

# TOWARD AN UNDERSTANDING OF THE DRIVERS OF SUCCESSFUL DRUG DEVELOPMENT

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## **SLOAN FOUNDATION INDUSTRY CENTERS MEETING**

Wednesday, April 21, 2004

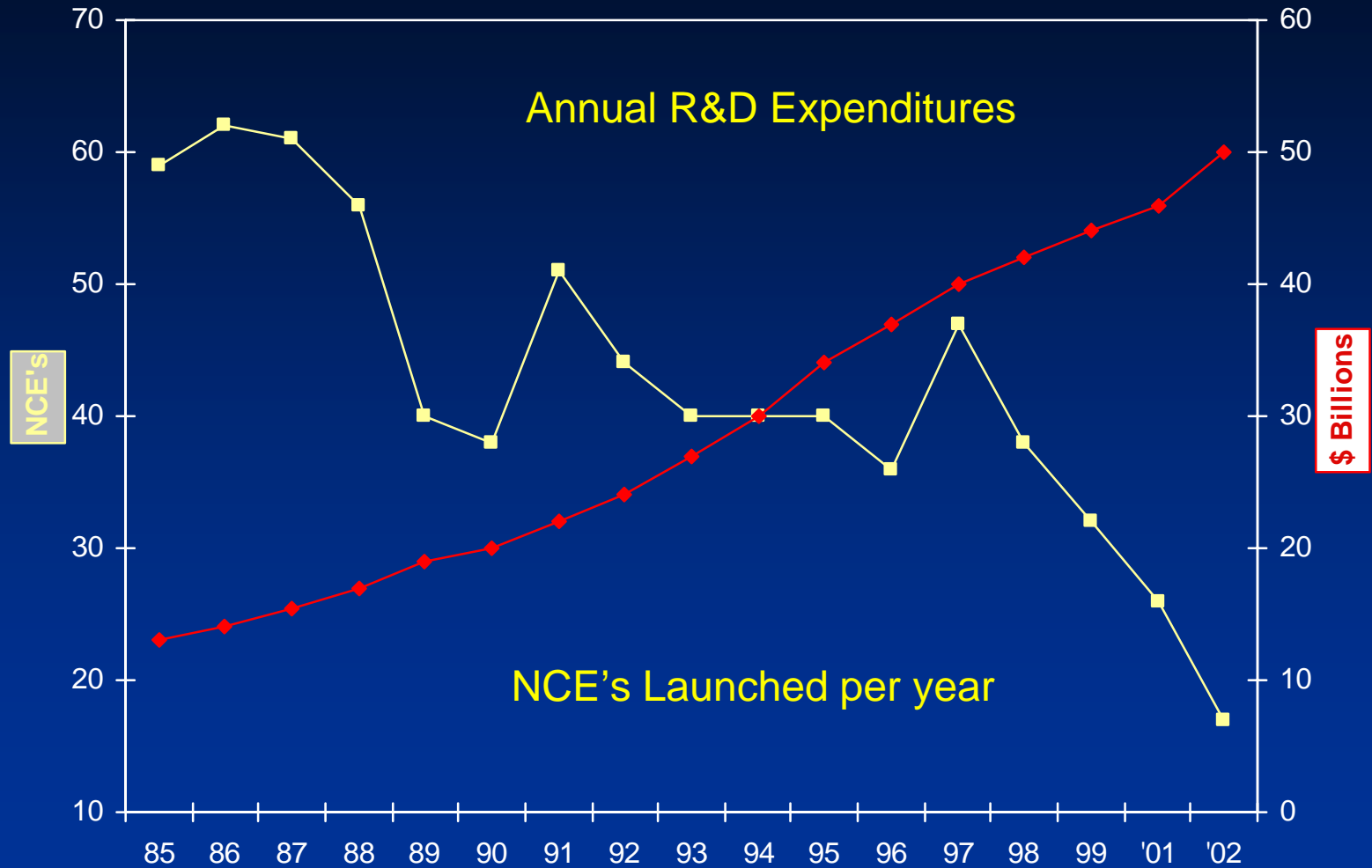
# Drug Development

- TCSDD 2003: \$897 000 000
- 70-90% of new chemical entities (NCEs) fail
- >60% of terminations: Phases II & III
- 2002: NDA approvals hit 5-year low

# Science and Technology are Revolutionizing Drug Discovery and Development

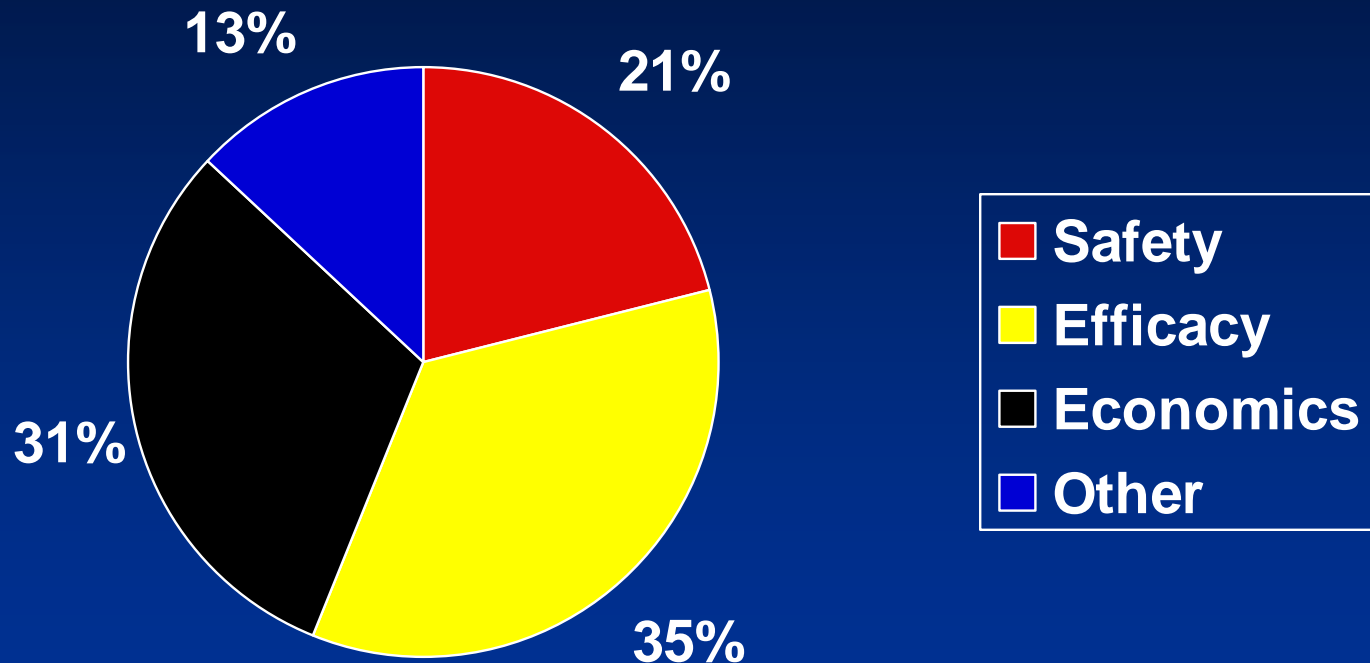
- Combinational Chemistry and Biology
- Parallel / High Throughput Processing
- Pharmacogenomics
- Functional Imaging
- Miniaturization
- “In Silico” Testing and Computer Modeling

# Big Pharma R&D Productivity is Falling



Source: IMS/Price Waterhouse Coopers

# Primary Causes of Failure in 348 Terminated NCEs



Ref: DiMasi, J. Clin Pharmacol Ther (2001) 69;297-307.

# Why Have We Not Yet Observed Much Impact From New Technologies?

- “The Easy Drugs Have Been Done”.
  - *Acute diseases or chronic diseases with simpler symptom profiles.*
  - *Simple endpoints (blood pressure, serum cholesterol) are being exploited.*
- New drugs, particularly for “complex” diseases (e.g. cancer, diabetes, autoimmune diseases) will require new approaches to disease and patient satisfaction and staging.
- Historically, long lag times have been observed between initial, enabling scientific advances and market introduction of the new drug.
- “Convergence” of multiple scientific and technological advances have often been required to fully realize benefits.

# Lag from Initial Discovery to Product Persists

	Pharmaceutical	Date of Key Enabling Discovery	Date of Market Introduction	Lag Time
Random	fluconazole (Diflucan®)	1978	1990	12
	gemfibrozil (Lopid®)	1962	1981	19
	ketoconazole (Nizoral®)	1965	1981	16
	nifedipine (Procardia®)	1969	1981	12
	tamoxifen (Nolvadex®)	1971	1992	21
Mechanism-Driven	captopril (Capoten®)	1965	1981	16
	cimetidine (Tagamet®)	1948	1977	29
	finasteride (Proscar®)	1974	1992	18
	fluoxetine (Prozac®)	1957	1987	30
	lovastatin (Mevacor®)	1959	1987	28
	omeprazole (Prilosec®)	1978	1989	11
	ondansetron (Zofran®)	1957	1991	34
	sumatriptan (Imitrex®)	1957	1992	35
Basic Science	cisplatin (Platinol®)	1965	1978	13
	erythropoietin (Epogen®, Procrit®)	1950	1989	39

*Source: Iain Cockburn, & Rebecca Henderson*

# Objectives

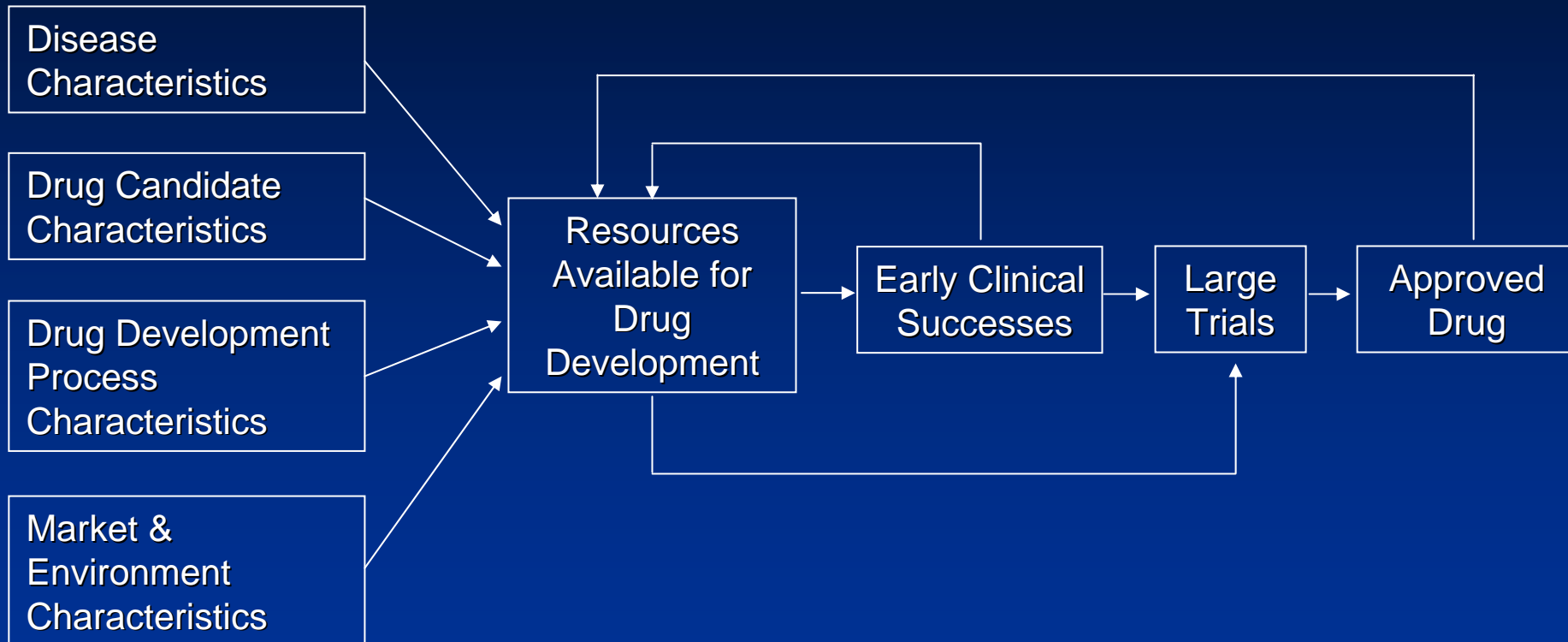
- To explore the consequences of the scientific and technological evolution of drug development over the past 10 – 15 years.
- To examine whether impacts of new technology on drug development can be discerned from observations about the progress of ongoing drug development.
- To identify metrics providing evidence that newer drugs are “better”, and/or the process is becoming more productive.
- To build a “Predictive Model” of the drug development domain.

# Kinds of Observations that could Indicate Favorable Impact of Evolving Science and Technology on Drug Development:

- Drugs are safer.
- Drugs are more effective.
- Development times are shorter.
- Fewer patients required in clinical trials.
- Development termination decisions made at earlier, less costly stages.

# What Drives Successful Drug Development?

## Inputs



# Examples of Input Variables

## Drug Candidate and Disease Characteristics

- Therapeutic class
- Molecular type
- Life saving
- Therapeutic index – vital organs
- Therapeutic index – target disease
- Drug and disease biomarkers

# Examples of Input Variables *(continued)*

## Drug Development Process Characteristics

- Name source – geographical
- Name source – large vs. small firm vs. university
- Testing site
- Number of patients / trials
- License status and timing

## Market and Environment Characteristics

- Potential market size
- Performance of public investment markets
- Performance of private investment markets
- Market performance of developing firms

# Examples of Output Variables

- Latest development stage achieved.
- Elapsed time in development.
- Clinical success probability distribution.

# Bayes Net

- Automated stochastic modeling approach.
- Interface of artificial intelligence and statistics.
- Graphical relationships are symbolic and intuitive.
- Helps to select from alternative models of how a set of variables are interrelated.
- Preferred model is the one with highest posterior probability, given the data.

# Bayes Net *(continued)*

- Bayes theorem affords the calculation of a “marginal likelihood” of how each model generates the observed data.
- Ratios of marginal likelihood are “odds ratios” referred to as Bayes factors.
- “Global” models can be used early in research to explore the “big picture” in qualitative terms.
- New models can be built later in research to examine magnitude of quantitative relationships.

# Predictive Modeling

- **Aim:** fail the true failures early
- **Impetus - NCE failures:**
  - ✓ financial costs:
    - borne by elderly
    - “steal” from potential successes
  - ✓ patient risk
    - ineffective &/or unsafe trial drugs
    - impede pediatric drug development

# Implementation

- Java (ProjectBuilder), Apple OSX V2
- Validated against Discoverer (<http://bayesware.com>)

# rhAPC (Xigris)

- Based only on pre-Phase IIb data:
  - ✓  $P(\text{Clinical Success} = T \mid \text{data}) = 5\%$
  - ✓  $P(\text{Safety} = T \mid \text{data}) = 2.1\%$
  - ✓  $P(\text{Efficacy} = T \mid \text{data}) = 6.7\%$
- NDA-approved for Rx of sepsis in 11/2001.
- Safety & Efficacy concerns: Care Med 31, S94-6 (2003) - i.e. after NDA approval.

# Directions: Data Sources

- AIM: optimization, validation
- Pharma Sources
  - ✓ Wyeth Research, Novartis, Roche, Baxter
  - ✓ Obstacles: confidentiality, data accessibility
- Public Sources: manual data extraction
  - ✓ Oncology: 2460 Phase I abstracts
  - ✓ Centerwatch