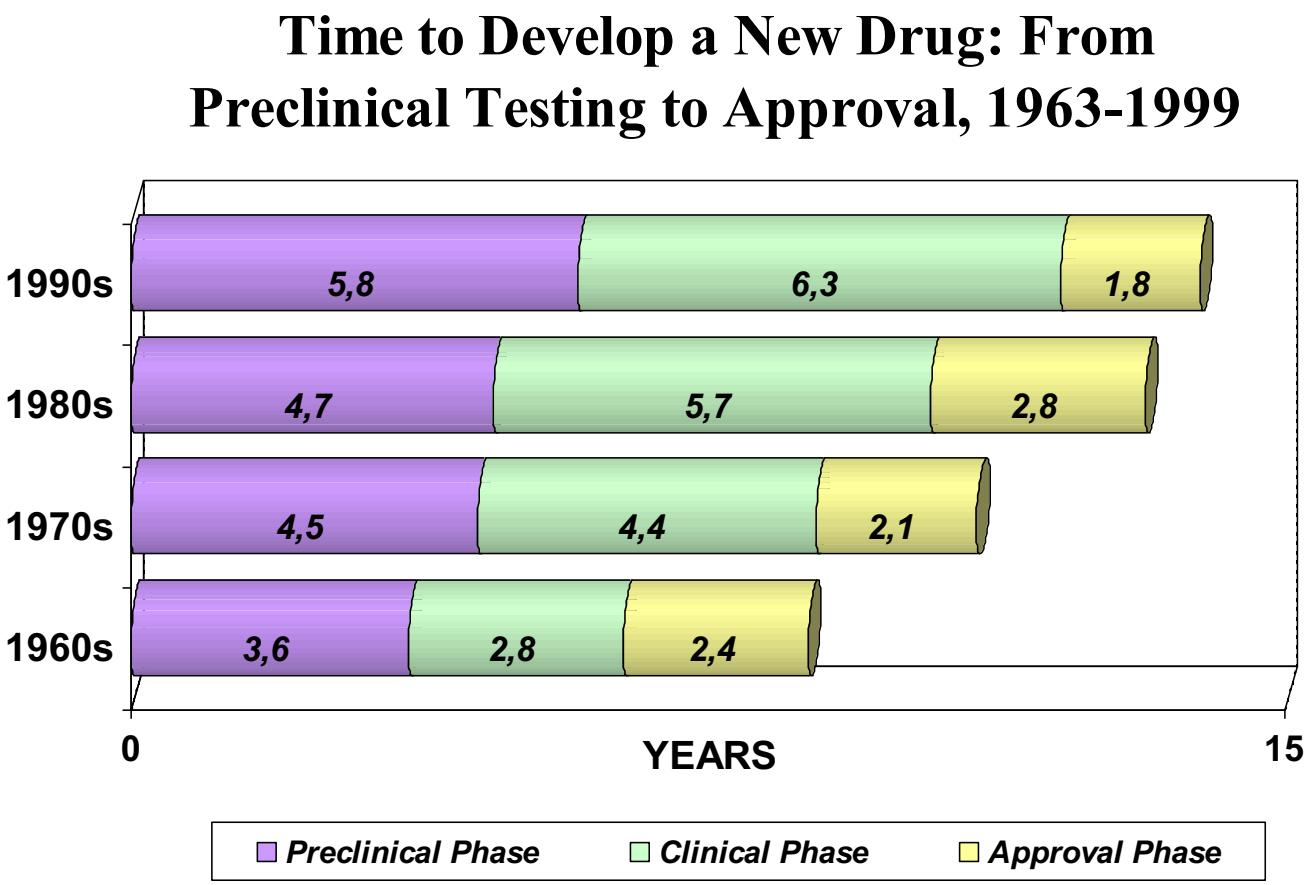


R&D expenditures adjusted for inflation
Source: Tufts CSDD Approved NCE Database, PhRMA

Reliance on Blockbusters



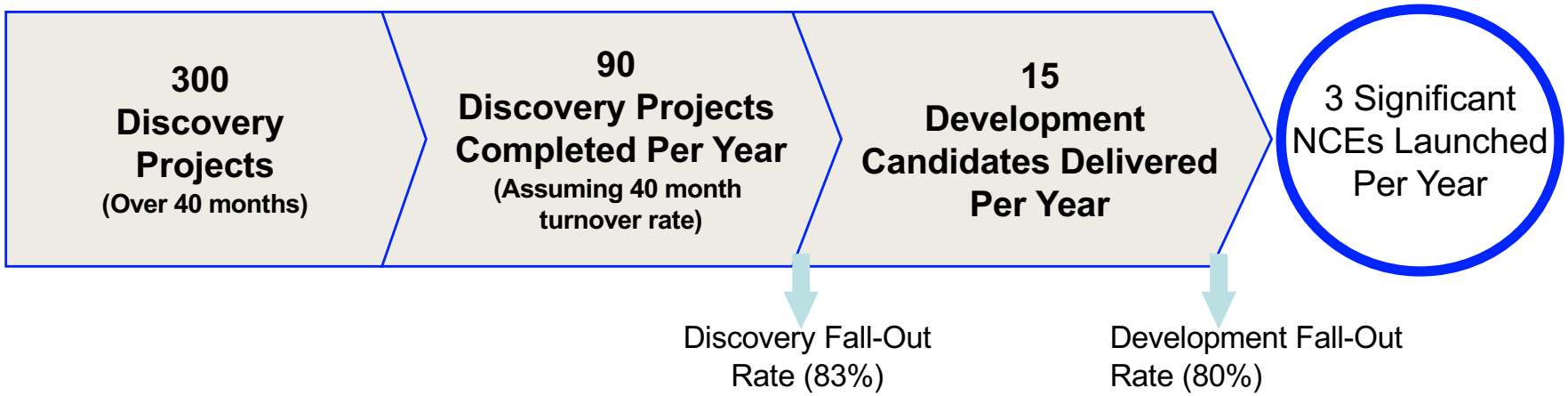
Lengthy Cycle Times Persist



Source: Tufts CSDD, 2001

Companies will need to focus on capacity, speed, attrition to drive results for the future

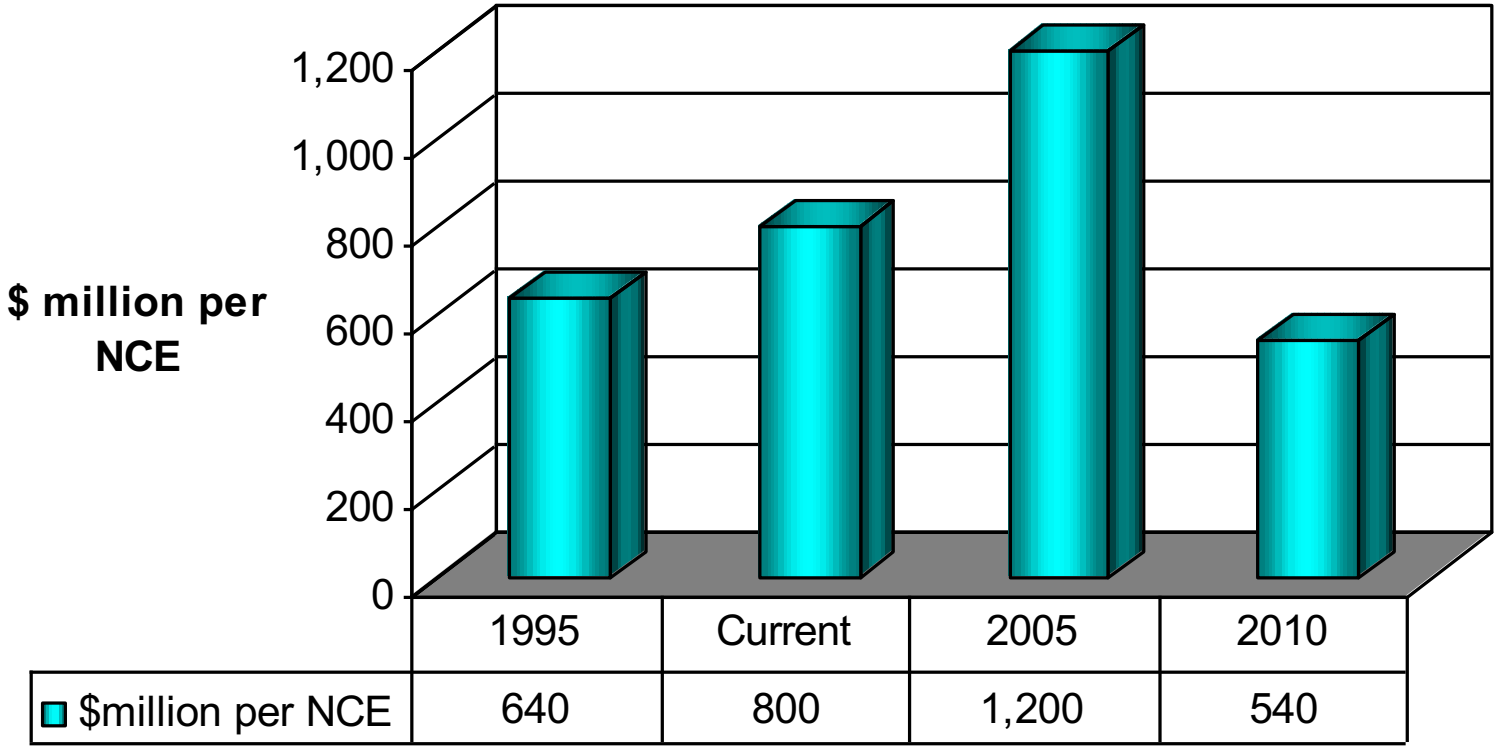
— Discovery /Development Pipeline Requirements, $15 Billion Company —



Capacity	Speed	Attrition
• Capacity has increased only due to higher resources in most areas • On average 250-275 FTE/years to produce an IND	• Except for target identification, have only improved cycle times by 5% or less annually since 1996	•Attrition rates have not improved in the last few years •Discovery Costs per successful drug run close to $350 Million (assuming 80% attrition)

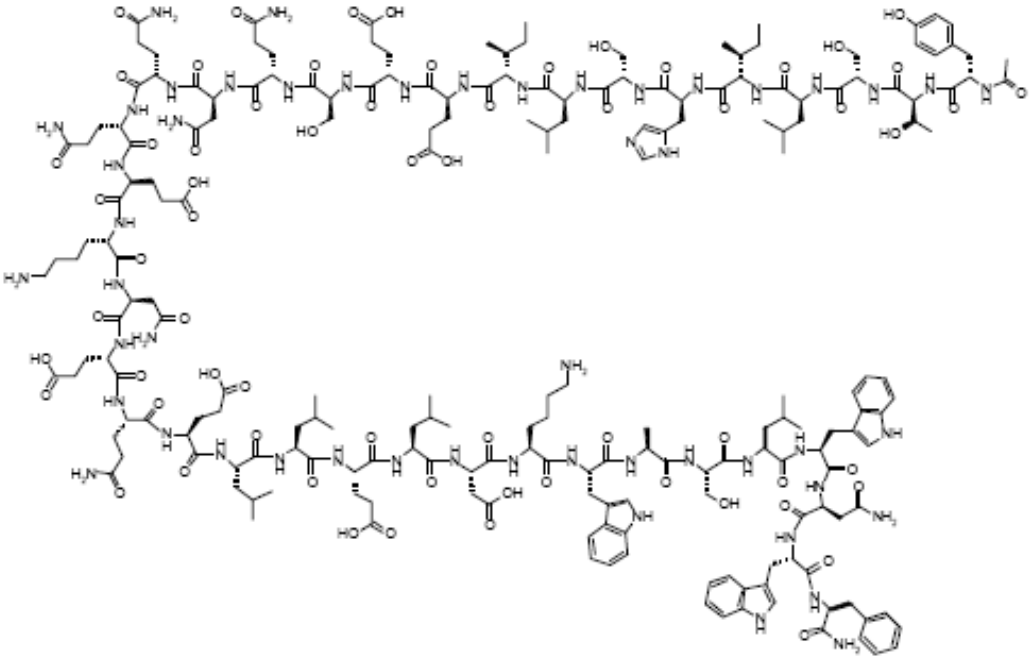
Source : © Accenture 2000

…. But it will take time to achieve improvements



Approved Drugs 2003 – Enfuvirtide, Fuzeon™

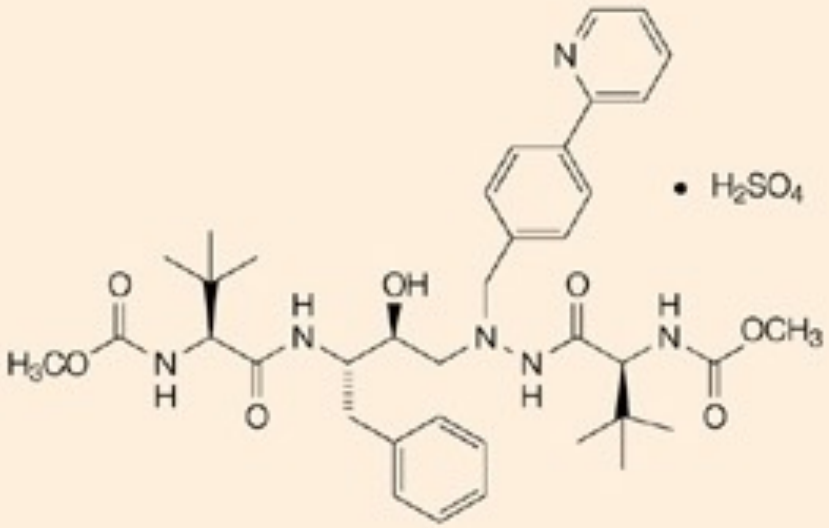
- Inhibits viral entry into host cells
- T-20 is a linear 36-amino-acid peptide
- Requires a chemical synthetic manufacturing process involving 106 production steps that take several months to complete
- Price is about $20,000 per year treatment



Complexity of drug drive COGS and retail prize

Approved Drugs 2003 – Atazanavir sulphate

HIV protease Inhibitor



Atazanavir sulphate

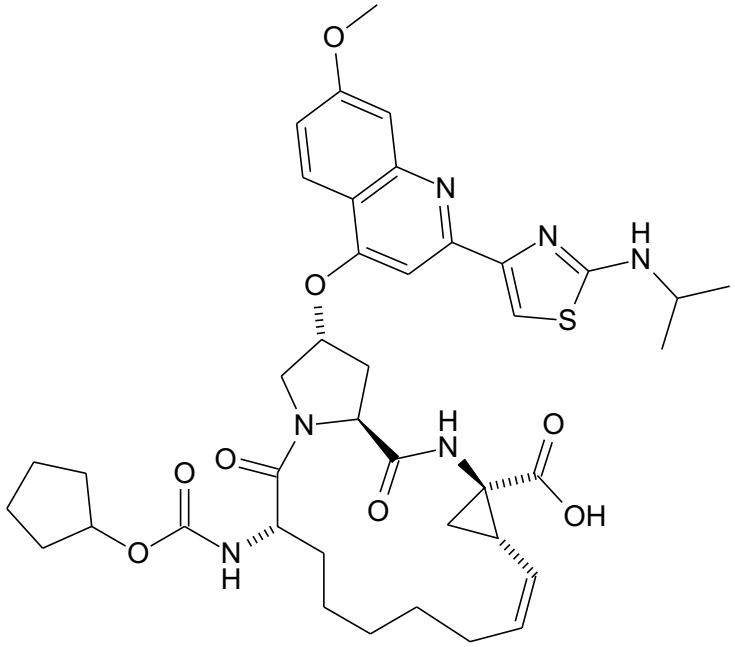
(3*S*,8*S*,9*S*,12*S*)-3,12-Bis(1,1-dimethylethyl)-8-hydroxy-4,11-dioxo-9-(phenylmethyl)-6-[[4-(2-pyridinyl)phenyl]methyl]-2,5,6,10,13-pentaaza tetradecanedioic acid dimethyl ester, sulphate (1:1);
$C_{38}H_{52}N_6O_7 \bullet H_2SO_4$; M_r = 802.9

New drugs in general contain multi-chiral centers and are stereo-chemically pure

Nature Reviews | Drug Discovery

Investigatinal Drug – BILN-2061

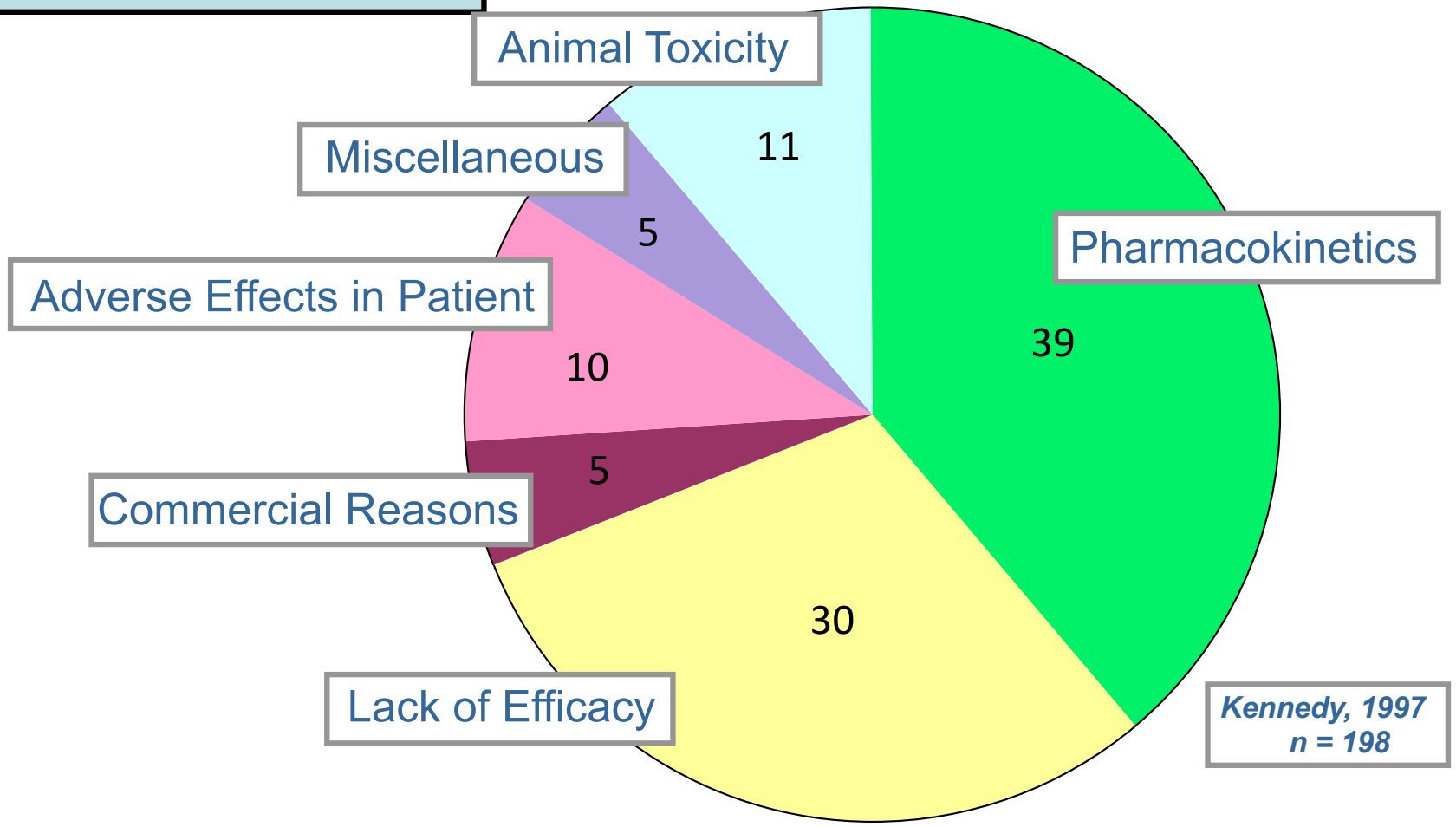
HCV protease inhibitor



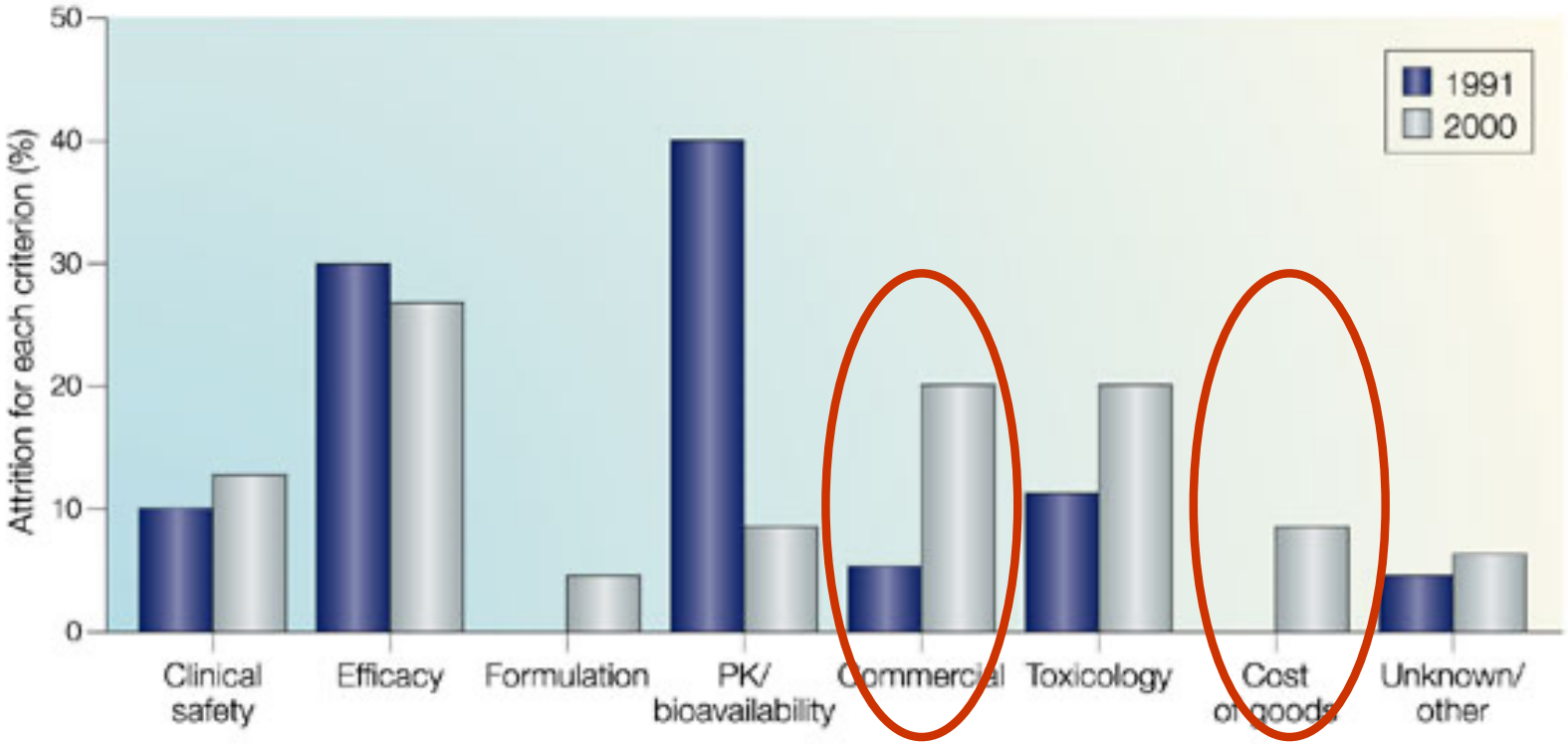
Will future drugs become increasingly complex and costly to manufacture

The drug discovery & development process

90% failure



Reason for Attrition of Investigational Drugs Today



COGS and commercial reasons are today having a major impact on the attrition rates in the clinical phase

Nature Reviews | Drug Discovery

- Is the increasing sophistication of organic chemistry leading to ever more complex drugs being delivered, driving COGS and in the end cost of new drugs
- If this is so, how can this trend be reverted in the future??