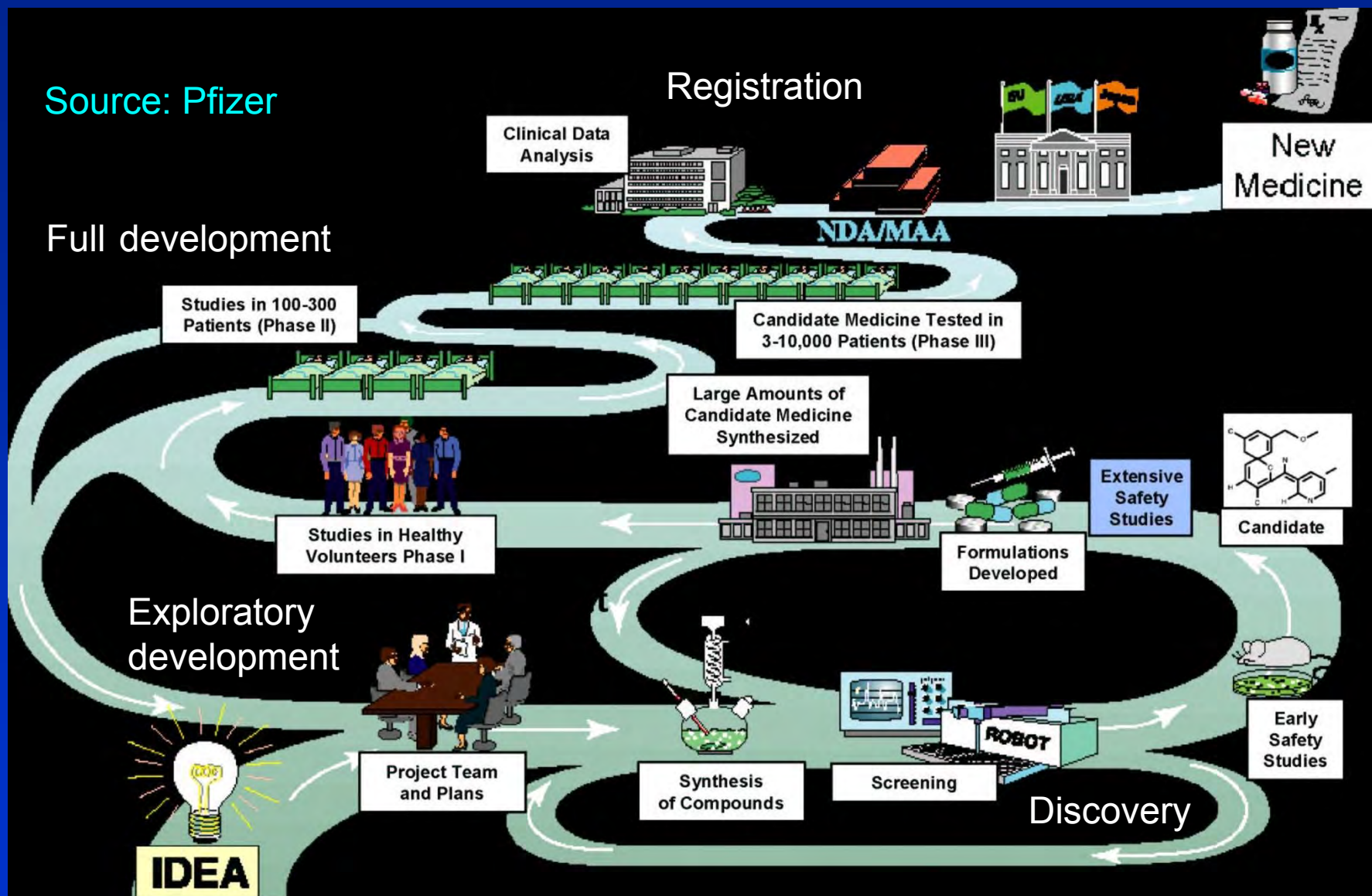


Adapt and Survive. The Way Forward in Research IS

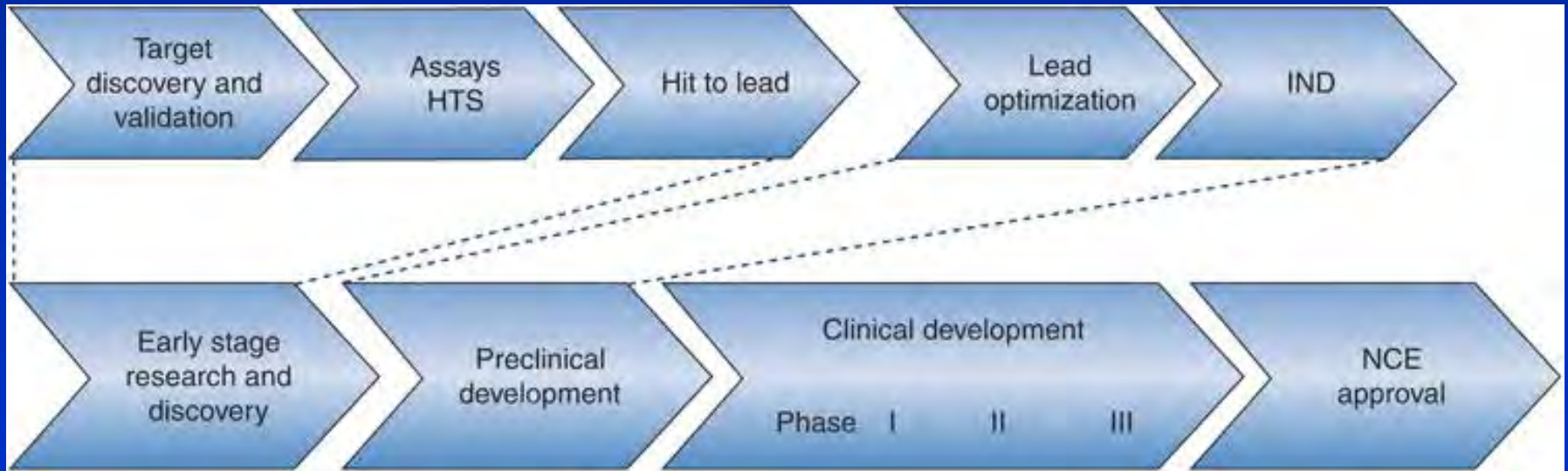
Dr. Wendy A. Warr
<http://www.warr.com>

The Long Road to a New Medicine

Source: Pfizer



Drug Discovery and Development



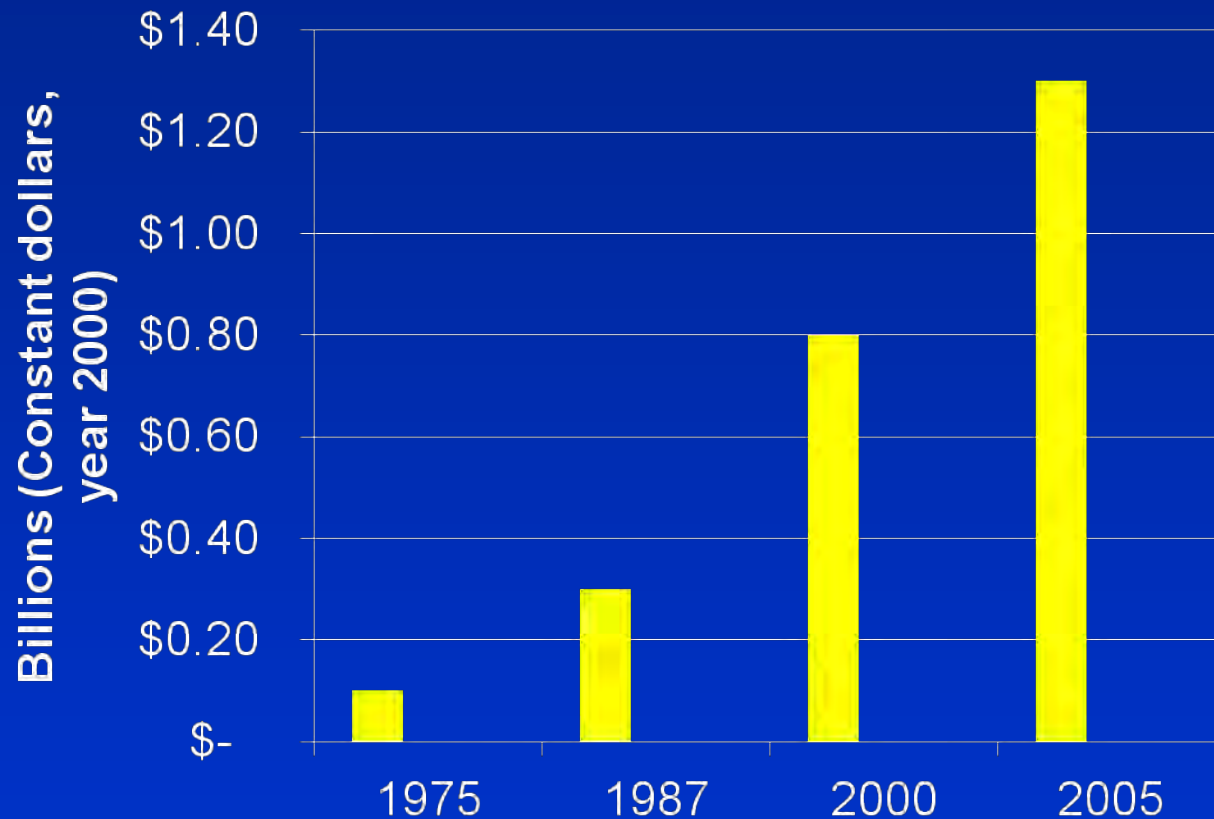
From Concept to Product: 10-15 Years

	Months/years
Target identification and validation	
Lead identification	4-6 months
Lead optimization	4-6 months
Preclinical development	4-6 months
Phase I	18 months
Phase II	12-24 months
Phase III	2-3 years
FDA review and scale up to manufacturing	6-24 months

Attrition

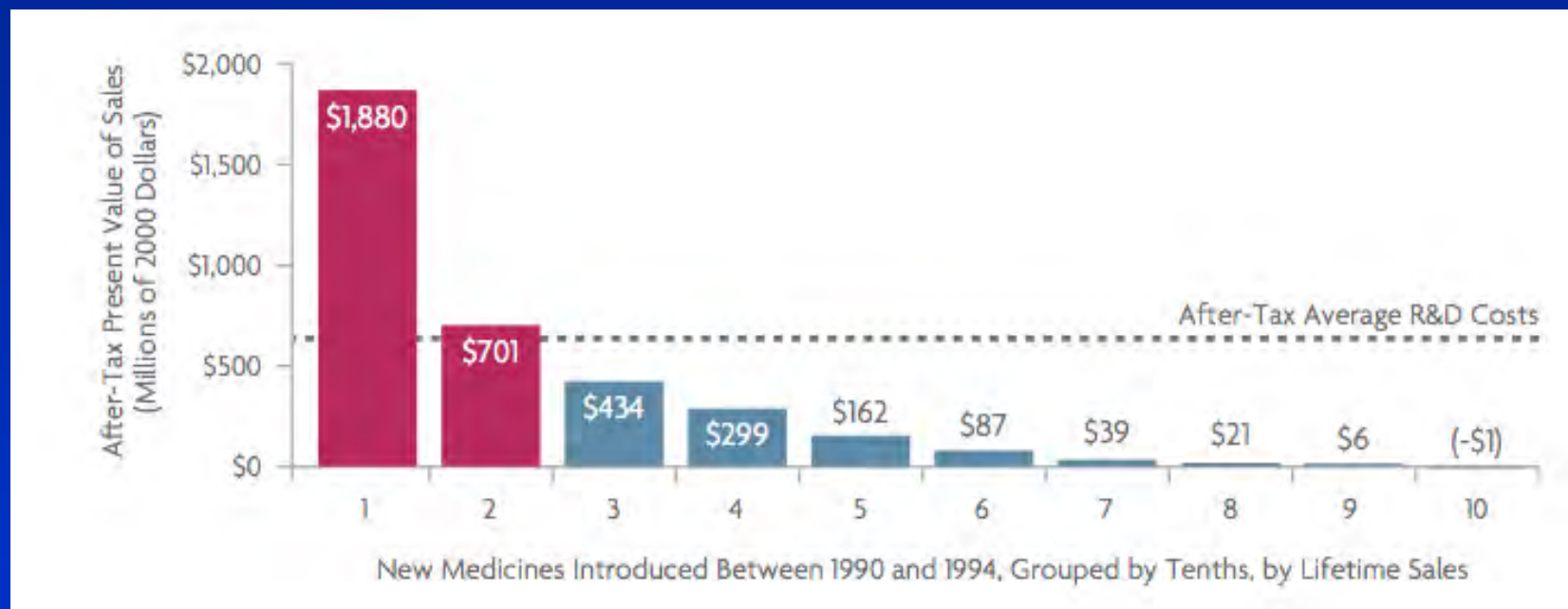
Stage	Compounds In	Compounds Out
Lead identification	Up to 50,000	100-200
Lead optimization	100-200	20
Preclinical	20	1-5
Phase I	1-5	1-3
Phase II	1-3	1-2
Phase III	1-2	1

The Cost



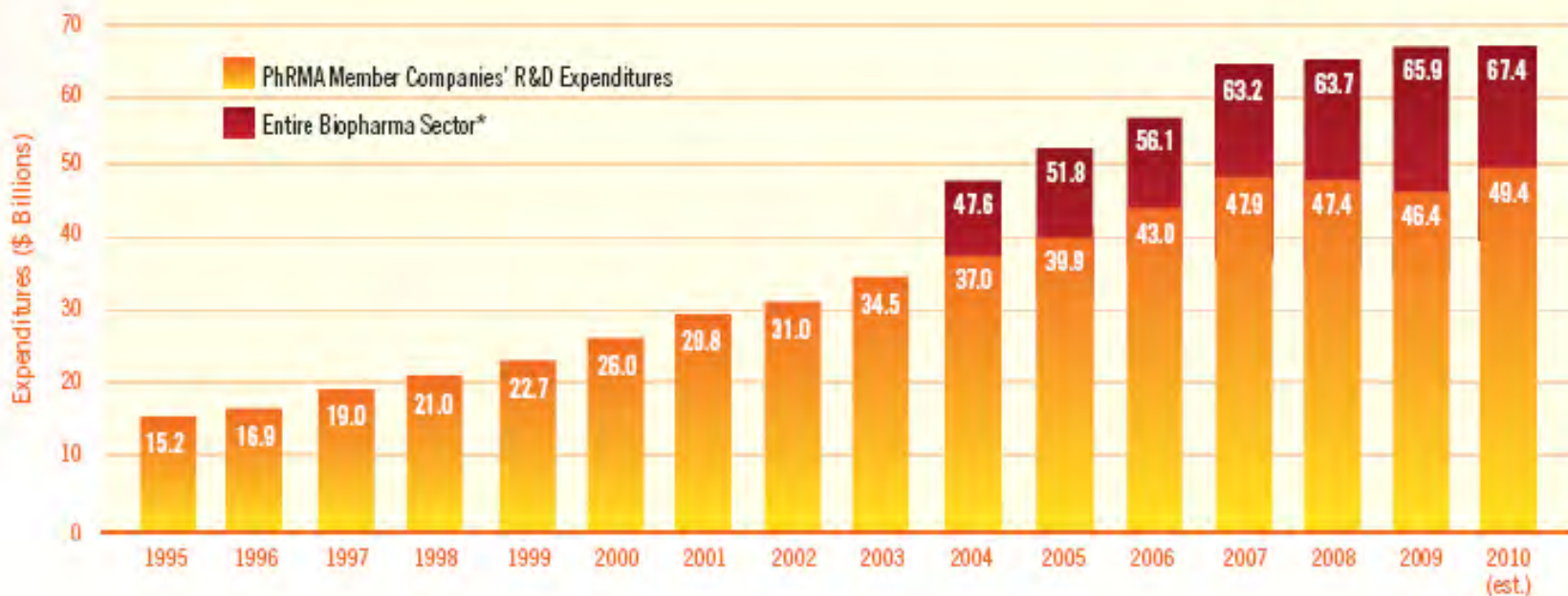
Source: DiMasi, Grabowski. *Managerial and Decision Economics* **2007**, 28, 469-479

Only Two in Ten Approved Drugs Produce Revenues That Exceed Average R&D Costs



Source: Vernon, Golec, DiMasi. *Health Economics Letters* 2009

R&D Spend

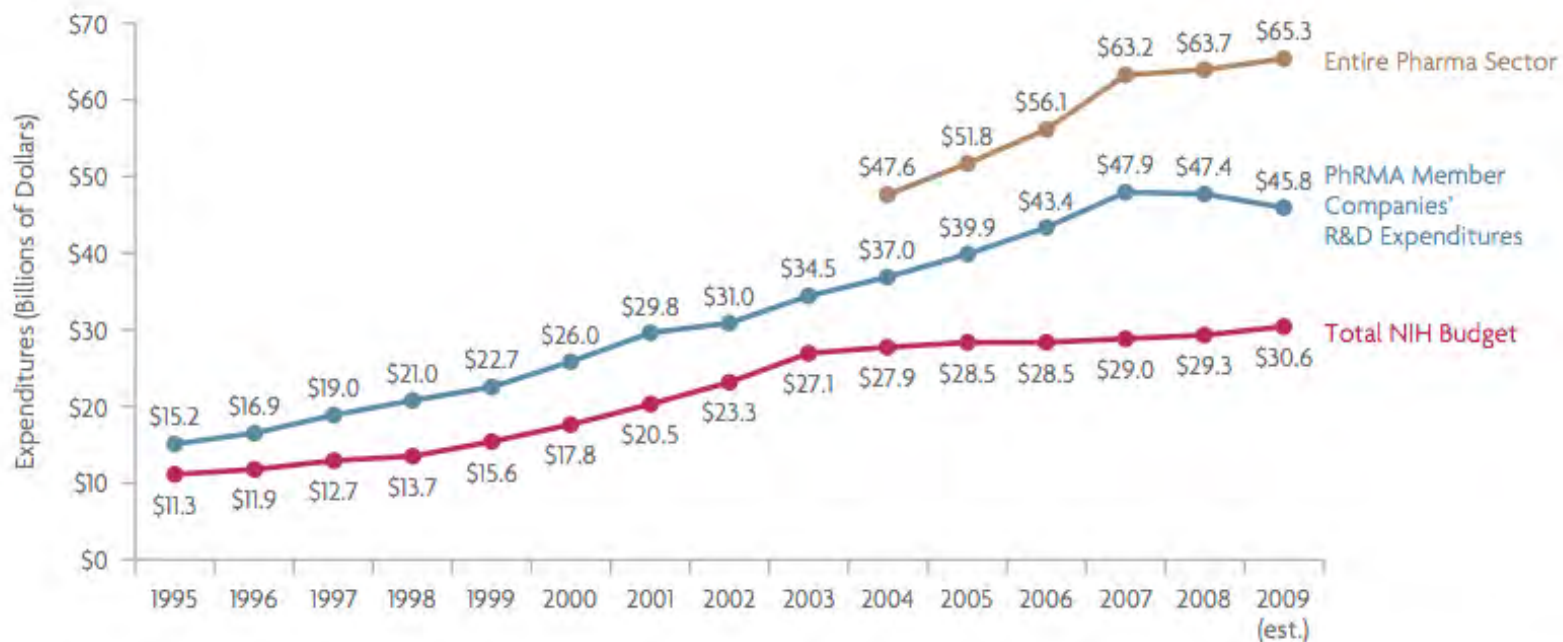


* The "Entire Biopharma Sector" figures include PhRMA research associates and nonmembers; these are not included in "PhRMA Member Companies' R&D Expenditures." PhRMA first reported this data in 2004.

Source: Burrill & Co., analysis for Pharmaceutical Research and Manufacturers of America, 2005–2010; Pharmaceutical Research and Manufacturers of America, *PhRMA Annual Member Survey* (Washington, DC: PhRMA, 1981–2010).

Source: PhRMA

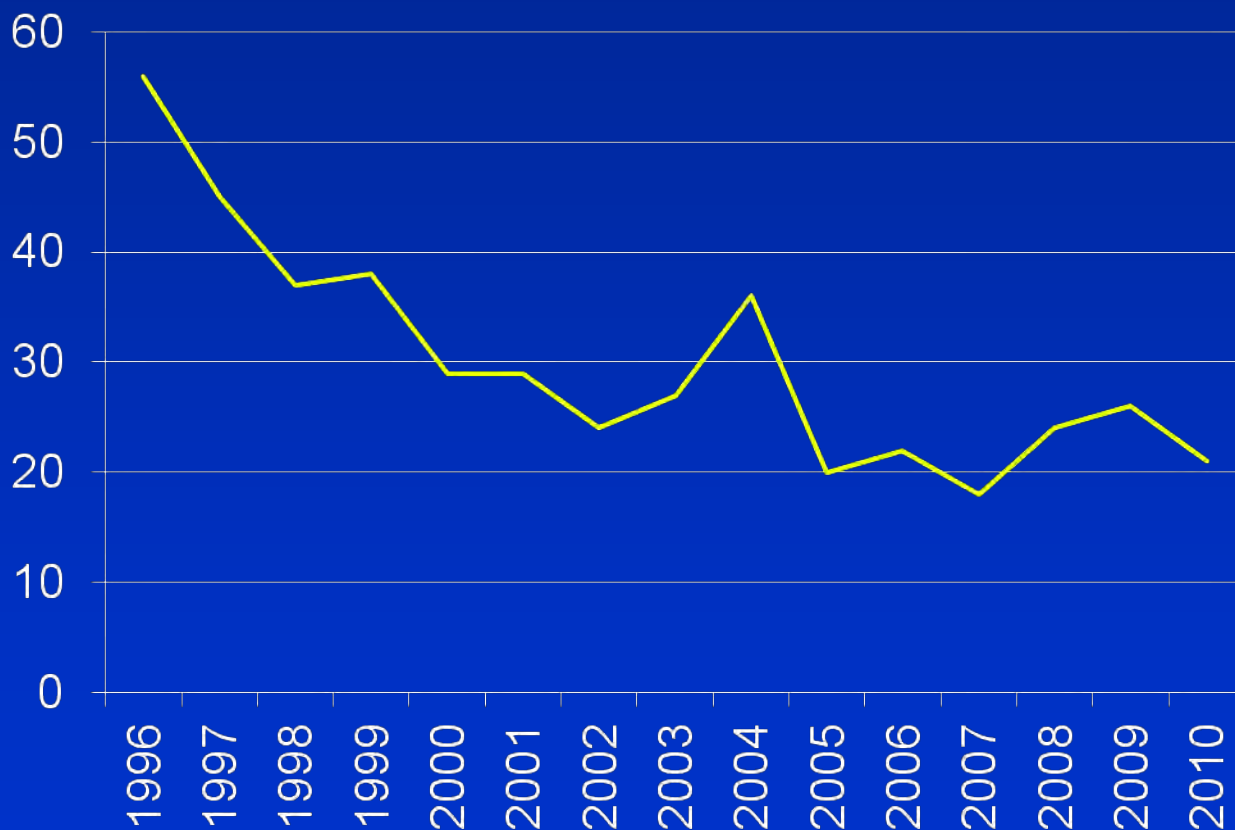
R&D Spend



Source: Burrill & Company, PhRMA, NIH Office of Budget¹⁰

Source: PhRMA

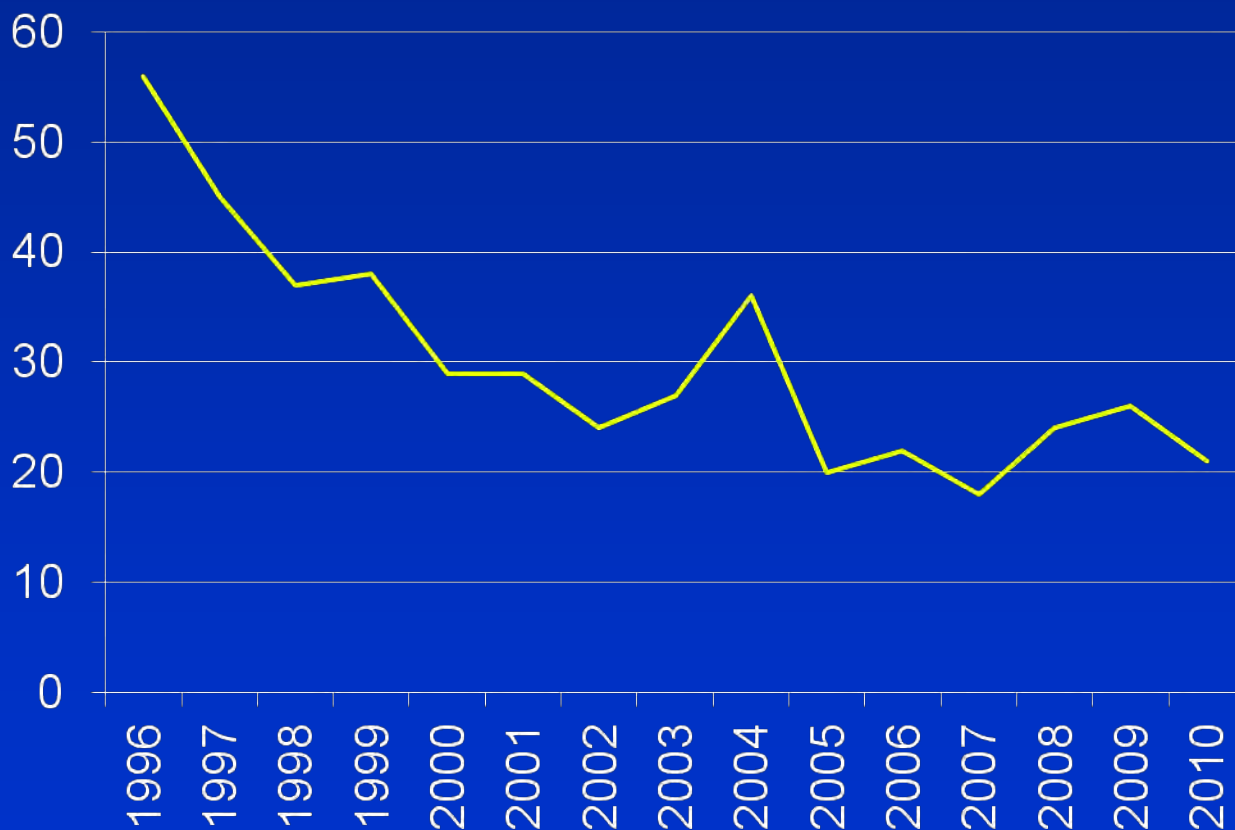
Number of New Molecular Entities Approved



Why the Fall in Numbers of NCEs?

- Easiest drugs already found
- Companies ultra-cautious about withdrawals
- Disruption from mergers
- Or is it just the normal cycle?

Number of New Molecular Entities Approved



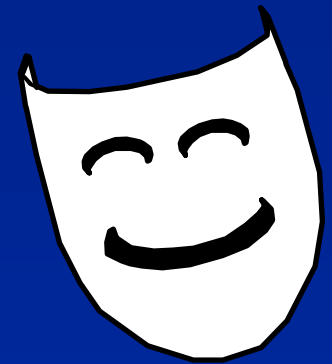
Measuring Return from Investment in R&D



- 10/12 top pharma saw internal rate of return (IRR) fall from 11.8% in 2010 to 8.4% in 2011
- Cost of bringing a drug to market increased by 21%
- Number of compounds in late stage development decreased from 23 to 18

Source: Deloitte and Thomson Reuters

Measuring Return from Investment in R&D



- More value from product commercialization than lost from late-stage failures
- Non-R&D costs have declined; higher operating margin
- To combat high costs in future, R&D organizations will share capabilities in non-competitive R&D areas

Source: Deloitte and Thomson Reuters

Global Pharmaceutical Market



*Constant \$ in billions based on Q410

Threats to the Industry

- CAGR in sales falling
- Generic competition (“the patent cliff”)
- Price pressures
- Crowded markets
- Increasing R&D budgets
- Declining productivity

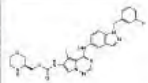
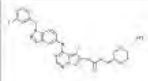
The Solution?

- Mergers and acquisitions
- Cost cutting
- Restructuring
- Diversification
- In-licensing
- Alliances and outsourcing
- Target emerging markets
- Personalized medicine
- Portfolio management techniques
- Life cycle management

Drug Pipeline Databases

- Pharmaprojects/Citeline Pipeline
- R&D Focus
- R&D Insight
- Thomson Reuters Pharma
- Thomson Reuters Integrity

BizInt Smart Charts: Drug Pipeline Report

	Product	Common Drug Name	Database	Originator	Highest Phase	Commercial Intro	Structure	Mechanism of Action
12	AC-480	AC 480	Thomson Pharma	Bristol-Myers Squibb Co	Phase 2 Clinical	Ambit Biosciences, under license from Bristol-Myers Squibb, is developing AC-480 (formerly BMS-599626), an orally active inhibitor of multiple HER tyrosine kinases, for the potential treatment of cancer [639937], [895412]. In December 2008, it was reported that phase II trials for solid tumors had begun [969747].		Anticancer EGFR family tyrosine kinase receptor inhibitor ErbB2 tyrosine kinase receptor inhibitor ErbB4 tyrosine kinase receptor inhibitor Anticancer protein kinase inhibitor Epidermal growth factor antagonist
13	BMS 599626	AC 480	Adis R&D Insight	Bristol-Myers Squibb (Originator)	Phase II	Bristol-Myers Squibb and Ambit Biosciences Corporation are co-developing BMS 599626 for the treatment of cancer. The orally administered, pyrrolotriazine compound is a dual inhibitor of both epidermal growth factor receptor (EGFR/ErbB1/HER1) and HER2 (ErbB2/neu) protein tyrosine kinases. EGFR and HER2 have been found to be frequently overexpressed in a variety of tumour types. [CONT.]		Epidermal growth factor inhibitors HER2 inhibitors
14	BMS-599626	AC 480	Citeline Pipeline	Bristol-Myers Squibb	No Development Reported	BMS-599626 is a small-molecule dual kinase inhibitor which targets the HER1 and HER2 receptors, which was under development by Bristol-Myers Squibb for the treatment of breast cancer (229th ACS (San Diego), 2005, MEDI 21).		ErbB-1 tyrosine kinase inhibitor ErbB-2 tyrosine kinase inhibitor Protein kinase inhibitor Tyrosine kinase inhibitor
15	AC-480 (free base)	AC 480	Thomson Reuters Integrity Compounds	Bristol-Myers Squibb	Phase I	BMS-599626 is a small molecule inhibitor of the human epidermal growth factor receptor (HER) kinase family in early clinical trials at Bristol-Myers Squibb for the treatment of metastatic solid tumors. The drug candidate targets both the HER1 and the HER2 receptors, which are frequently co-expressed in a range of tumor types and possess the ability to form heterodimers. [CONT.]		HER4 (erbB4) Inhibitors EGFR (HER1 erbB1) Inhibitors HER2 (erbB2) Inhibitors
16	AC 480	AC 480	IMS R&D Focus	Ambit (USA)	Phase II	Ambit is developing AC 480 (BMS 599626), an orally active pan-HER tyrosine kinase inhibitor, as a potential treatment for solid tumors. In August 2008, a phase II trial of the agent in the treatment of nonsmall cell lung cancer (NSCLC) was initiated in the USA. Ambit acquired rights to AC 480 from Bristol-Myers Squibb in November 2007. A phase II trial of AC 480 in the treatment of nonsmall cell lung cancer (NSCLC) has initiated in the USA (Ambit, AUG 2008) [CONT.]		EGF receptor inhibitor protein kinase inhibitor signal transduction inhibitor tyrosine kinase inhibitor

11.

AC 480

AC 480

11.1 Adis | [link](#)

11.2 IMS | [link](#)

11.3 Integr | [link](#)

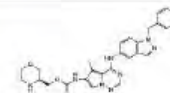
11.4 Pipeln | [link](#)

11.5 TPharm | [link](#)

Bristol-Myers Squibb (Originator)

Phase II

BMS-599626 is a small molecule inhibitor of the human epidermal growth factor receptor (HER) kinase family in early clinical trials at Bristol-Myers Squibb for the treatment of metastatic solid tumors. The drug candidate targets both the HER1 and the HER2 receptors, which are frequently co-expressed in a range of tumor types and possess the ability to form heterodimers. [CONT.]



ErbB-1 tyrosine kinase inhibitor
ErbB-2 tyrosine kinase inhibitor
Protein kinase inhibitor
Tyrosine kinase inhibitor

11.2 IMS

11.1 Adis

11.1 Adis

11.3 Integr

11.5 TPharm

11.4 Pipeln

Senior Management



Source: <http://www.flickr.com/photos/yukariryu/>

M&As: the Impact on Productivity

- Rationalization needed after merger
 - TAs, research sites, conflicting informatics
- Disruption
- Momentum lost in research
- Entrenched camps develop
- Decision making loses objectivity
- Growth is largely from cost savings
- Benefits of scale not proven beyond a certain size
- M&As are self-limiting

Product Lifecycle Management

- New indications
- Reformulations
- Combination drugs
- Rx to OTC
- Branded generics
- Mergers and acquisitions
- Alliances
- Pricing
- Patent protection strategies
- New markets
- Refocusing R&D spend
- Reducing development time
- Branding and rebranding

Making R& D More Virtual

- Semantic technologies
- Computer-aided molecule design
- Predictive biosimulation
 - virtual cells, organs, animals
 - complete digital model of man

Source: Steve Arlington, Pricewaterhouse Coopers

Rational Drug Design

- Receptor structure unknown, ligand structures unknown
- Receptor known, ligand known
- Receptor known, ligand unknown
- Receptor unknown, ligands known

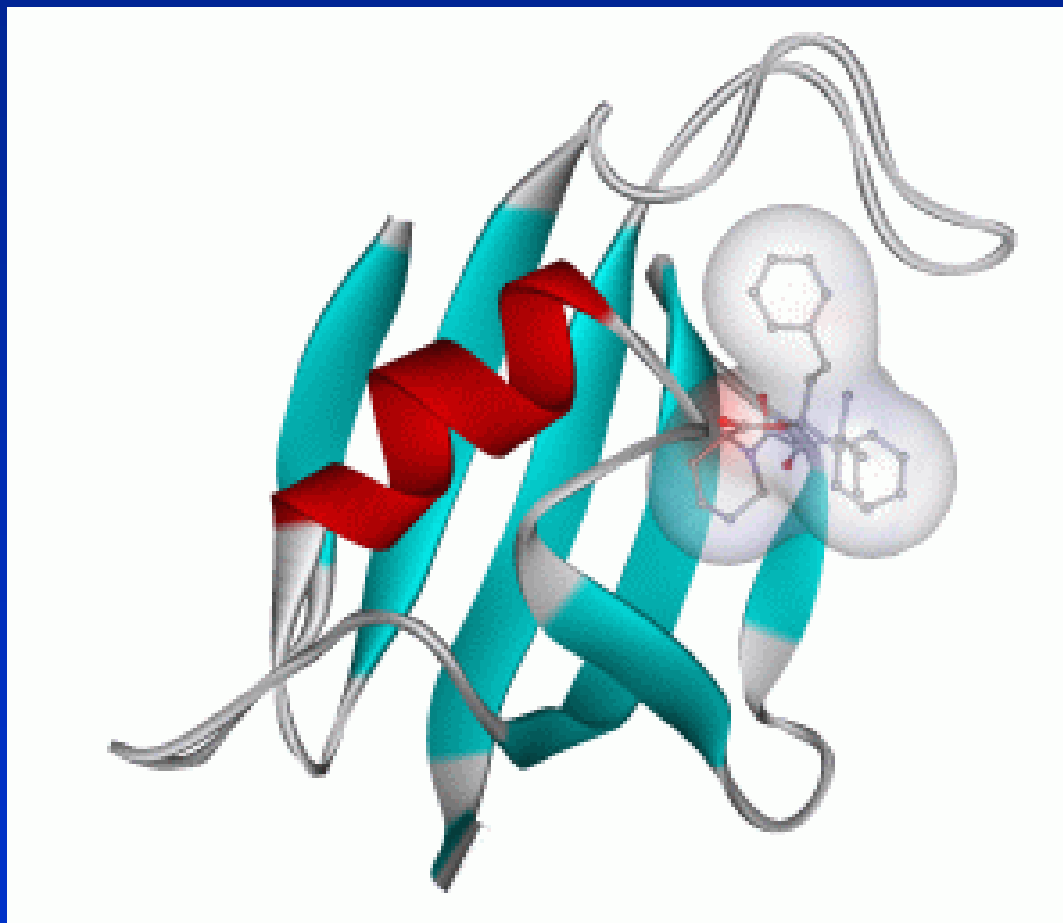
Rational Drug Design

- Receptor structure unknown, ligand structures unknown
- Receptor known, ligand known
- Receptor known, ligand unknown
- Receptor unknown, ligands known

Rational Drug Design

- Receptor structure unknown, ligand structures unknown
- Receptor known, ligand known
- Receptor known, ligand unknown
- Receptor unknown, ligands known

Docking a Ligand in a Protein

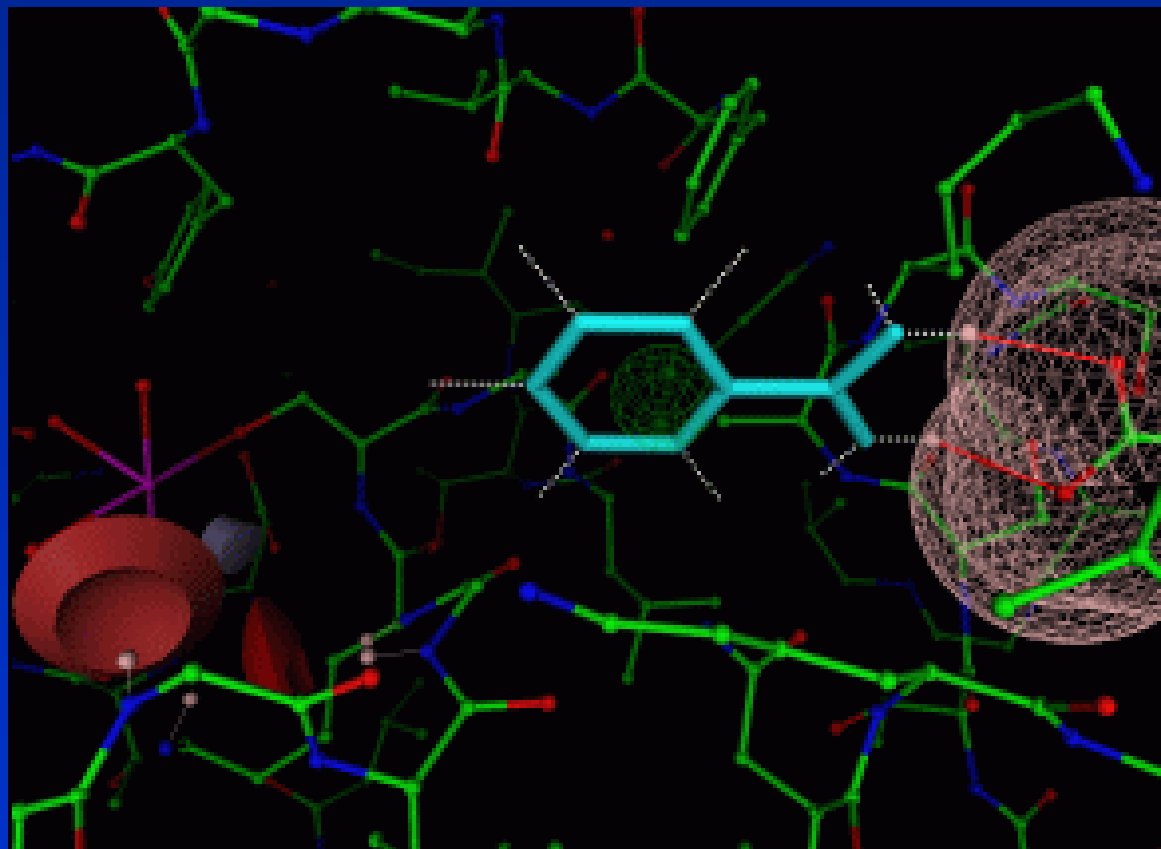


Source: Cambridge Crystallographic Data Centre

Rational Drug Design

- Receptor structure unknown, ligand structures unknown
- Receptor known, ligand known
- Receptor known, ligand unknown
- Receptor unknown, ligands known

De novo Drug Design

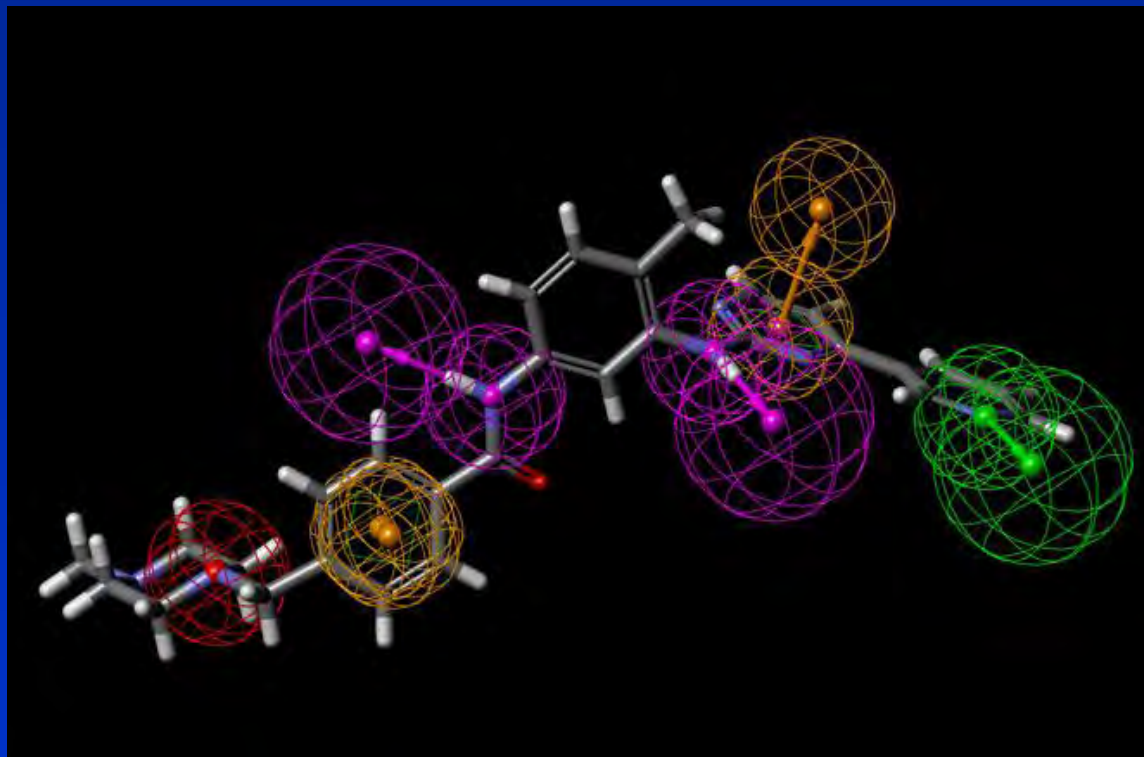


Source: SimBioSys

Rational Drug Design

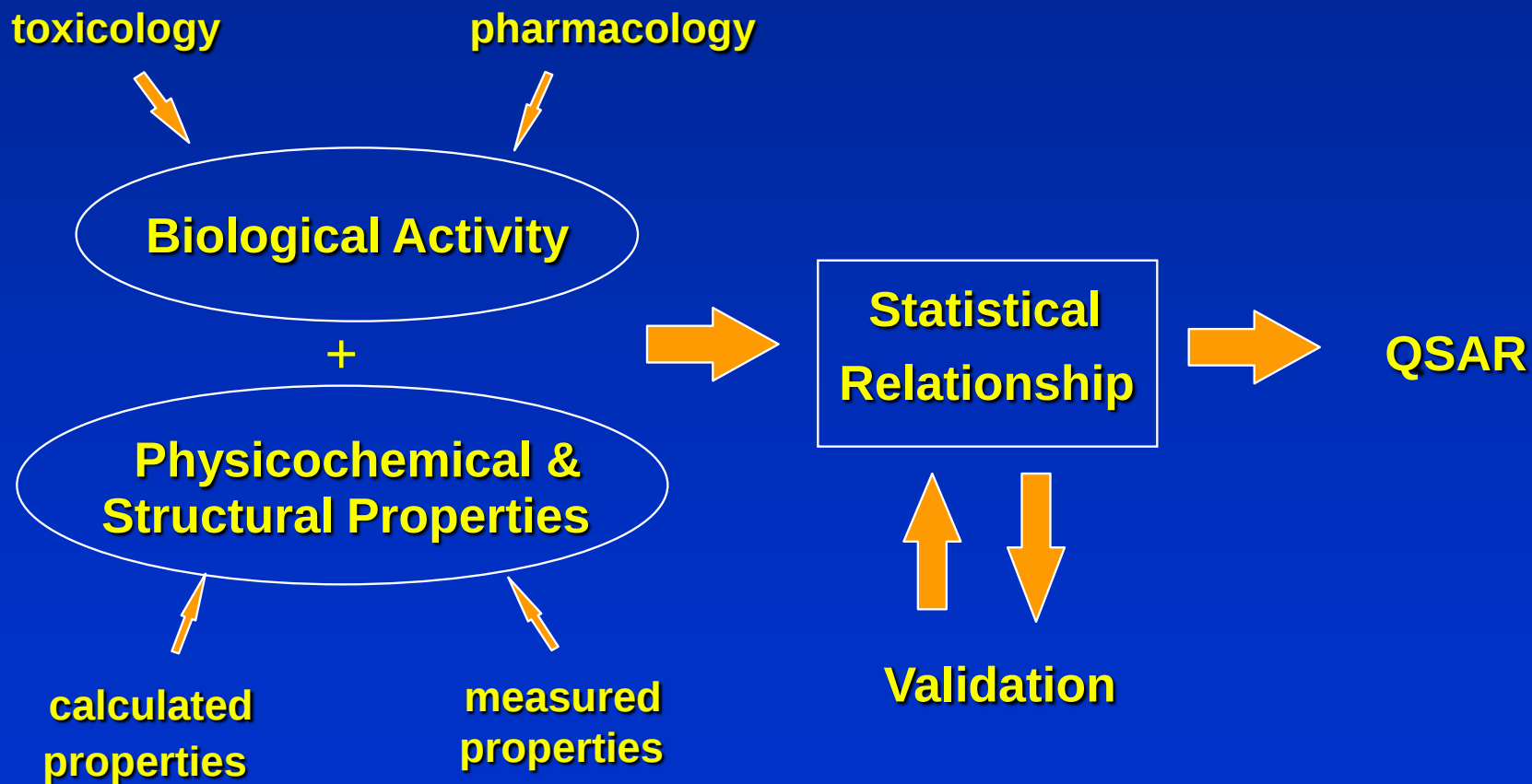
- Receptor structure unknown, ligand structures unknown
- Receptor known, ligand known
- Receptor known, ligand unknown
- Receptor unknown, ligands known

Pharmacophore Model



Source: Accelrys

Quantitative Structure Activity Relationships (QSAR)



Drug Discovery in the 1970s



Drug Discovery in the 1970s

- Unplanned innovation
- Serendipity
- Drugs based on natural products
- Chemists used intuition
- Random screening
- Linear workflow
- Informatics only peripheral

Advances of the 1990s

- The human genome project
- Genomics
- Proteomics
- Growth in knowledge of protein structures
 - X-ray crystallography
 - NMR
 - homology modeling
- High throughput screening (HTS)
- Combinatorial chemistry
- Bioinformatics and cheminformatics

Drug Discovery Today

- Start with knowledge of a biological target
 - and maybe a known protein structure
- Screen the fewest compounds needed
- Vast quantities of data
- Informatics is of strategic importance
- Informatics supports decision making
- Multi-disciplinary teams share knowledge
- “Fail early”: predict druglikeness

Changing strategies

- Pharma 1.0
 - Blockbuster model
 - Focus on top line
- Pharma 2.0
 - Strategies addressed in this talk
 - Focus on bottom line
- Pharma 3.0
 - Delivering health outcomes
 - Being customer-centric
 - Being payer-insightful

Source: Carolyn Buck Luce, Ernst &Young