Pharmaceutical Productivity.

Factors Influencing & Tactics to Increase Productivity

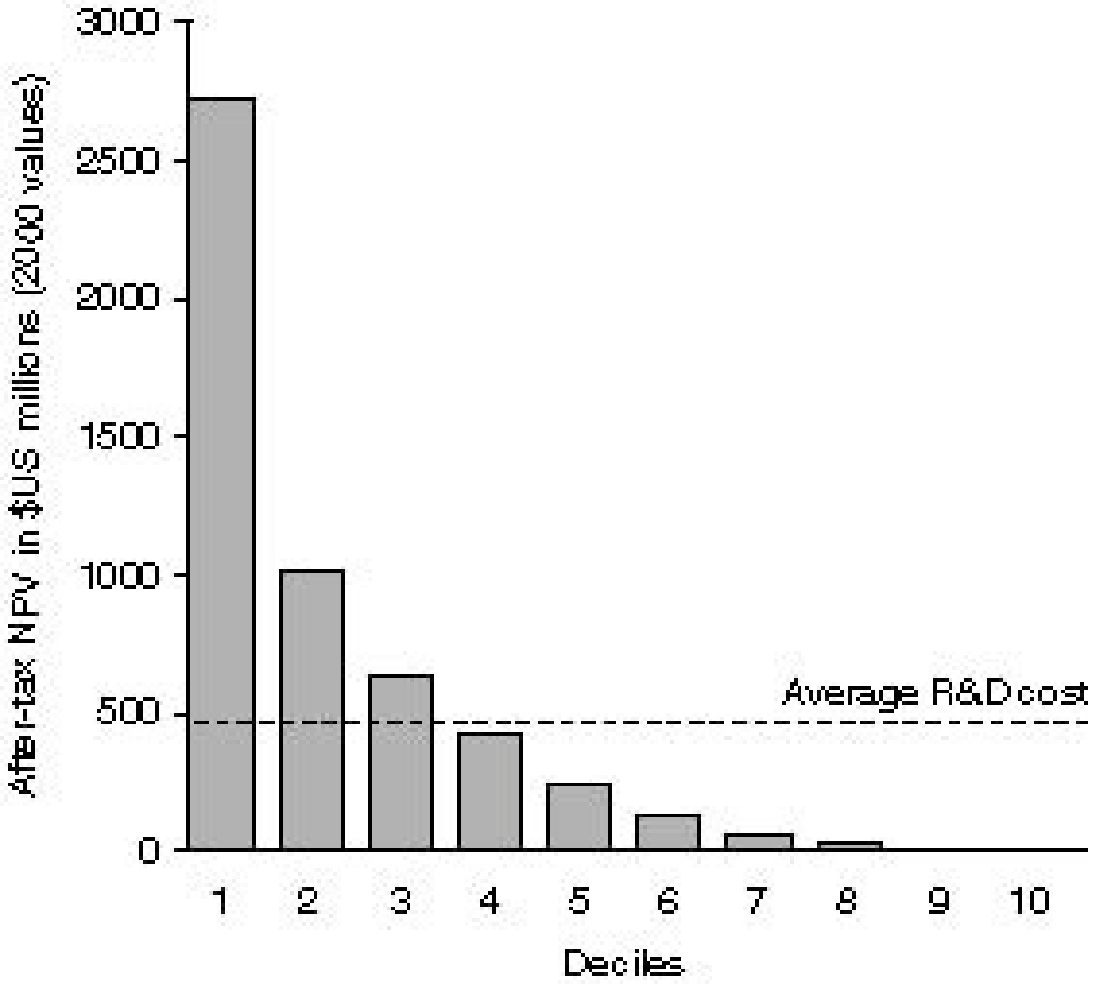
Bob Powell, PharmD
Roche Shanghai
john.powell@roche.com

Pharmaceutical Industry Today

'*the best of times, the worst of times*'

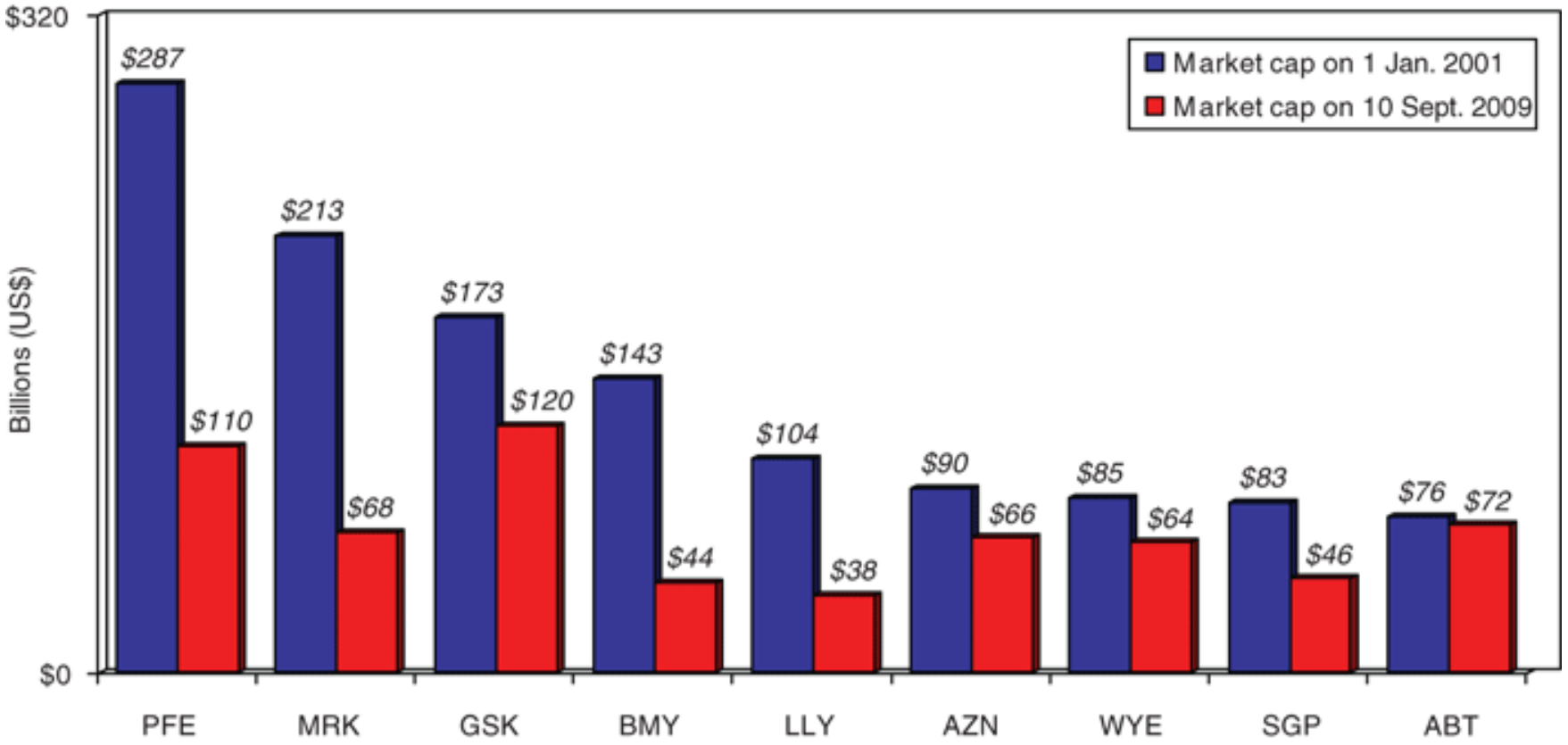
- Amazing new opportunities to both prevent and improve difficult diseases
- Key is understanding disease mechanisms & therapeutic opportunity
- ↑ pressure to ↑ benefit & ↓ risk by understanding both and using personalized medicine when possible
- Industry sales and profits are flat
- Industry size and distribution is changing
  - Mergers continue. Short-term weakness sign
  - Downsizing in U.S., growing in China
- Current economic model failing (↑ investment → ↓ productivity) + controlling all key processes & competencies
- Regulatory expectations keep increasing

Net present value relative to average R&D cost for new drug introductions 1990-94



Pharmacoeconomics 20:11-29, 2002

Pharmaceutical Company Market Capitalization 2001 & 2009



Cumulative loss ~ $626B

Clinical Pharmacol Ther 87: 356, 2010

Why are pharmaceutical companies investing in China?

- Pharma sales and income 2010-2018 flat or decreasing
  - Maturing markets
  - Price controls based on value
  - Fixed productivity model
- Chinese market is expanding
  (http://www.bloomberg.com/apps/news?pid=20601103&sid=acxSkkthtQJM)
  - Currently 20% global population, 3% global consumption
  - Pharmaceuticals market investment: $44B 2008, $110B 2015
  - 2009-2012 $125B additional health care spending
  - 2020 universal health-care coverage

Outline

- The current state of pharmaceutical productivity
- Macro productivity relationships. Government, academic and industry
- Changing the business model. Leveraging external partnerships to enhance productivity

Current State of Pharmaceutical Industry Productivity

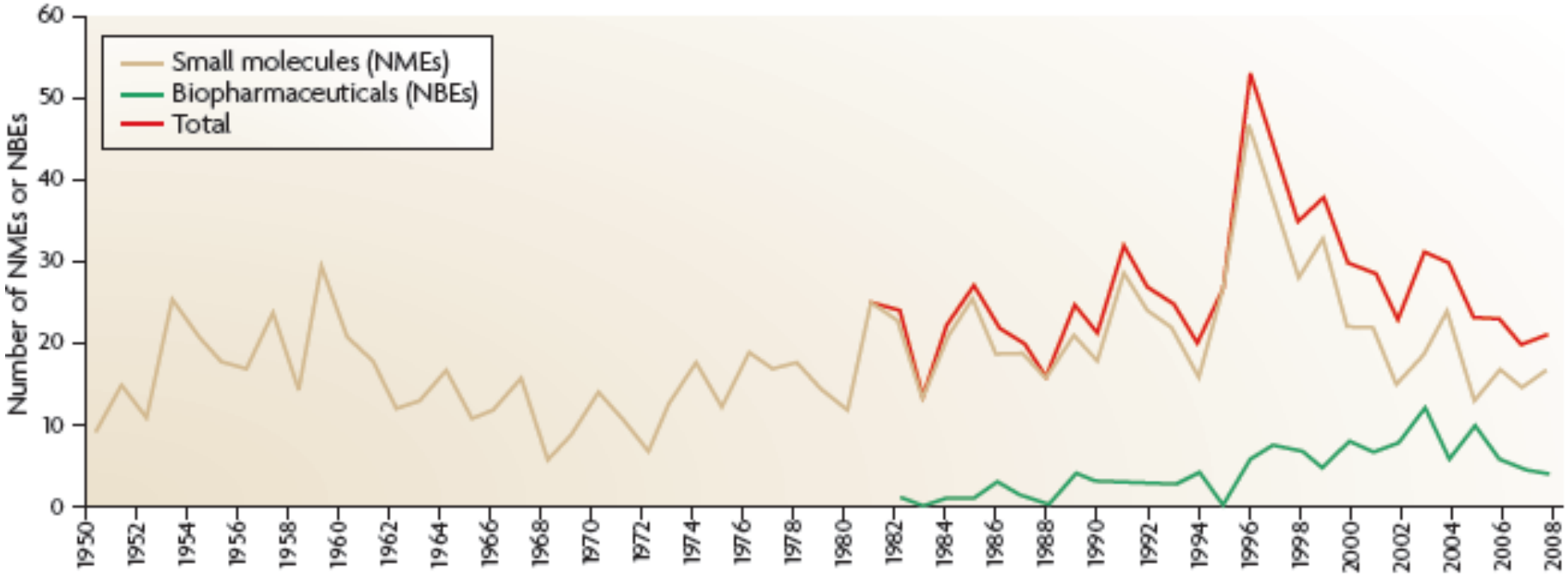
“The leaders of major corporations including pharmaceuticals have incorrectly assumed that R&D was scalable, could be industrialized and could be driven by detailed metrics and automation. The grand result: a loss of personal accountability, transparency, and the passion of scientists in discovery and development.”

Jean-Pierre Garnier

Harvard Business Review 86: 68-76, 2008

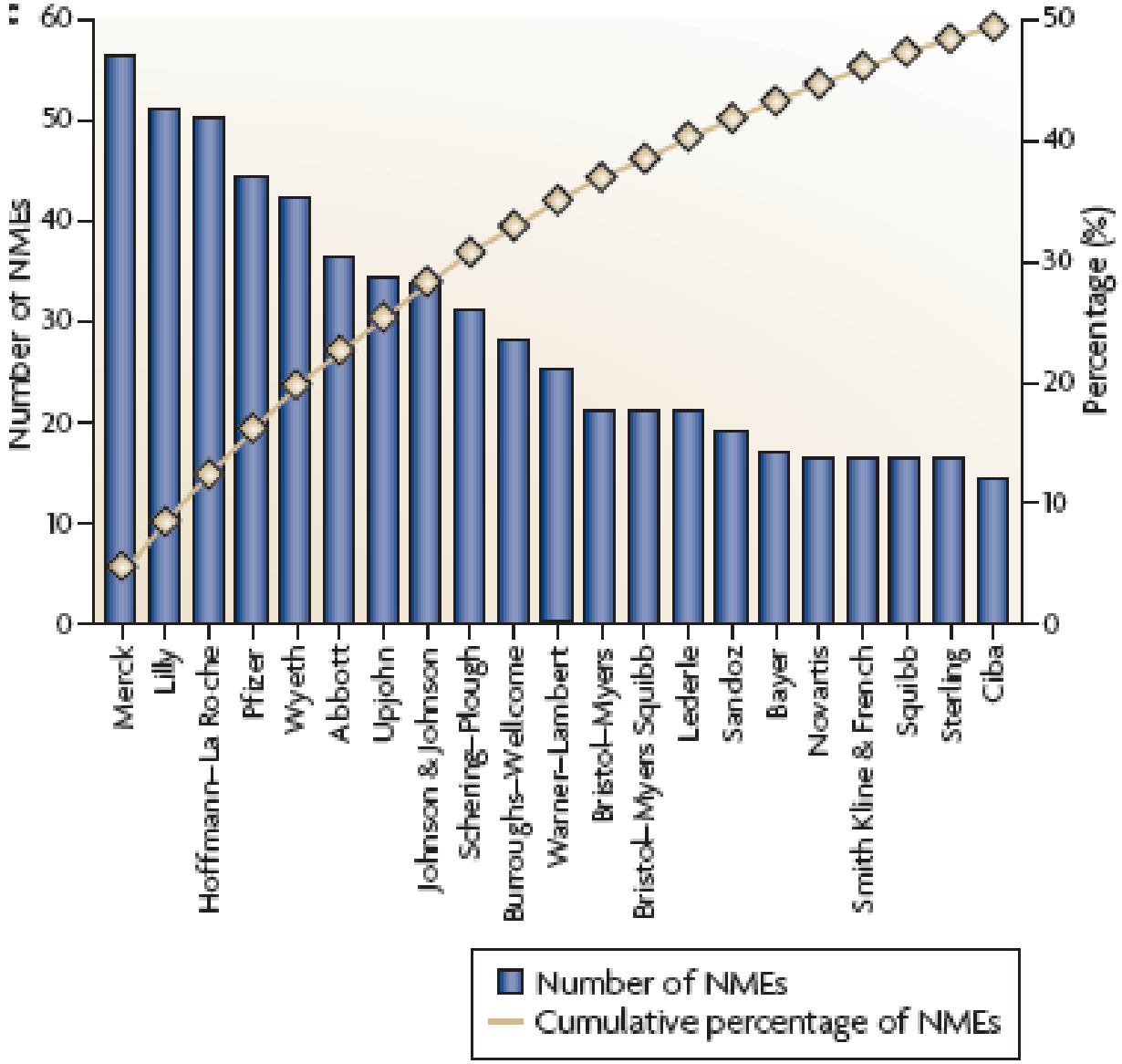
Lessons from 60 Years of Pharmaceutical Innovation (Marketed New Molecular Entities)

- **Studied pharmaceutical company productivity 1950-2008 rendering 1222 NMEs**
- **Productivity rate is constant and insensitive to ↑ investment or company size**
- **Flattening financial performance leading to change in R&D model**



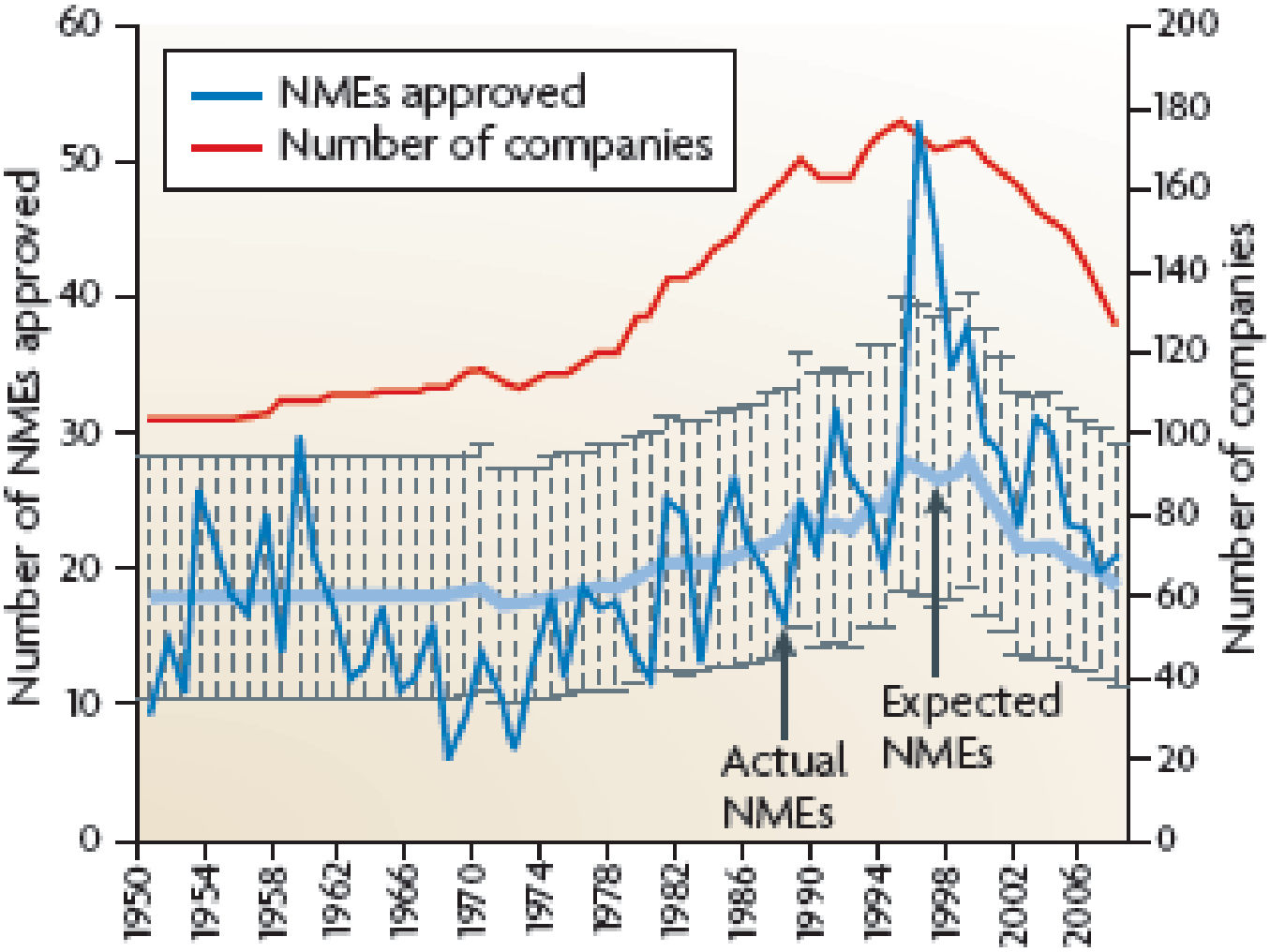
Nature Reviews Drug Discovery 8:959, 2009

New Molecular Entity (NME) Number by Company 1950-2008



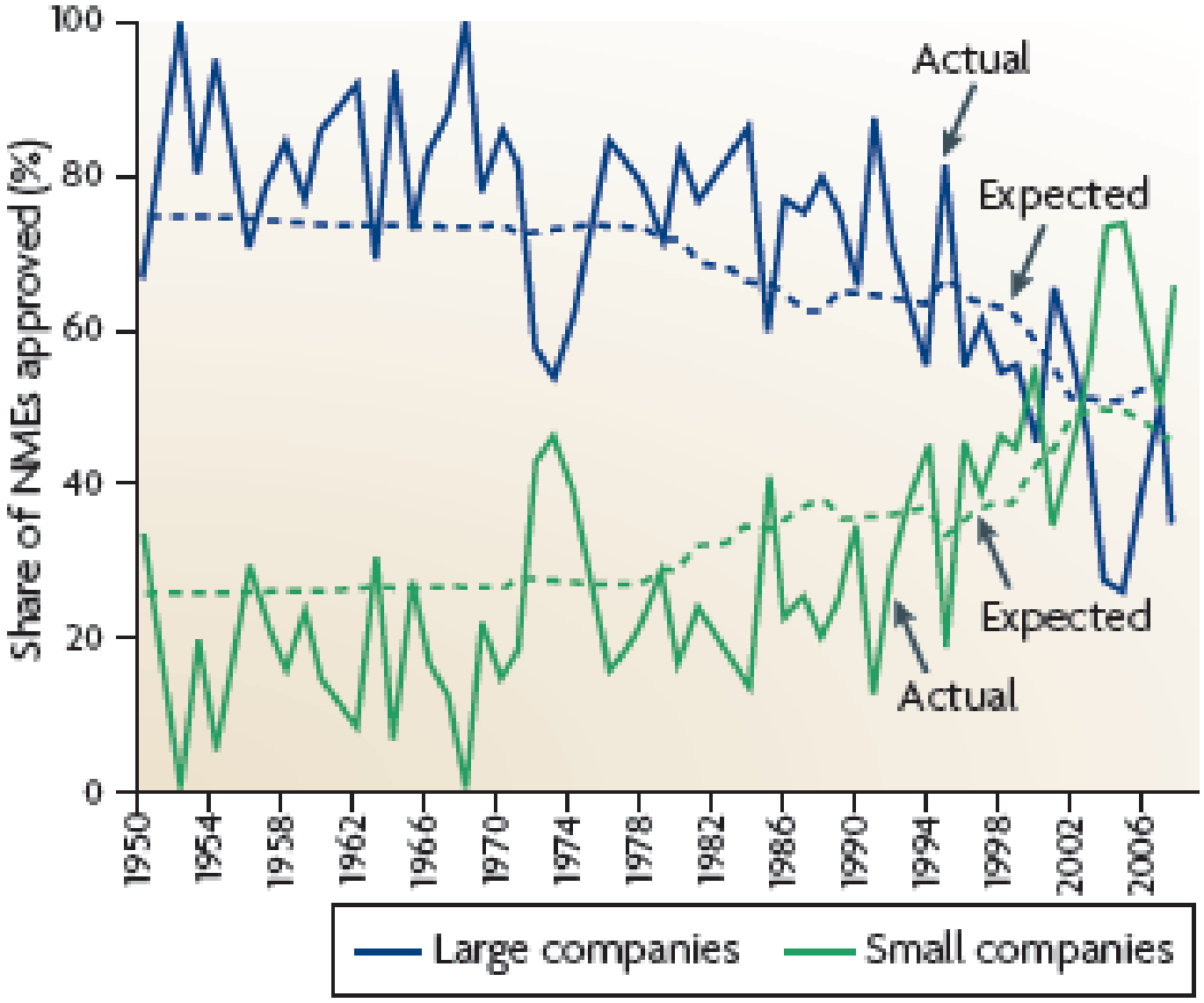
Nature Reviews Drug Discovery 8:959, 2009

Number of Companies & Productivity



Nature Reviews Drug Discovery 8:959, 2009

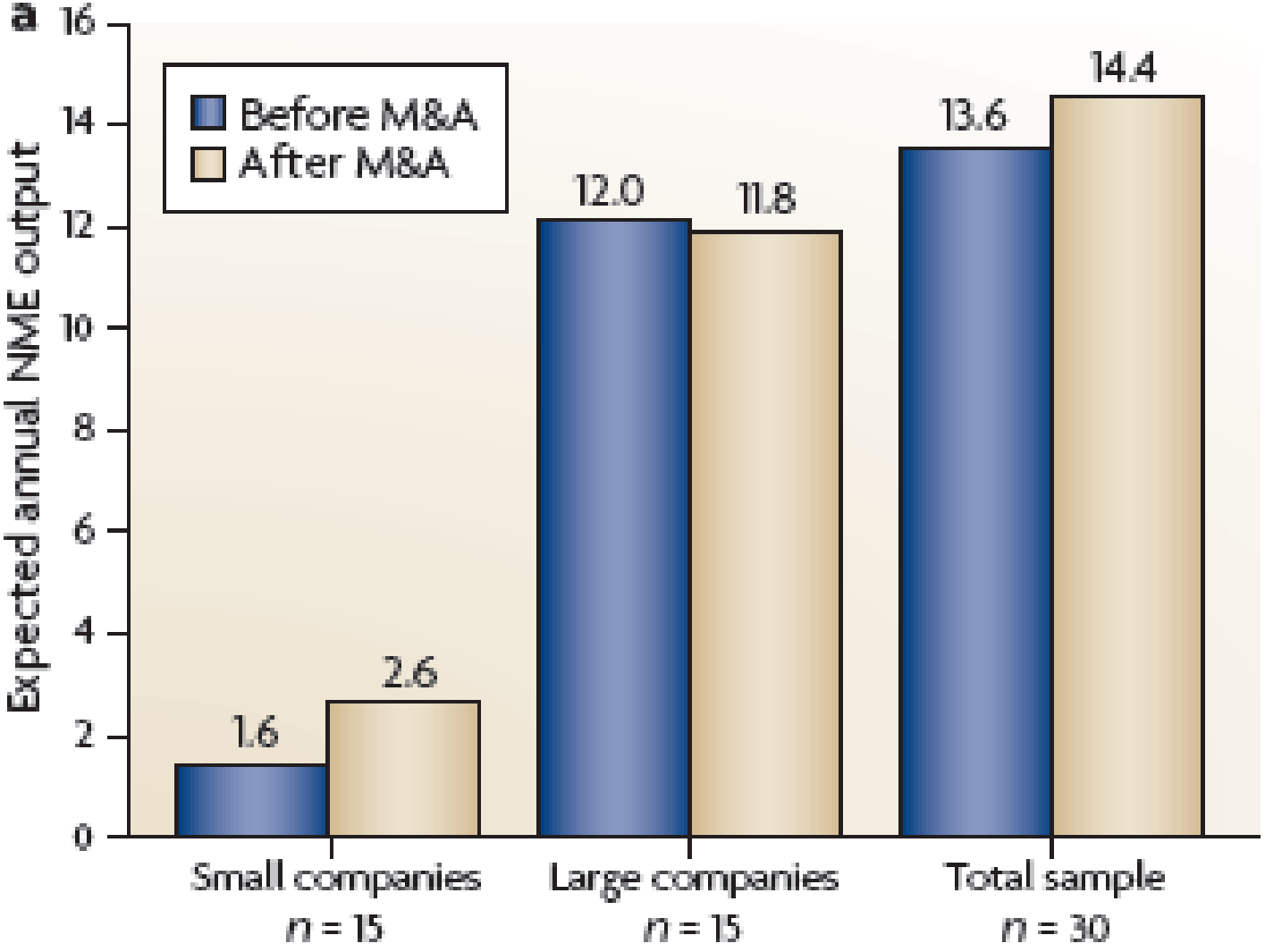
Company Size & Productivity



Nature Reviews Drug Discovery 8:959, 2009

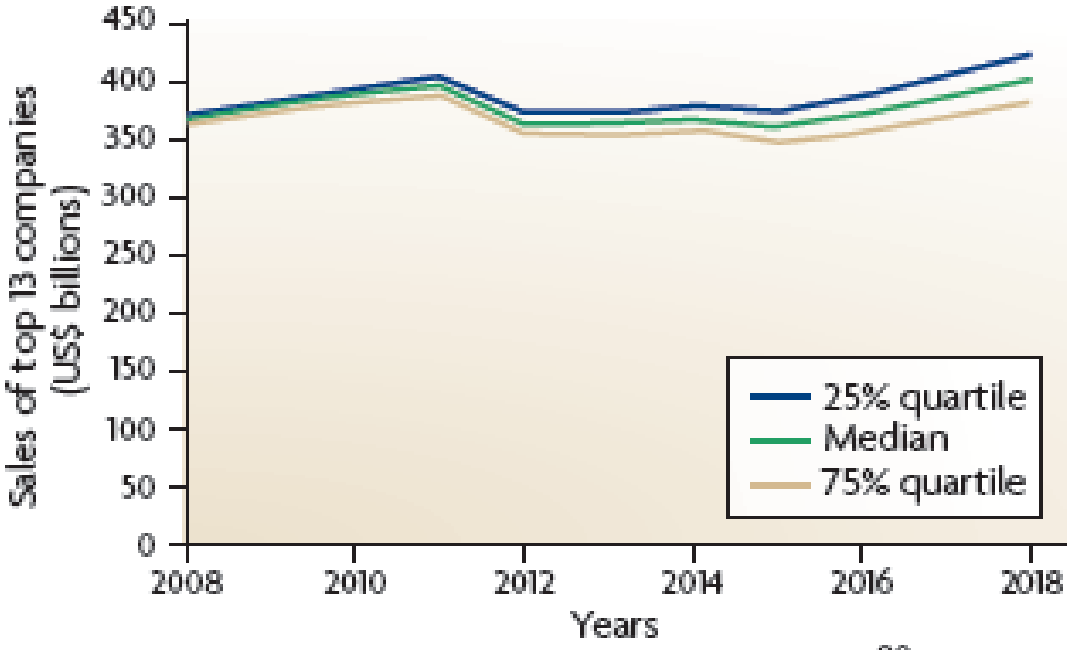
Productivity After Merger

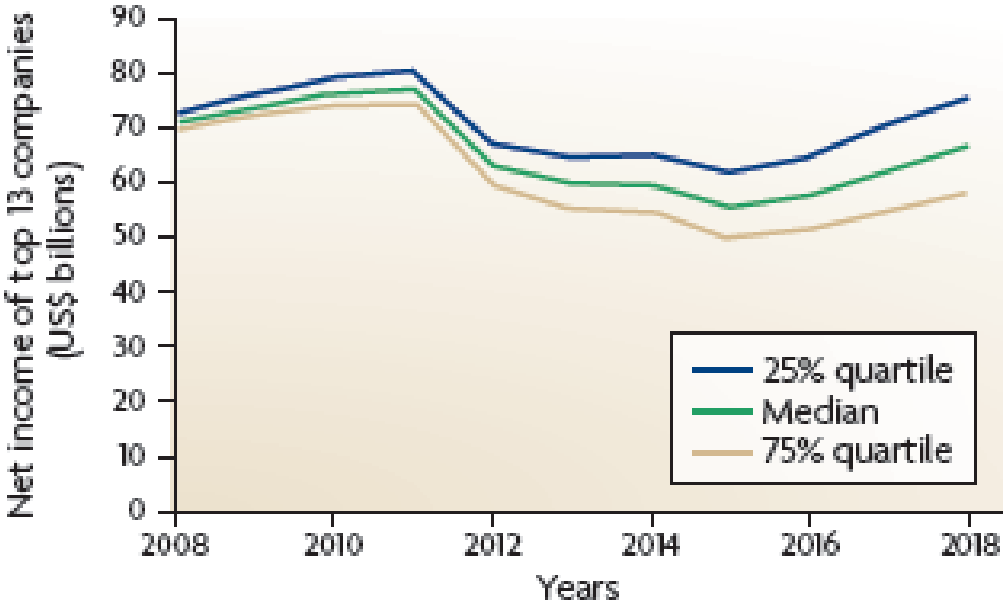
(strategic or survival?)



Nature Reviews Drug Discovery 8:959, 2009

Predicted Sales & Net Income of Top 13 Pharmaceutical Companies





Nature Reviews Drug Discovery 8:959, 2009

Inability to ↑ Productivity Leading to Change

- Munos' recommendations
  - Dedication to Change R&D model
  - Investing in obstacles to innovation & Sharing knowledge (e.g. disease pathogenesis, public private partnerships)
  - Separate short-term market priorities from long-term research & innovation incubation
  - Change the current culture of managed, scalable industrialized innovation

Factors Contributing to Current Drug Development Challenges

- Choice of more complex, chronic disease targets (CNS, cancer)
- ↑ Protocol complexity → ↑ time & cost (global, safety, biomarkers, adaptive)
- Blockbuster strategy → ↑ time, cost, risk (unmet needs in smaller populations can be different)
- ↑ Regulatory demands (safety, local markets, risk management)
- Proving value for reimbursement
- Company size, mergers, re-organizations, leadership (business-science)

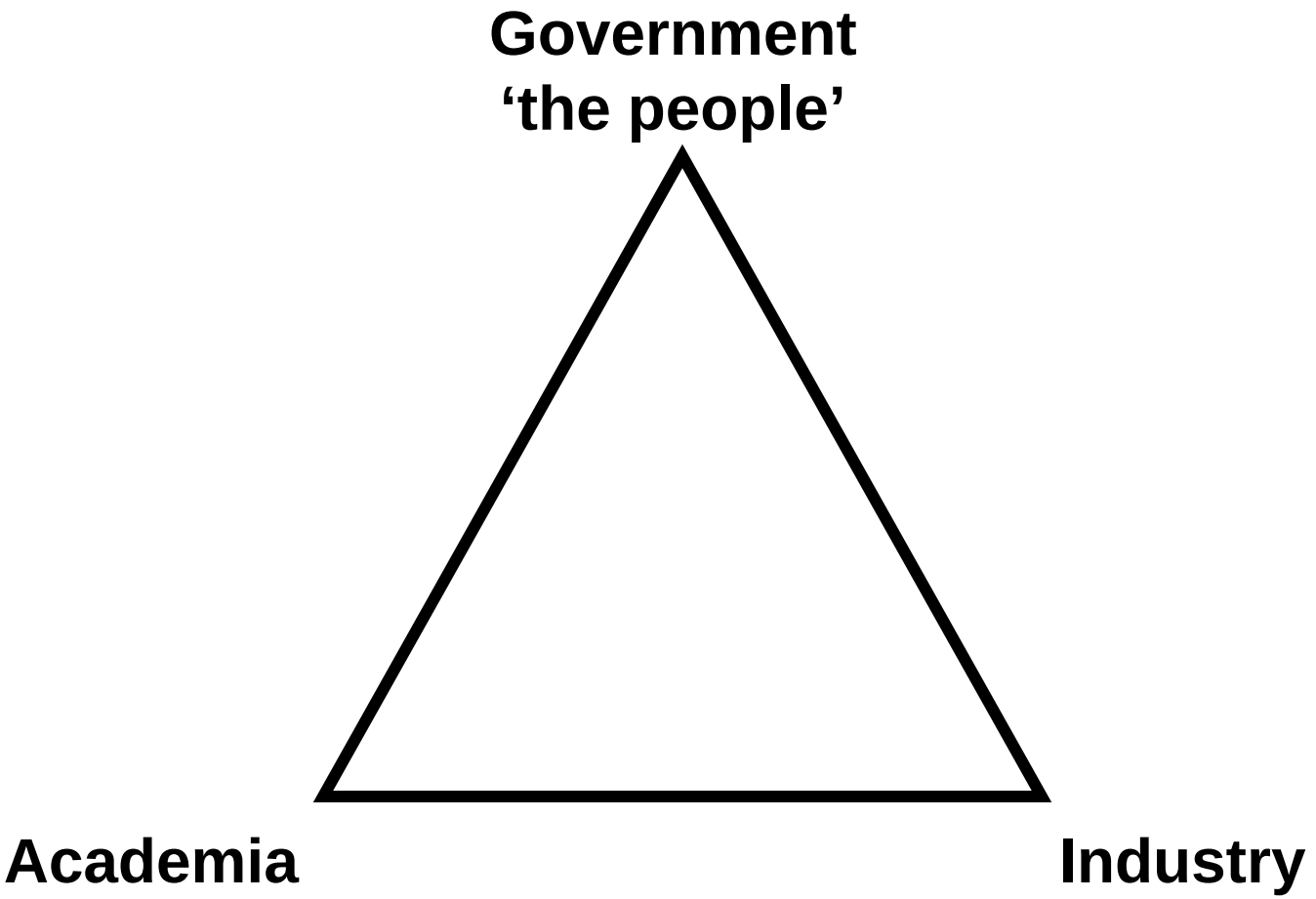
Pharmaceutical R&D Productivity

Questions

- Are you surprised?
- How did one of the most profitable industrial sectors become ‘at risk’?
- What do you believe are the leverage points for increasing productivity?

External Productivity Influences

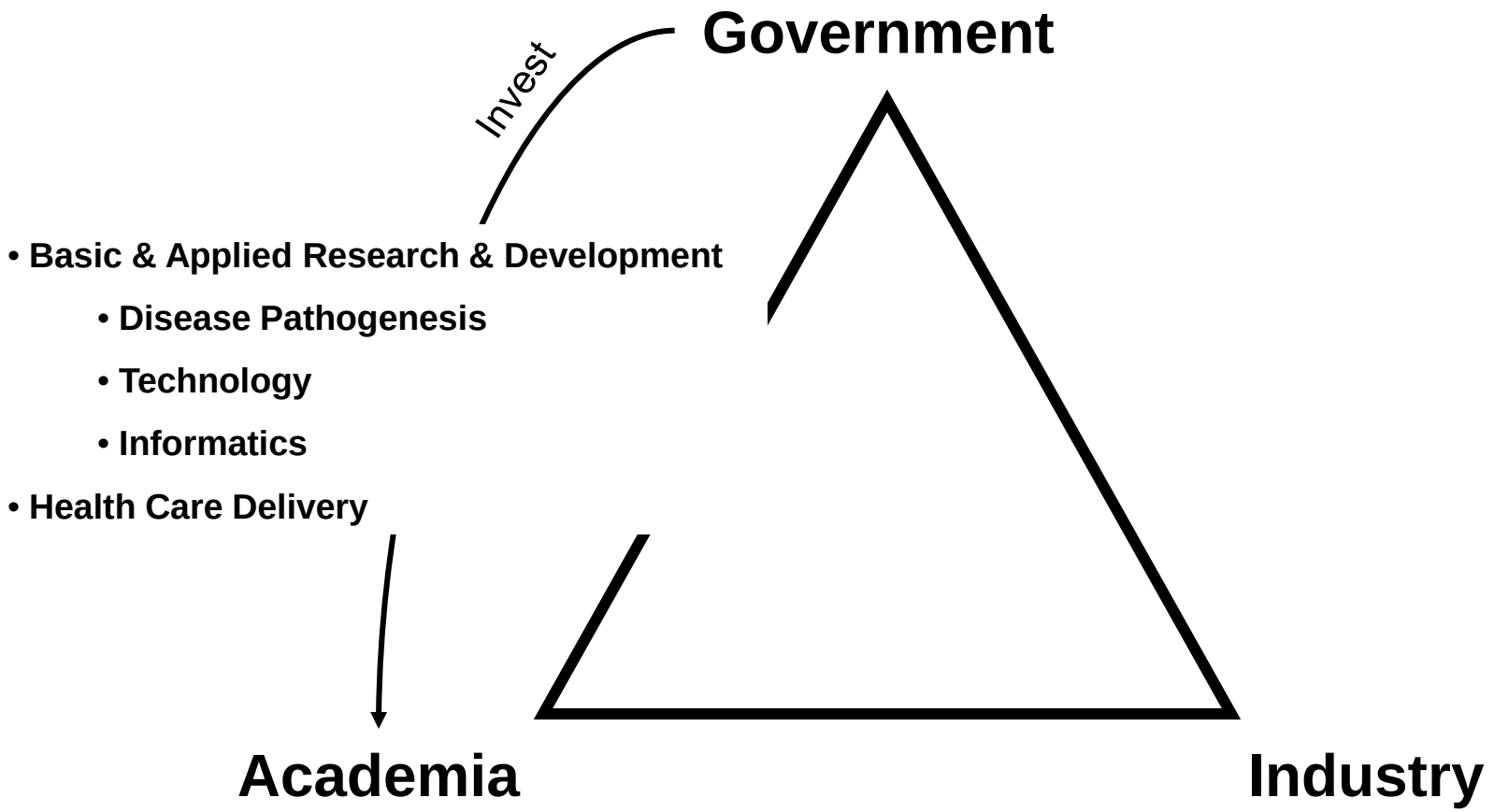
Pharmaceutical Innovation Relationships



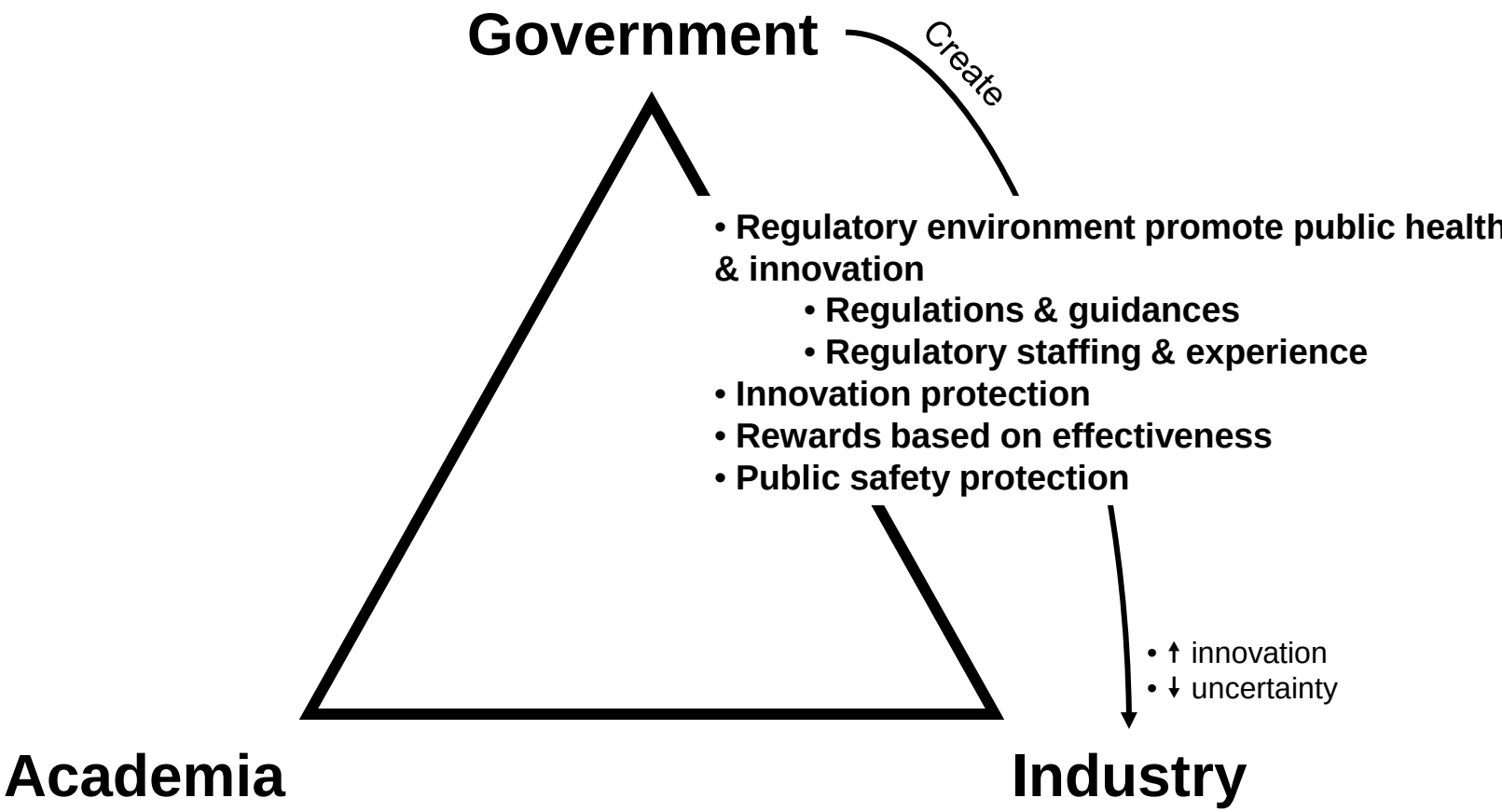
Overall balance required for optimal productivity.

Weakest link is rate limiting

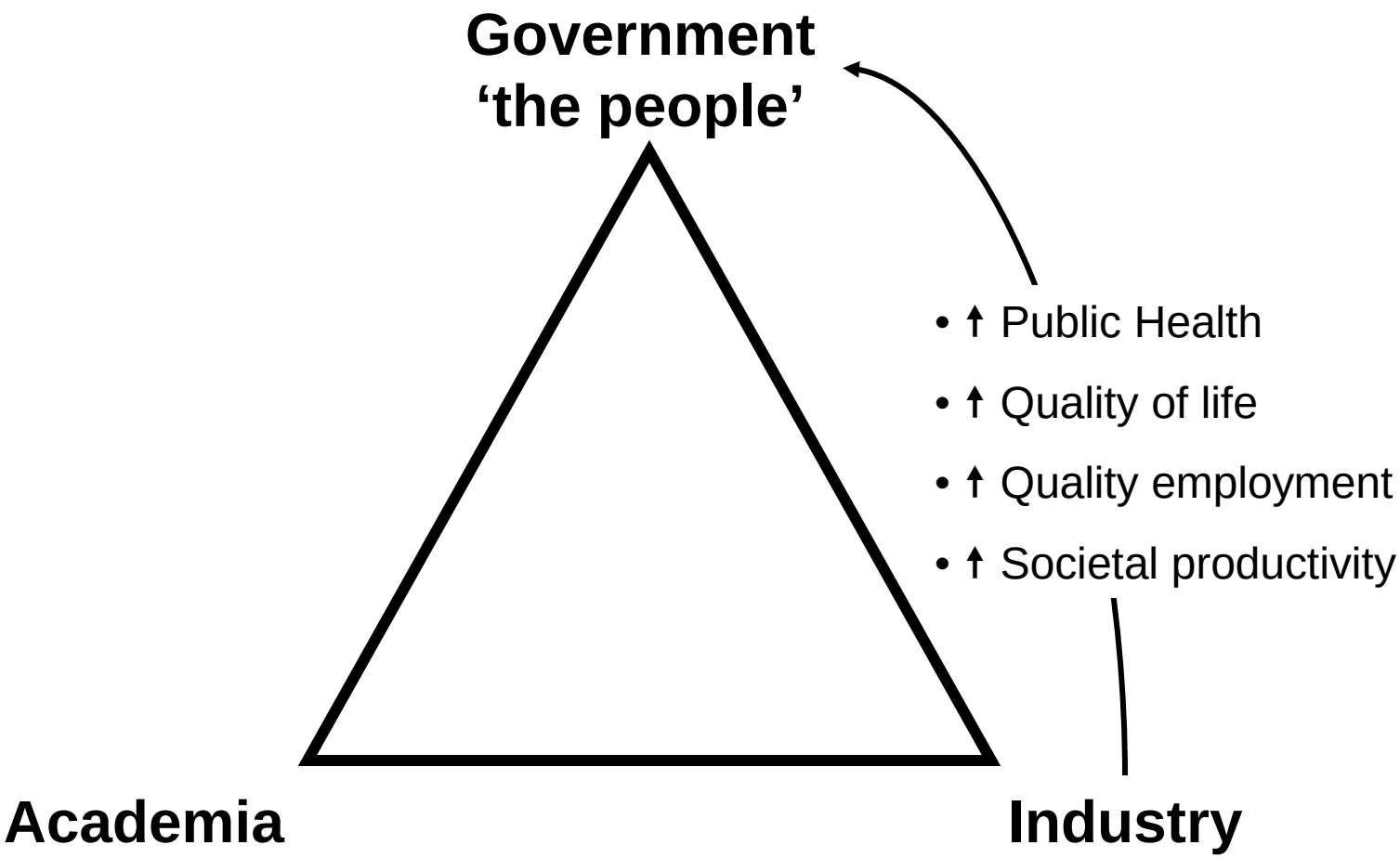
Pharmaceutical Innovation Relationships



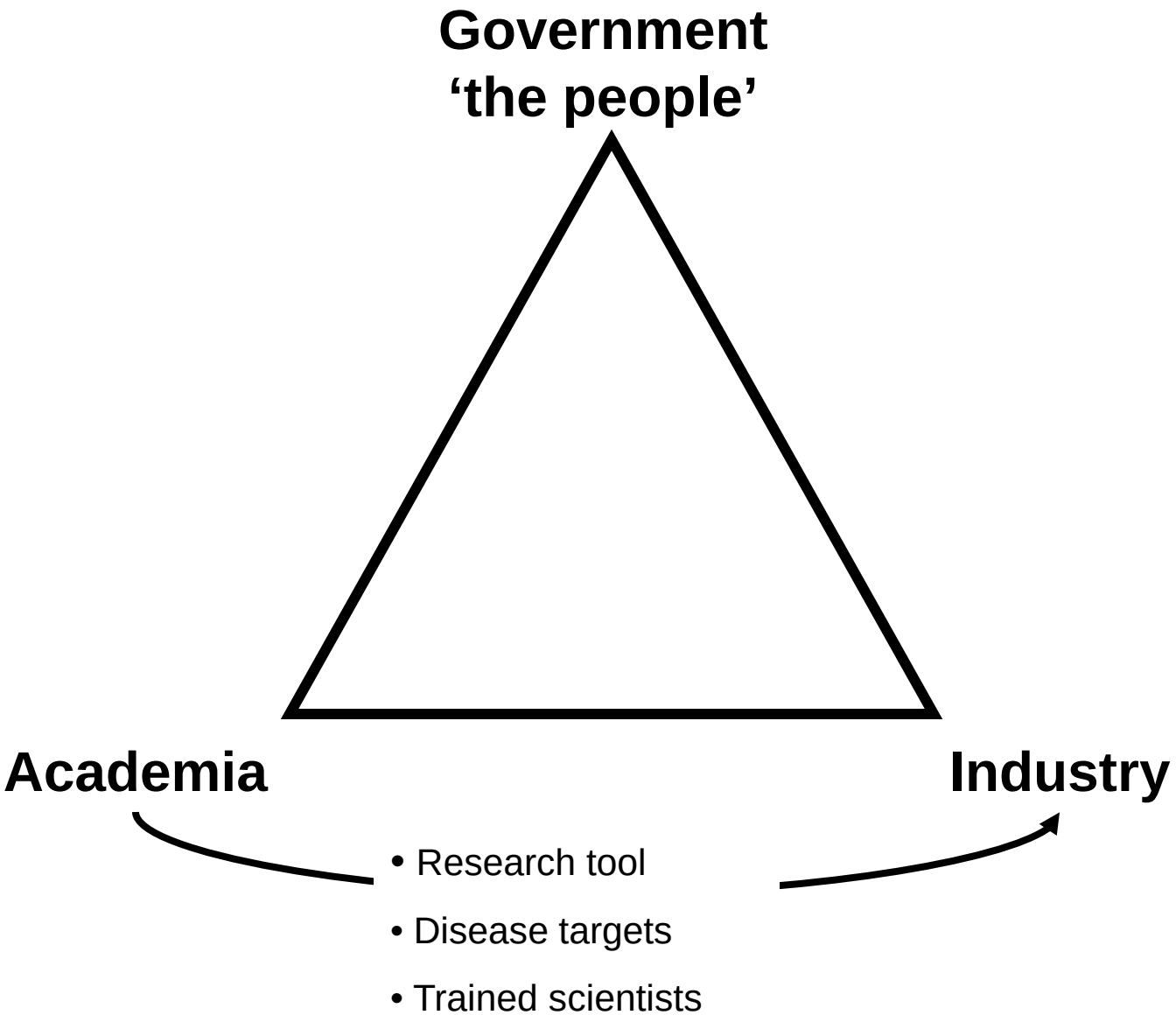
Pharmaceutical Innovation Relationships



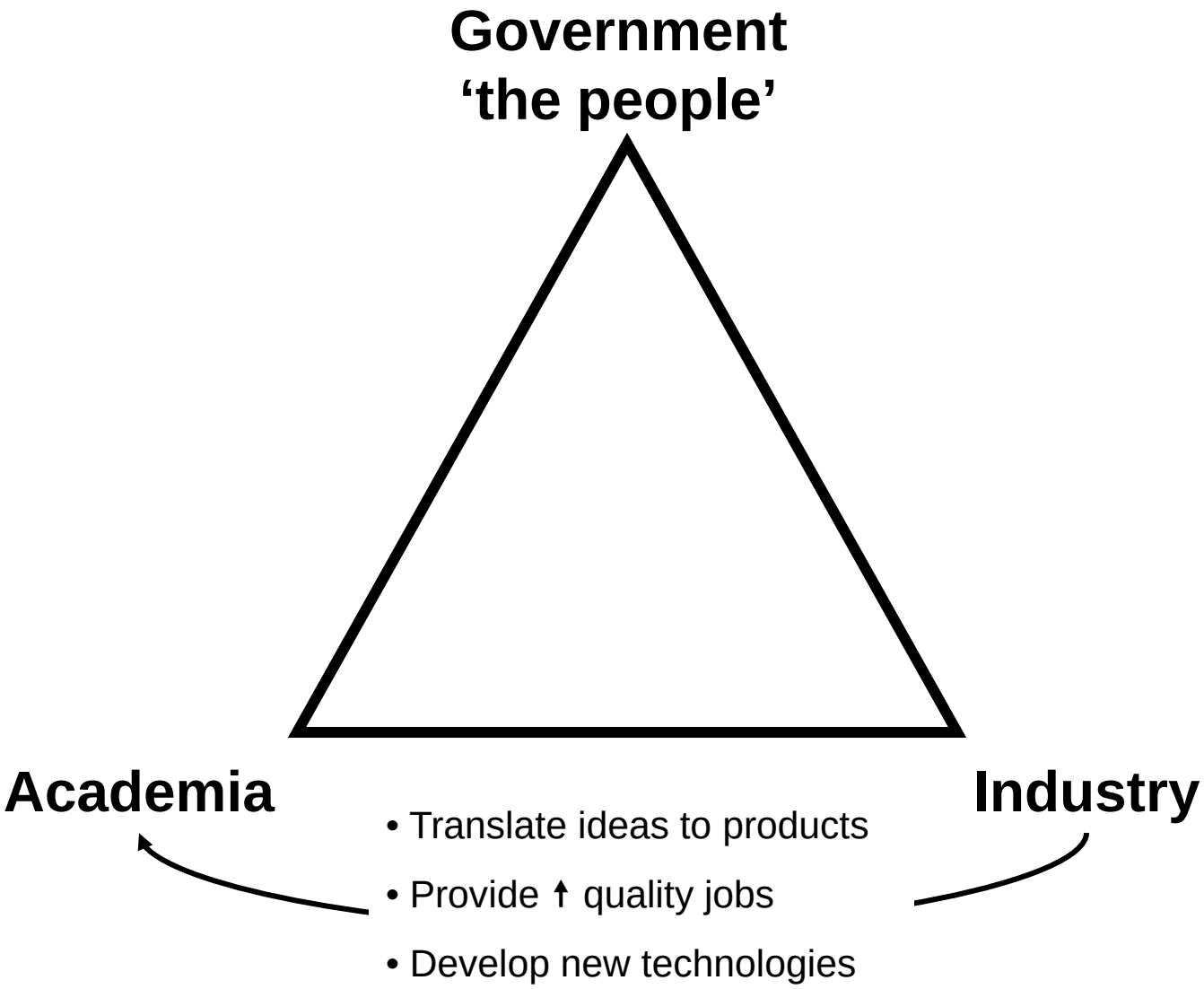
Pharmaceutical Innovation Relationships



Pharmaceutical Innovation Relationships



Pharmaceutical Innovation Relationships



What is the situation in China?

- If industries invest R&D in China without similar investments from government & academia, how successful will it be?
- In your opinion, what are the relative strengths of government, academia and industry in China and the Pacific rim?
- What can you do to influence the ‘triangle’?

Internal Productivity Influences

- Industry productivity is low and not increasing relative to investment
- Cost to bring drug to market $1.8B/NCE, rising sharply & unsustainable
- Current pharmaceutical industry is failing
- Investment in industry has decreased
- Moves to change industry model

Goal in Increasing R&D Productivity (Lilly's model)

- '…industry's profitability can only be mitigated by substantially and sustainably increasing the number and quality of innovative as well as cost-effective new medicines: but only if accomplished at reasonable R&D costs.'

Nature Reviews Drug Discovery 2010

Pharmaceutical Productivity

$$P \propto \frac{WIP \times p(\mathrm{TS}) \times V}{CT \times C}$$

P = productivity

WIP = work in progress (i.e., pipeline)

p(TS) = probability of technical success

V = value

CT = cycle time

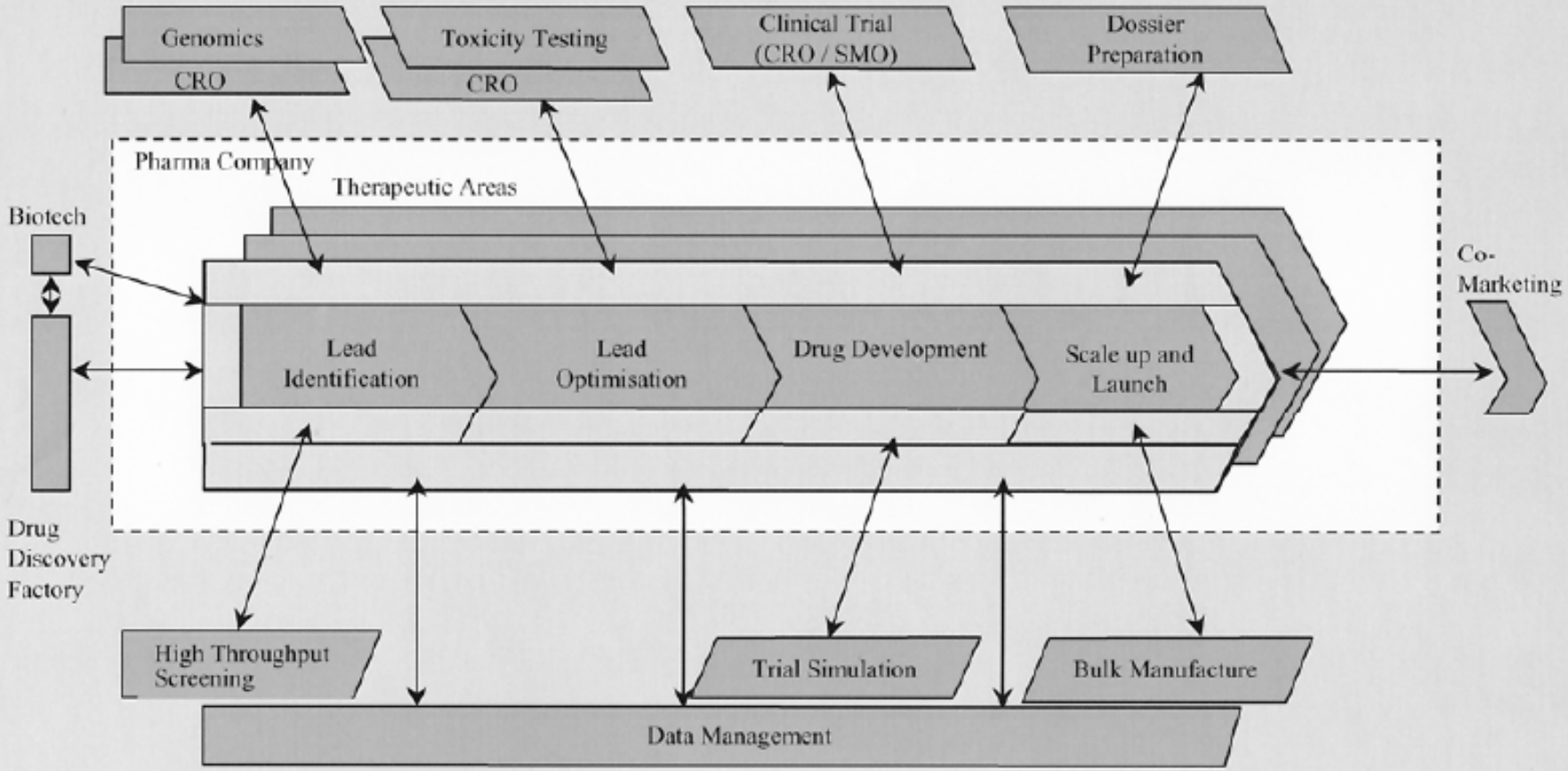
C = cost

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R&D Skills and Capacity

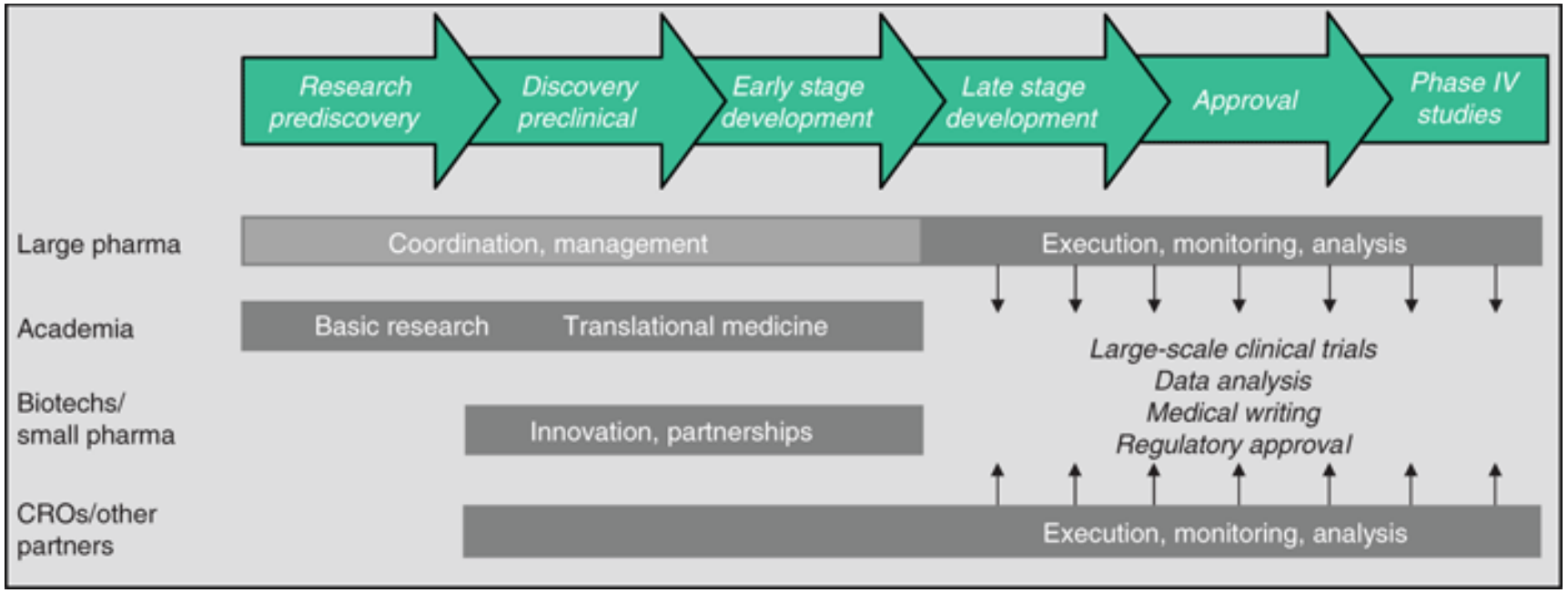
What to ‘own’ vs contract?

- **The increasing number of suppliers outside of the traditional value chain of big pharma offers new opportunities and potential disintegration of the industry**



Fully Integrated Pharmaceutical Network (FIPNet)

Model of Drug Development-USA



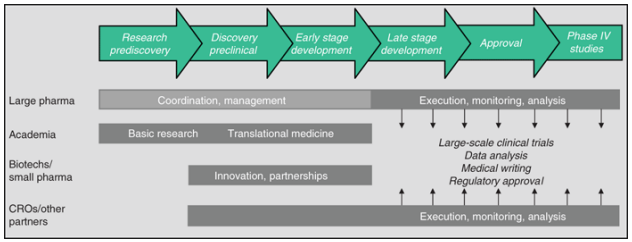
- **Large Pharma- decide inside-outside core competencies, own strategy & managing relationships**
- **Academia- NIH funded Clinical & Translational Research Centers (N~40 ➞ 60)-** ↑ targets & noncompetitive knowledge
- **Biotechs/small pharma-** ↑ pipeline for development, marketing & risk sharing
- **CROs- People (skills), tools, quality & risk sharing ➞** ↓ cycle time & cost
- **Foundations, Public Private Partnerships-** ↑ targets & noncompetitive knowledge

Clinical Pharmacol Ther 87: 356, 2010

Fully Integrated Pharmaceutical Network (FIPNet)

Model of Drug Development-USA

$$P \alpha \frac{WIP \times p(\mathrm{TS}) \times V}{CT \times C}$$

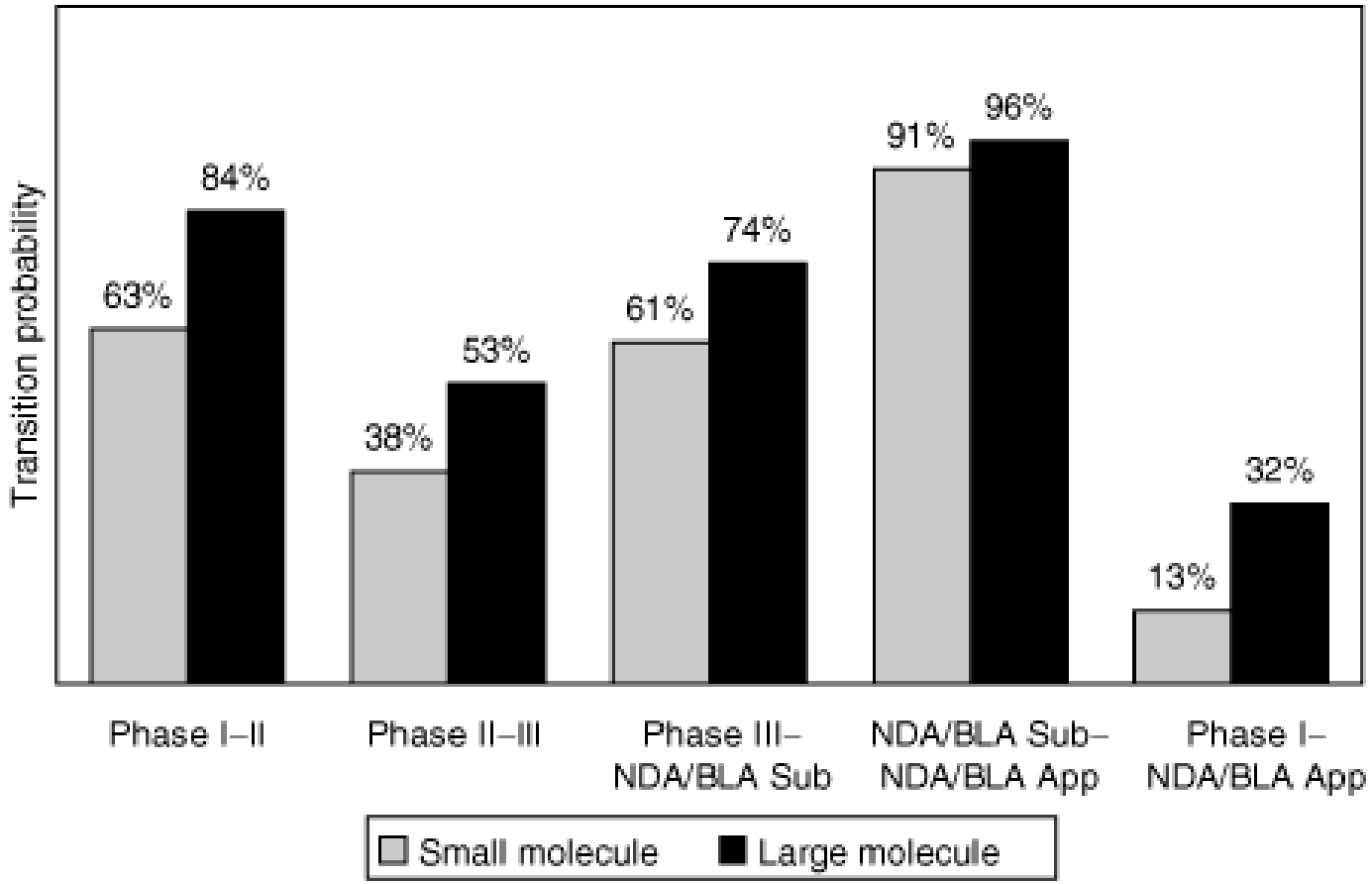


- .How can companies ↑ WIP, p(TS), V without increasing or ↓ C, CT?
- FIPNet proposed to allow a company to 'play bigger than its size'
- FIPNet proposed to allow greater access to intellectual property, molecules, capabilities, capital, knowledge and talent
- However, any change can have unintended consequences such as
  - ↑ complexity & interdependencies could further ↓ productivity
  - Quality of services and interdependencies must be maintained or ↑
  - No mention made of informatics requirements to support this change. Seems like a big topic that is not a strength in most companies

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Phase Transition Probabilies and Clinical Approval Success

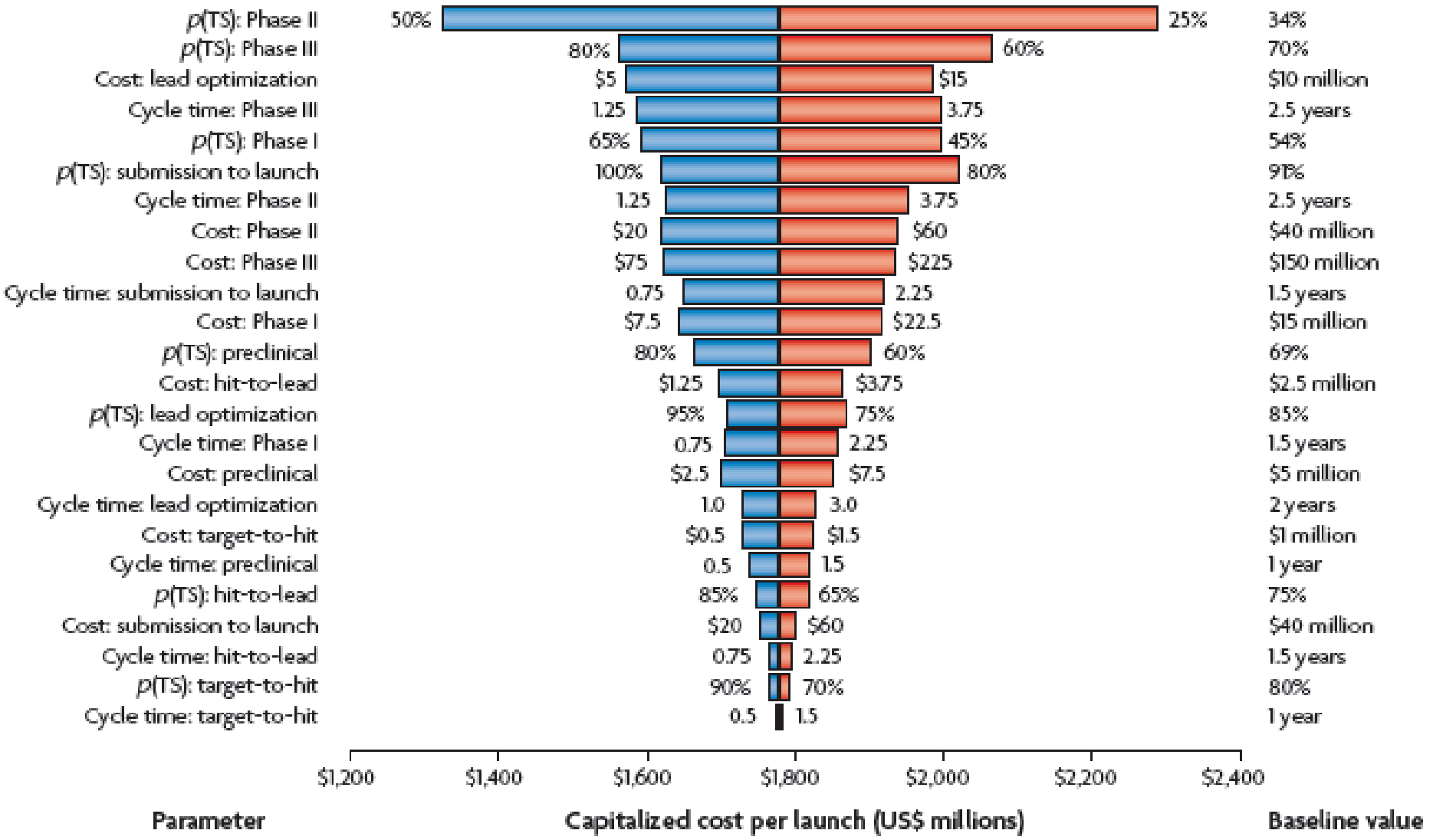
(self originated NCEs, 1st human dose 1993-2004)



Clin Pharmacol Ther 87: 272, 2010

R&D Productivity Model

(based on 13 large companies) Lilly

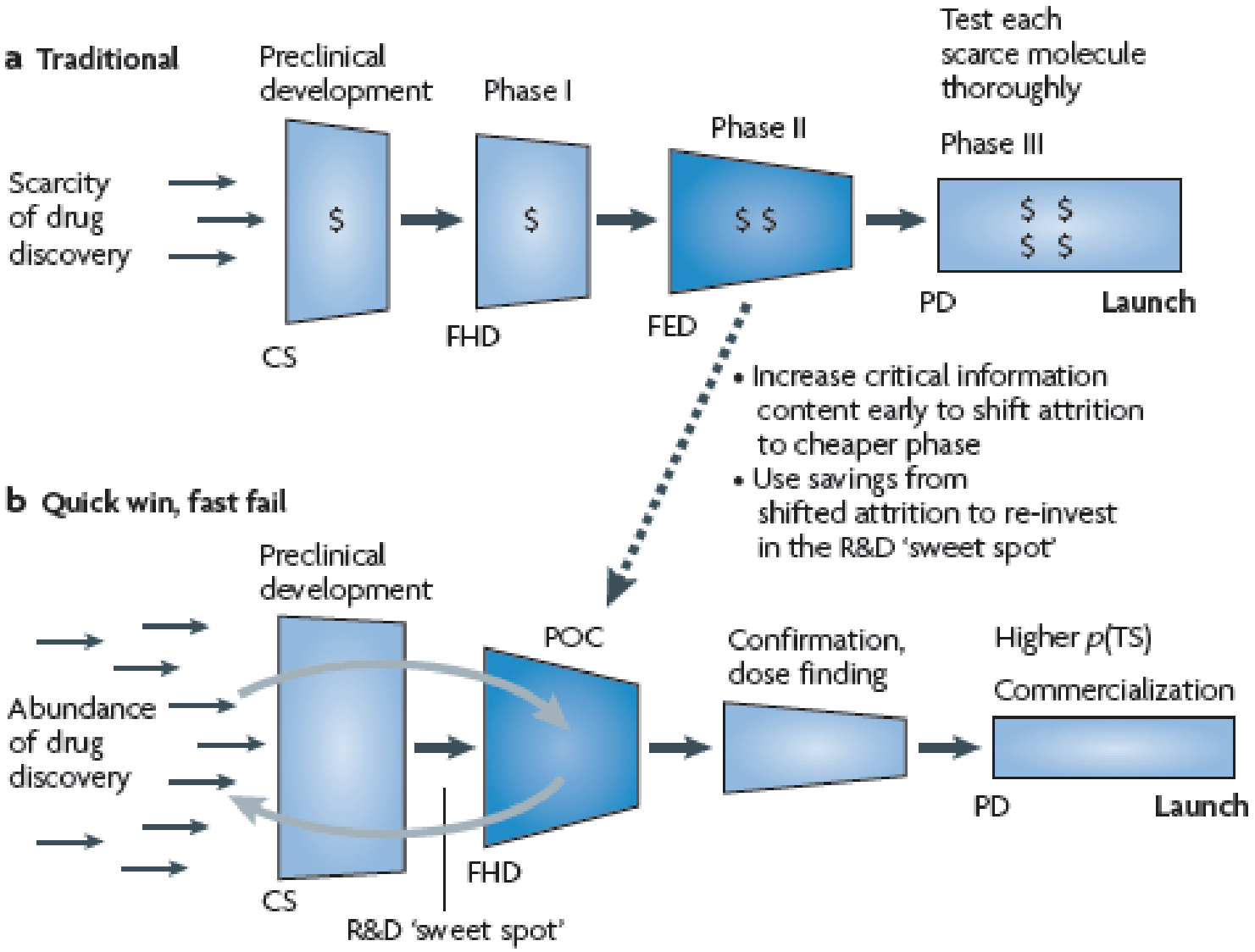


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Learning from the Model

- Clinical cost (I-III) 63% total, II-launch 53% total
  - Early kills & ↑ late phase efficiency preserves WIP investment
  - ↓ late phase spend funds enriching pipeline (WIP)
- Preclinical drug discovery >32% total (model does not include pre-target selection
- 8% NMEs will go from target selection to launch
- Cycle time 13.5 years target selection to launch
- 9 NMEs/year enter Phase I ➞ 1 drug launch/year
- Shifting investment to experimental medicine & predictive models to ↑ p(TS) & V

Lilly R&D Model Changes



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Summary

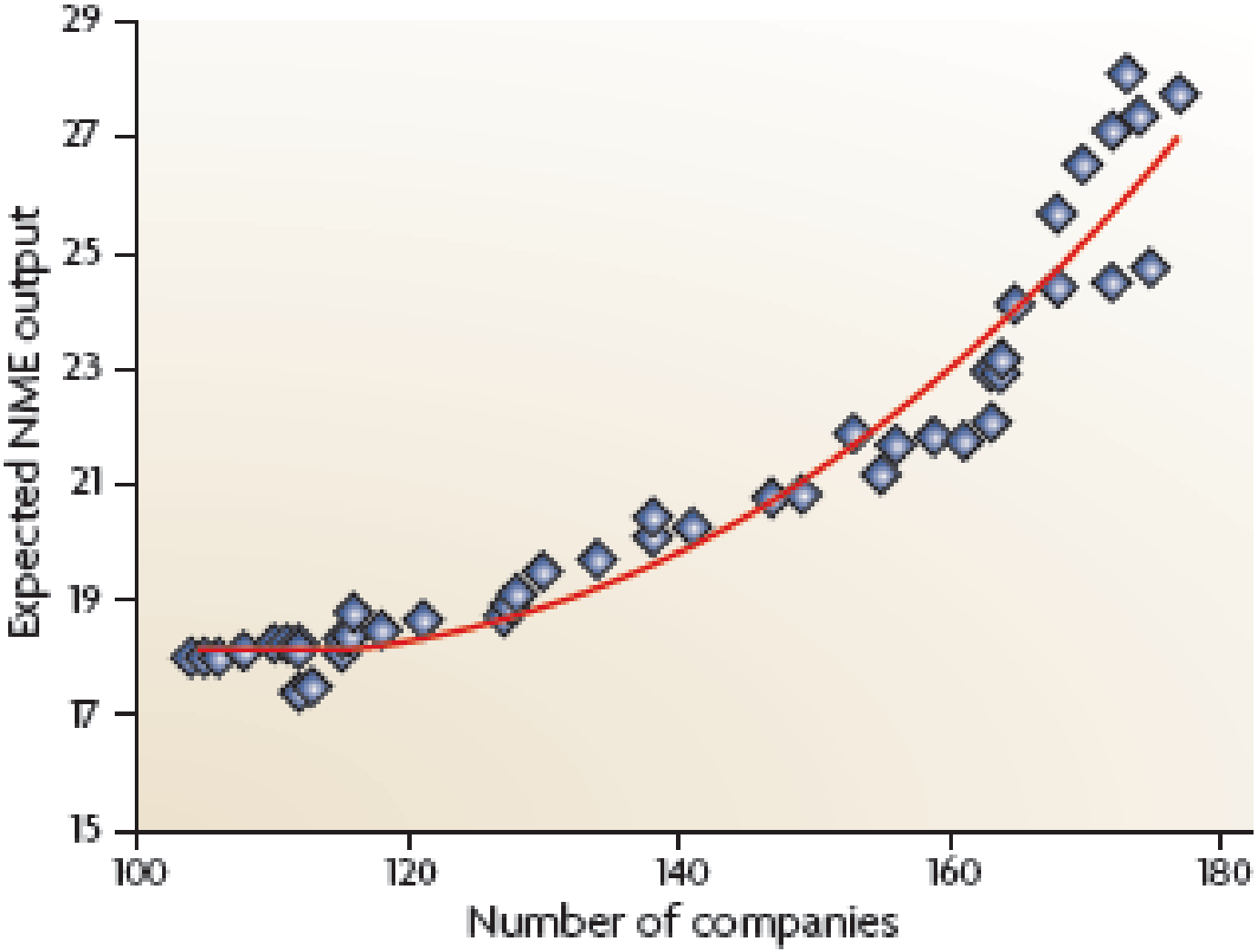
- Pharmaceutical industry simultaneously in serious trouble and has remarkable opportunities
- Externally, government and academia play key roles enabling new therapeutic products to emerge
- Internally, companies are experimenting with new R&D models that hold promise, but so did/do genomics, high throughput screening, combinatorial chemistry……
- Paradigm shift needed… not clear when breakout will occur
- Hopefully, China will develop a more effective model (government, industry, academia)

Recommended Reading

- Munos, B. Lessons from 60 years of pharmaceutical innovation. Nature Reviews Drug Discovery. 8: 959-968, 2009.
- Paul, SM et al. How to improve R&D productivity: the pharmaceutical industry's grand challenge. Nature Reviews Drug Discovery. Advance online publication 2010.
- Kaitin, KI. Deconstructing the drug development process: the new face of innovation. Clin Pharmacol Ther 87: 356-361.
- DiMasi, JA et al. Trends in risks associated with new drug development: success rates for investigational drugs. *Clin Pharmacol Ther* 87: 272-277, 2010
- Cuatrecasas, P. Drug discovery in jeopardy. J Clin Invest 116: 2837-2842, 2006.

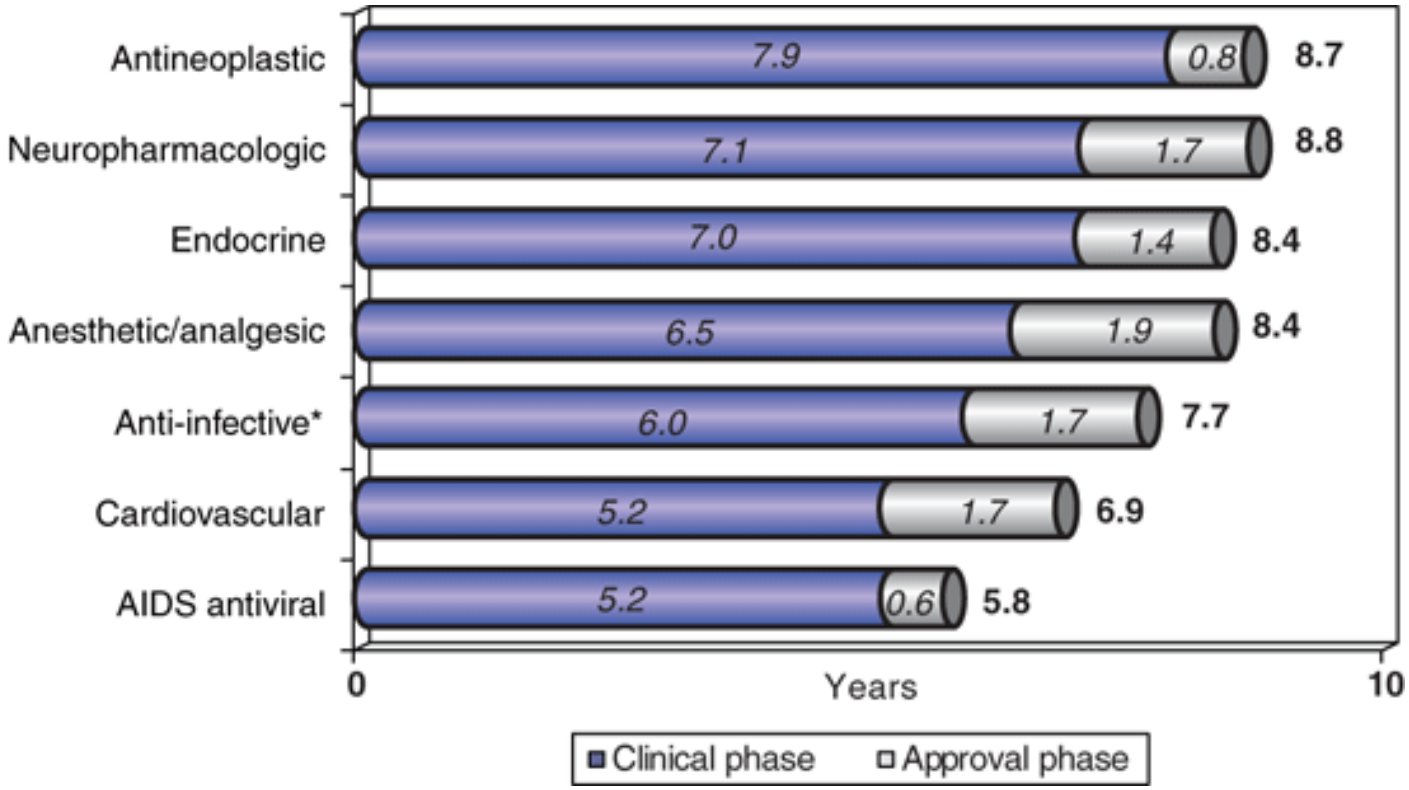
Backups

Number of Companies & Productivity



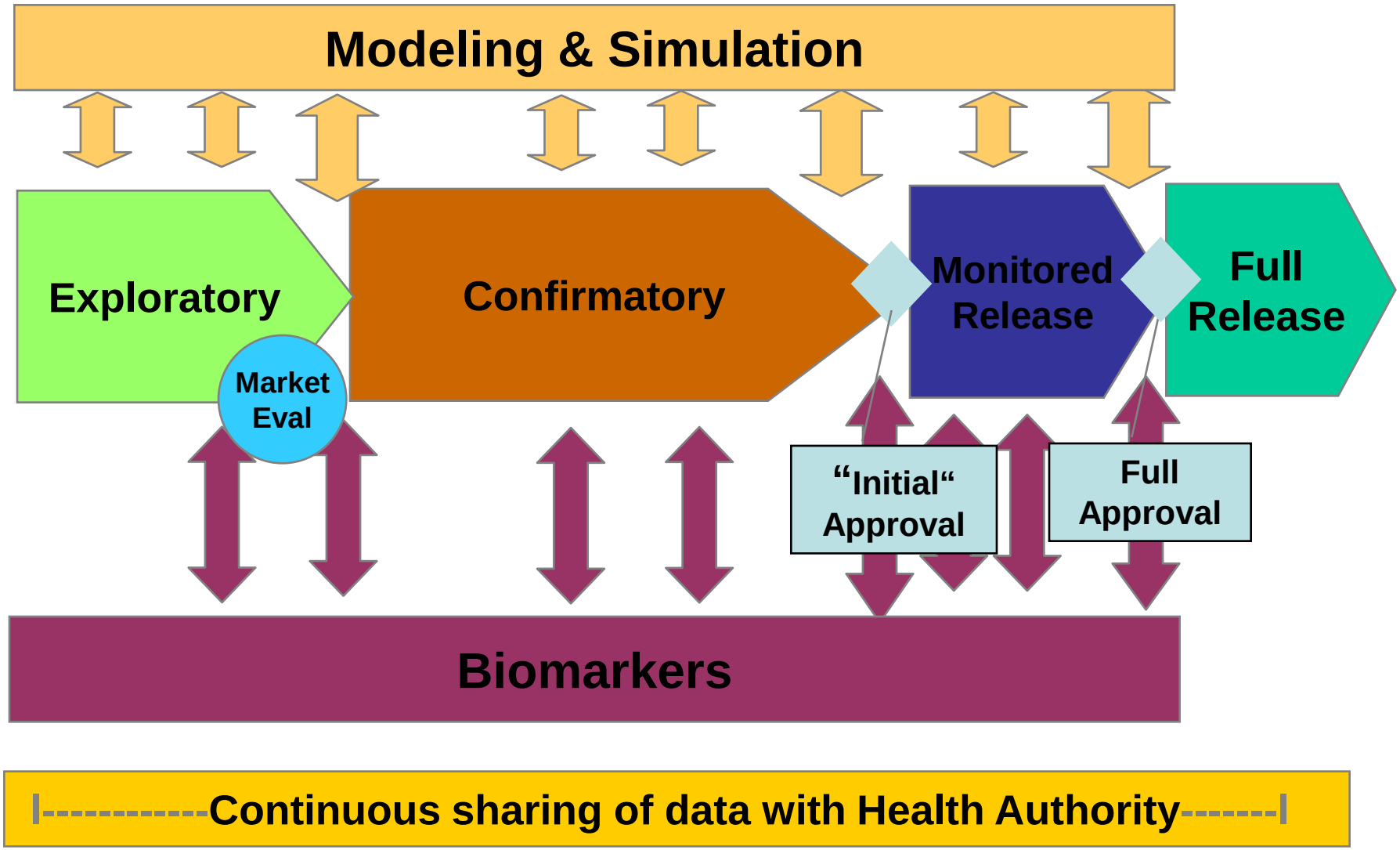
Nature Reviews Drug Discovery 8:959, 2009

Times for clinical development (IND filing-NDA submission) & FDA approval 2003-7

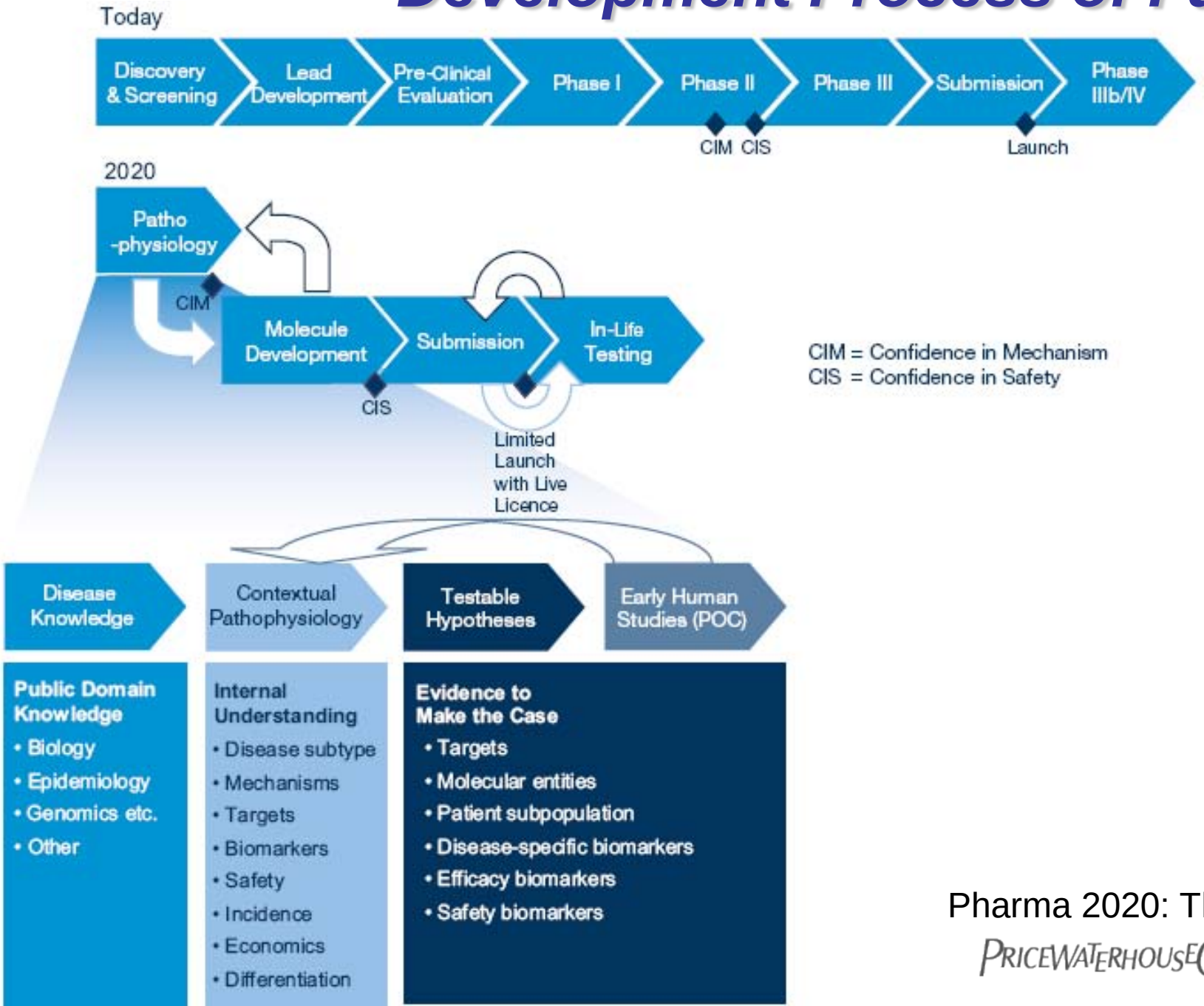


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Future Development Vision: Novartis



Development Process of Future



Pharma 2020: The Vision

PRICEWATERHOUSECOOPERS