CPBIS

Sloan 2004 Annual Conference

Toward an Understanding of the Drivers of Successful Drug Development

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Sloan Industry Centers Annual Conference
April 19-21, 2004 – Atlanta, GA

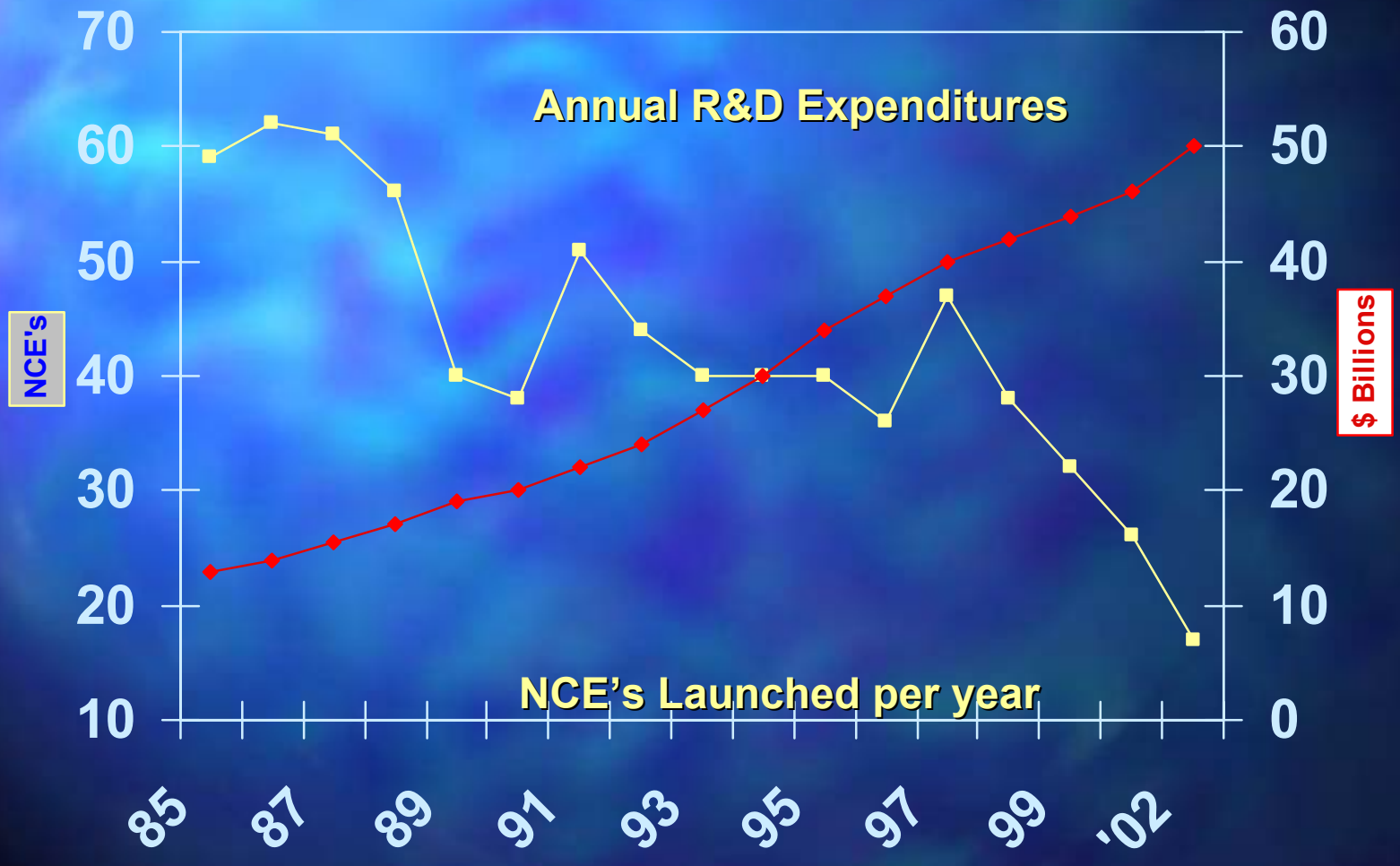
Drug Development

- 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

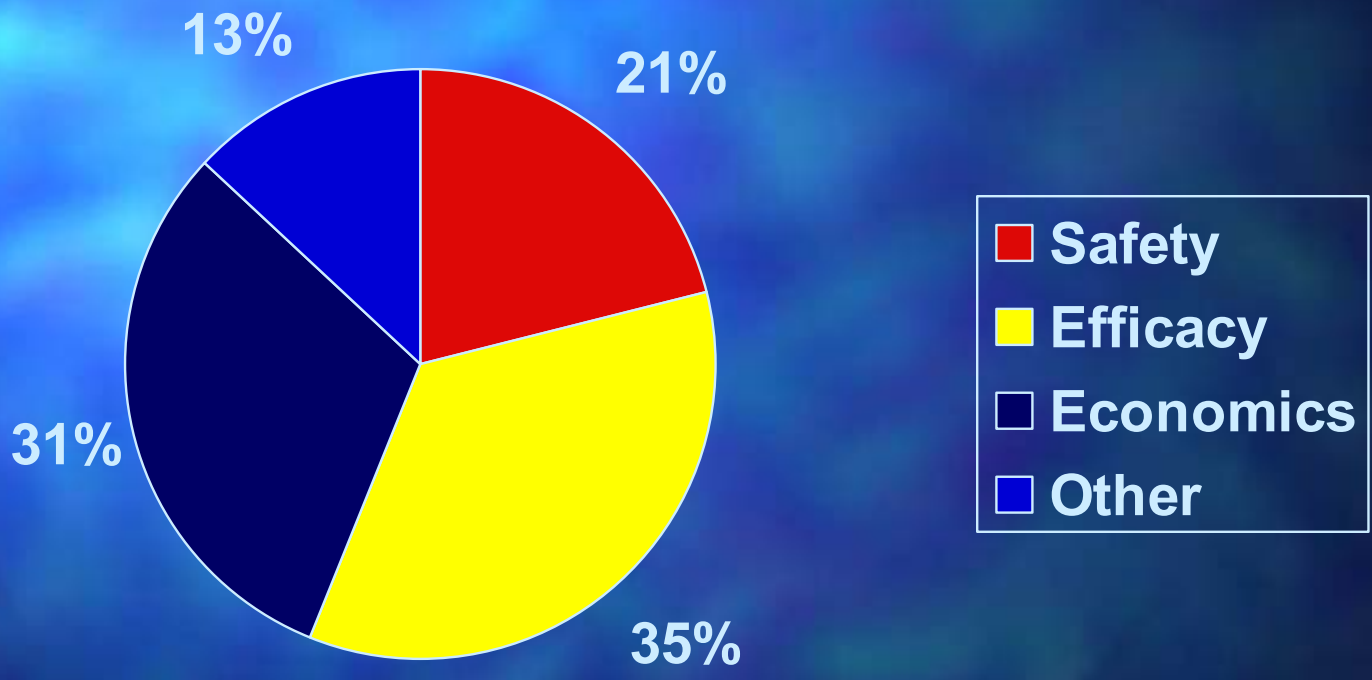
- Combinational Chemistry and Biology
- Parallel / High Throughput Processing
- Pharmacogenomics
- Functional Imaging
- Miniaturization
- *"In Silico"* Testing and Computer Modeling

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

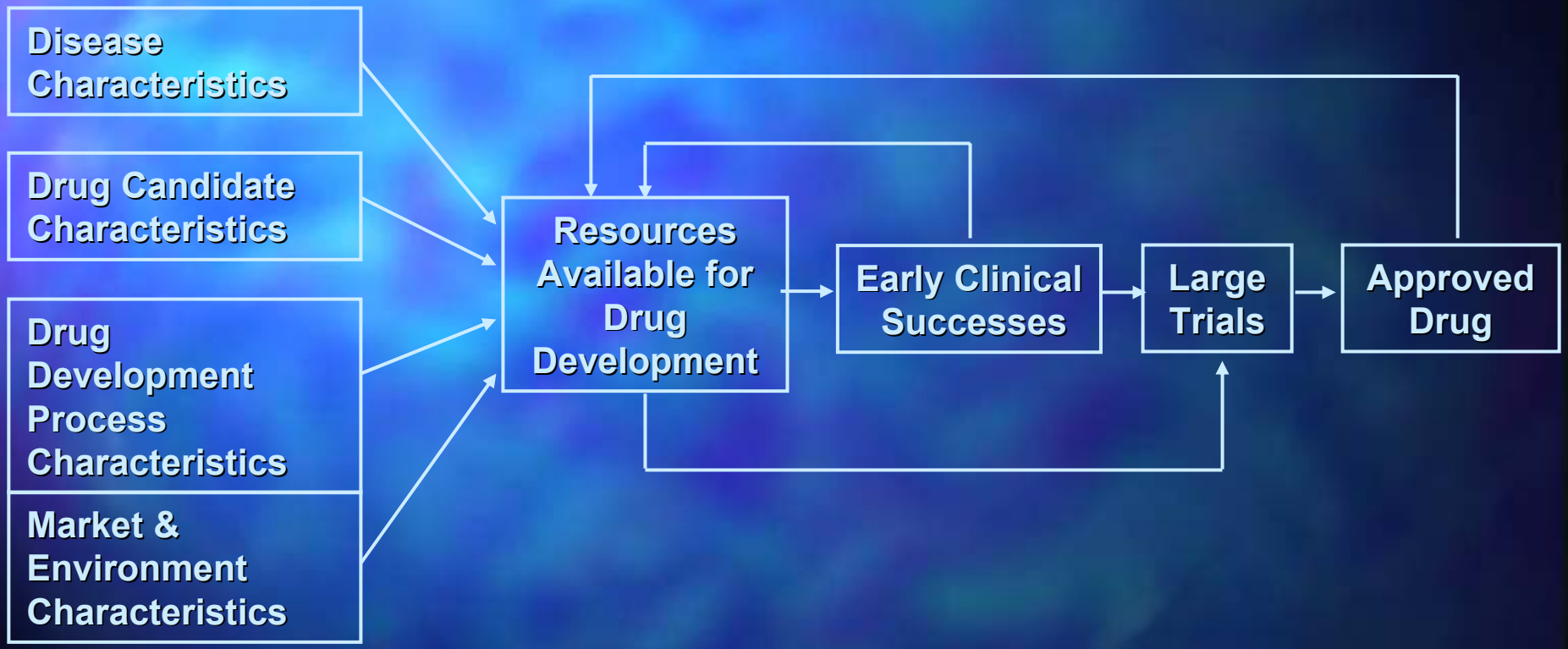
- To explore the consequences of the scientific and technological evolution of drug development over the past 10 – 15 years.
- To examine whether impacts of new technology on drug development can be discerned from observations about the progress of ongoing drug development.
- To identify metrics providing 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(Clinical Success= T | data) = 5%
  - ✓ P(Safety= T | data) = 2.1%
  - ✓ P(Efficacy= T | 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