June 2010 Land O'Lakes Conference

SCIENCE-DRIVEN DRUG PRODUCT DEVELOPMENT STRATEGIES TO ACHIEVE PROOF OF CONCEPT

52nd Annual International Industrial Pharmaceutical R&D Conference

June 7-11, 2010

Merrimac, WI

Conference Keynote Address

WHY SCIENCE-DRIVEN DEVELOPMENT IS (STILL) IMPORTANT

Jayne E. Hastedt, PhD

JDP Pharma Consulting, LLC

OUTLINE

- Audience Survey
- State of the Pharmaceutical Industry
  - Product Development: Track Record, Costs, Investments
  - Challenges: Challenging Therapies, Generics, Payers
  - Outcomes: Jobs, Productivity, and Pharma Reputation
- Enhancing Productivity
  - Pipeline: M&As and In-licensing
  - Product Development: Outsourcing and Fast to Fail models
  - Challenges: Managing Alliances and External Collaborations
- Evaluating the Situation: Why Do Drugs Fail?
  - Analysis by Stage and Therapeutic Class
  - Case Study – Post Approval Product Failure
- Conclusions
  - Science-Driven POC Strategies

AUDIENCE SURVEY: YEARS IN THE INDUSTRY

- How many of you have been in the Pharma industry for 1 year or more?
  - 5 years or more?
  - 10 years or more?
  - 15 years or more?
  - 20 years or more?

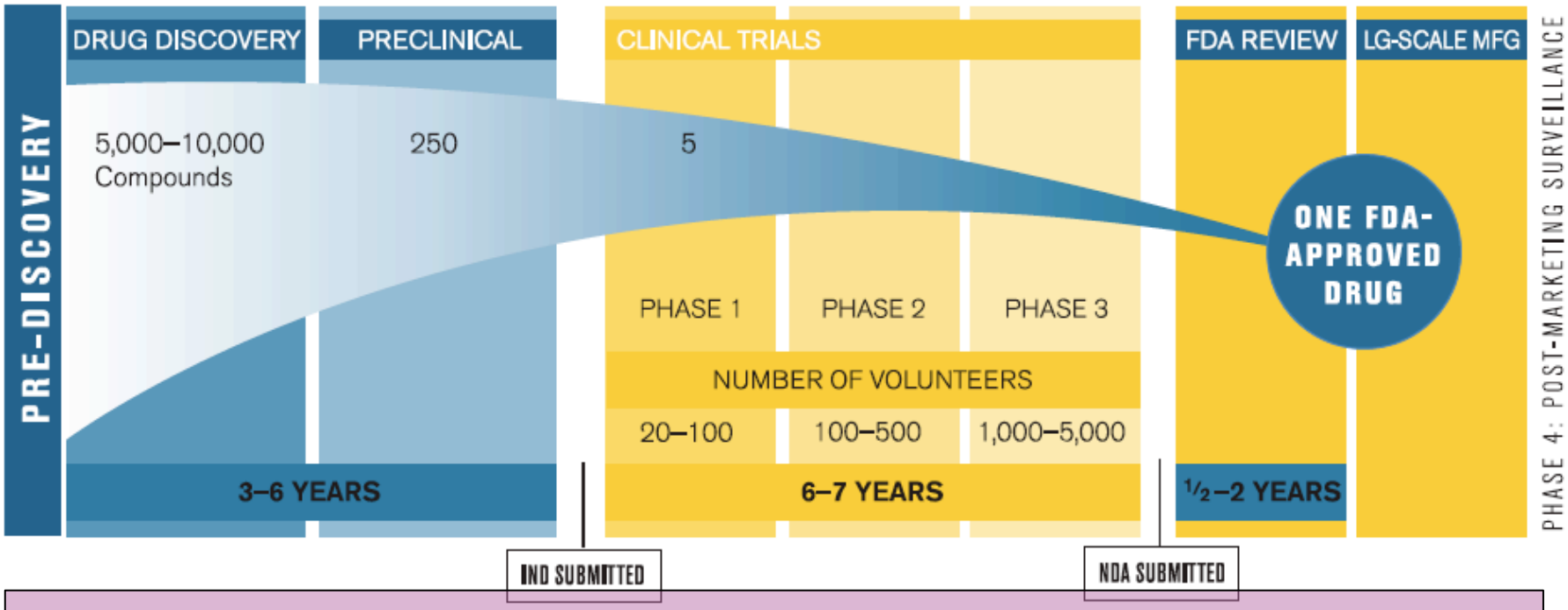
AUDIENCE SURVEY: PRODUCT DEVELOPMENT

- How many of you have worked on an innovator R&D development team:
  - Discovery Support?
    - Pre Phase 1
  - Early Development?:
    - Phase 1 - 2
  - Full Development?
    - Phase 3 – tech transfer to commercial
  - Commercial?
    - Launch and post approval?
  - Life Cycle Management?
- How many of you have been on a development team that launched a new product?

THE CURRENT STATE OF THE PHARMA INDUSTRY

Product development costs, track record, challenges, productivity, and reputation

THE COSTLY, COMPLEX, AND LONG INNOVATOR PRODUCT DEVELOPMENT CYCLE



10-15 years

$1.2 – 1.3 billion per drug*

R&D Spend in 2009:

- $65.3B
- 16.0% of total sales*

ONLY 2 of 10 marketed drugs every return revenues that match or exceed R&D costs.*

Pharmaceutical Research and Manufacturers of America, Pharmaceutical Industry Profile 2009 (Washington, DC: PhRMA, April 2009).

**Pharmaceutical Research and Manufacturers of America, Pharmaceutical Industry 2010 (Washington, DC: PhRMA, March 2010).*

PHARMA R&D INVESTMENT BY STAGE OF DEVELOPMENT

TABLE 5

R&D by Function, PhRMA Member Companies: 2008

(dollar figures in millions)

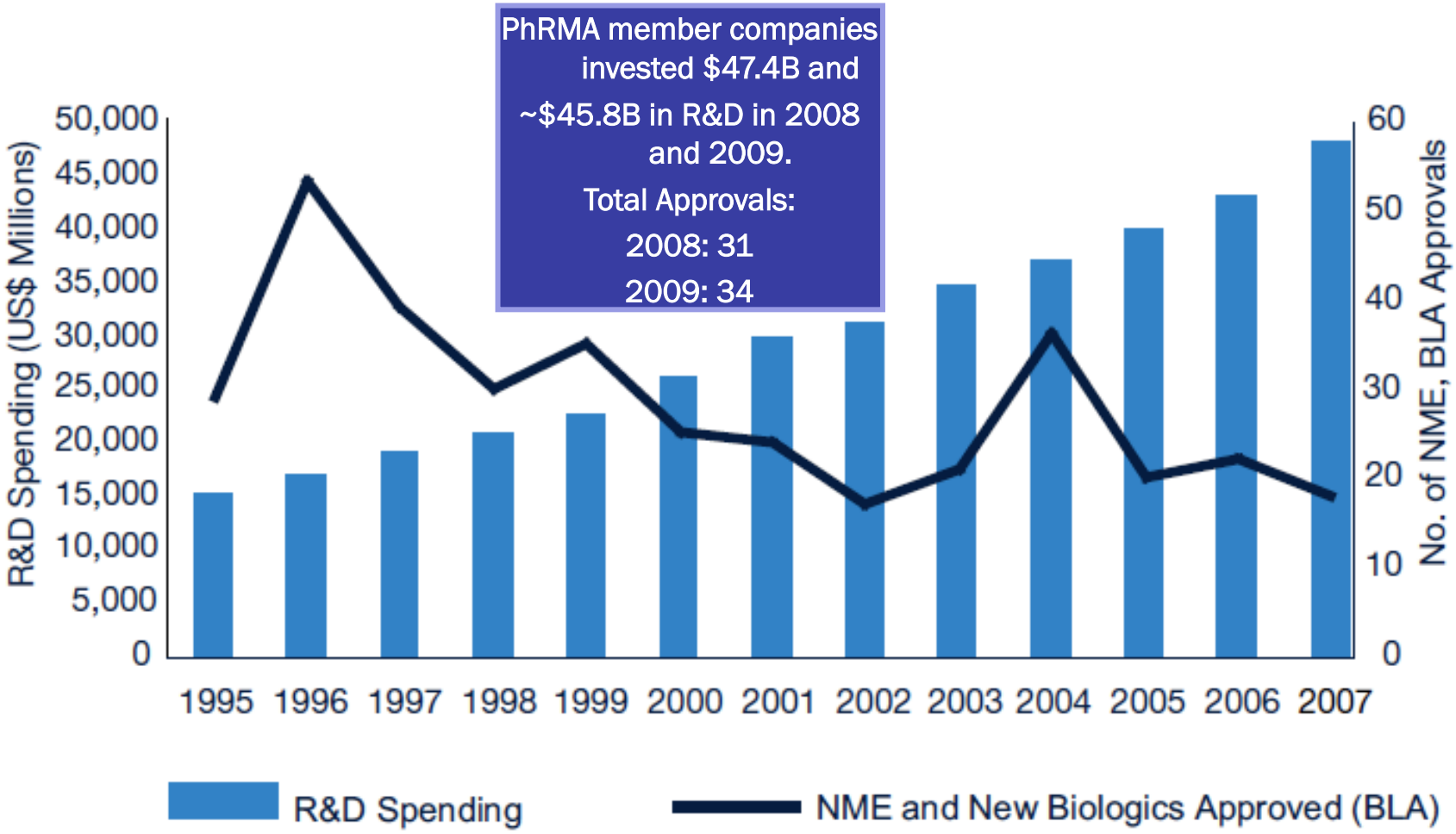
Function	Dollars	Share
Prehuman/Preclinical	$12,795.6	27.0%
Phase 1	3,889.6	8.2
Phase 2	6,089.7	12.9
Phase 3	15,407.4	32.5
Approval	2,225.8	4.7
Phase 4	6,835.8	14.4
Uncategorized	139.1	0.3
TOTAL R&D	**$47,383.1**	**100.0%**

Note: All figures include company-financed R&D only. Total values may be affected by rounding.

SOURCE: Pharmaceutical Research and Manufacturers of America, *PhRMA Annual Membership Survey*, 2010.

Pharmaceutical Research and Manufacturers of America, Pharmaceutical Industry 2010 (Washington, DC: PhRMA, March 2010).

INCREASING DEVELOPMENT COSTS AND DECREASING PRODUCTIVITY



Source: FDA CDER, PhRMA and PricewaterhouseCoopers analysis

Note: Data on R&D spending for non-PhRMA companies are not included here.

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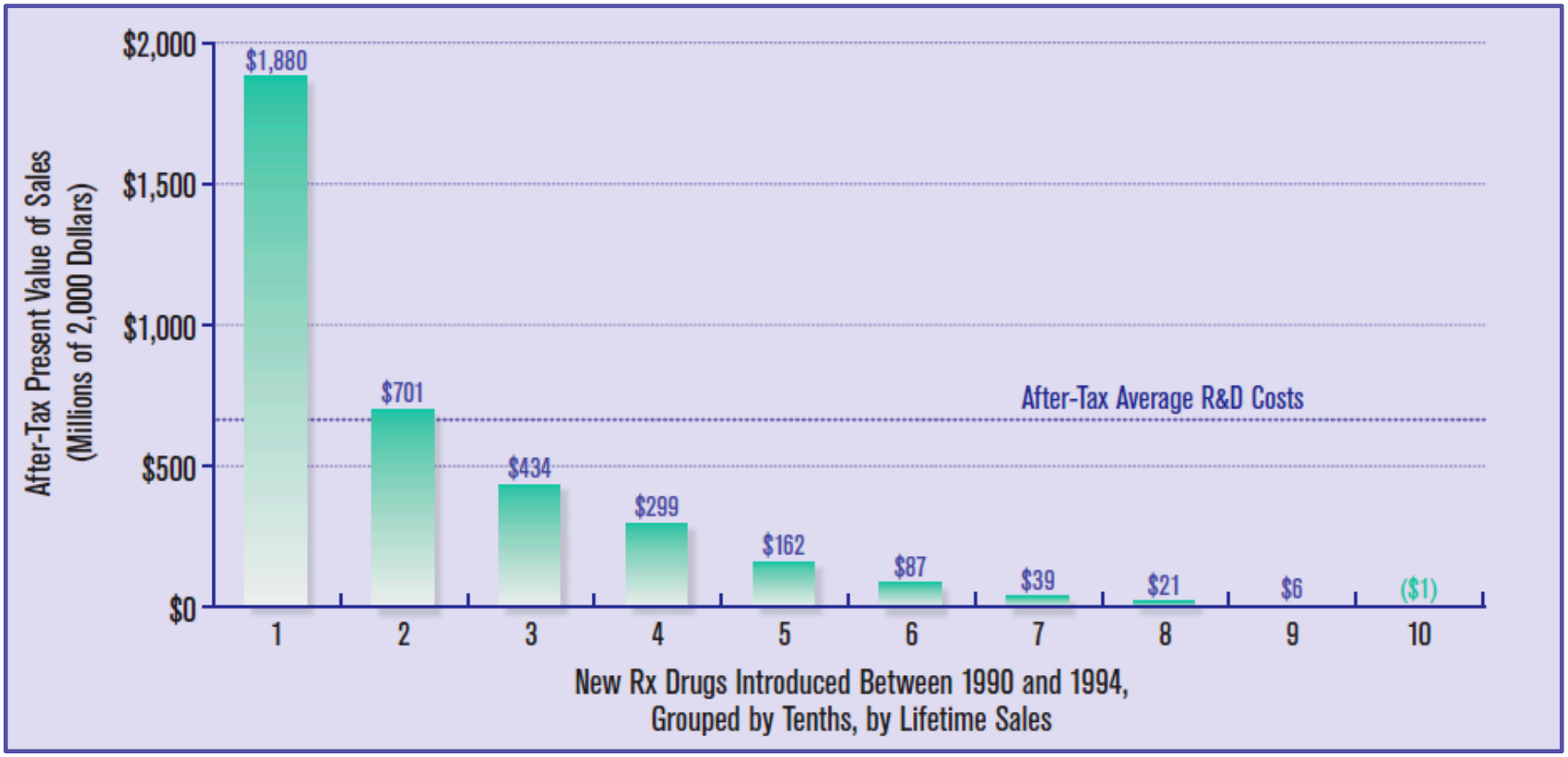
ONLY 20% OF PHARMA PRODUCTS HAVE A POSITIVE RETURN ON INVESTMENT

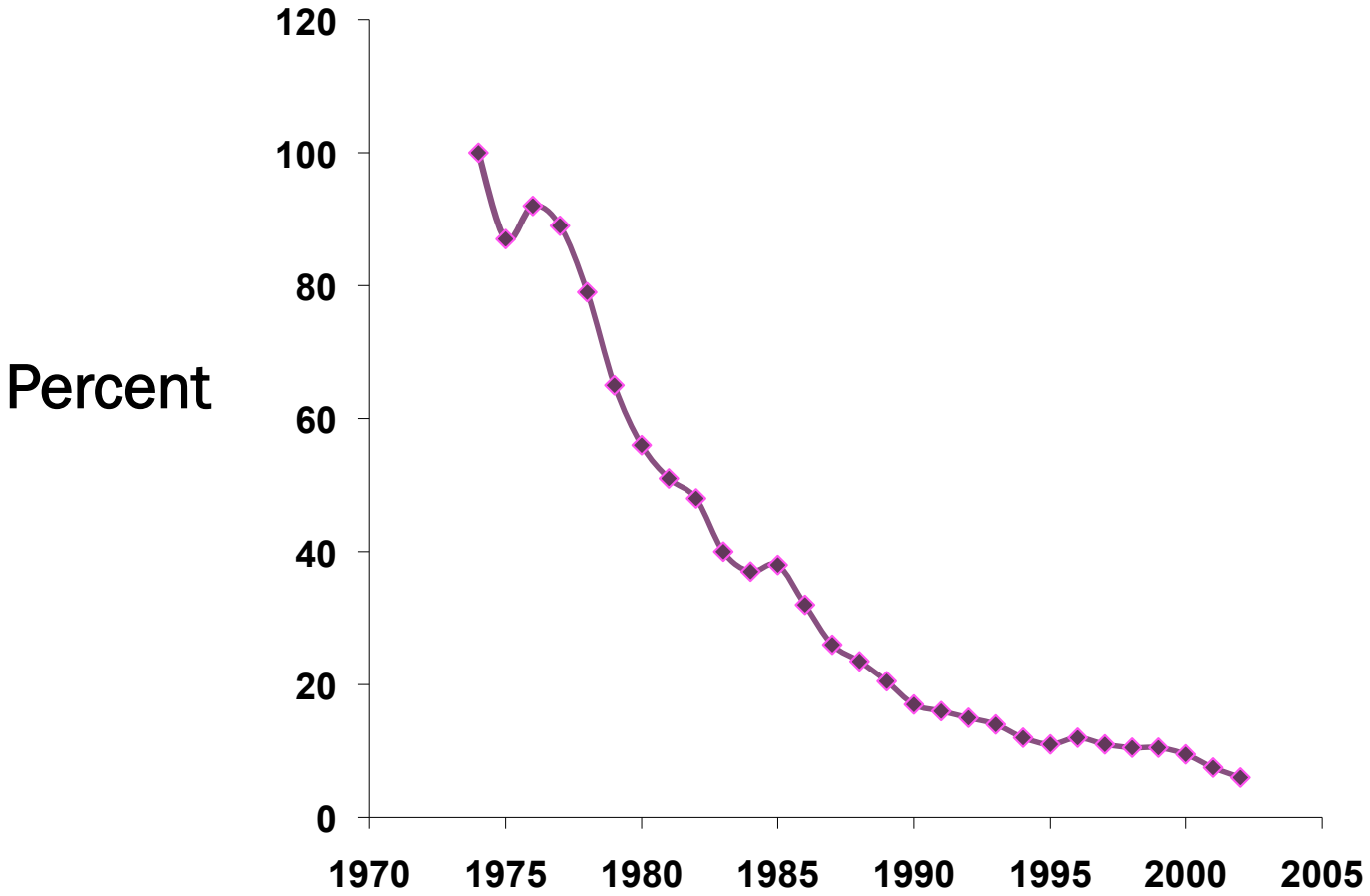


Pharmaceutical Research and Manufacturers of America, Pharmaceutical Industry 2010 (Washington, DC: PhRMA, March 2010.

WHY?

CHALLENGING THERAPIES: A MAJOR IMPACT ON PHARMA PRODUCTIVITY

Productivity: NME output per R&D spend (normalized to 1970-1975)



Source: McKinsey analysis

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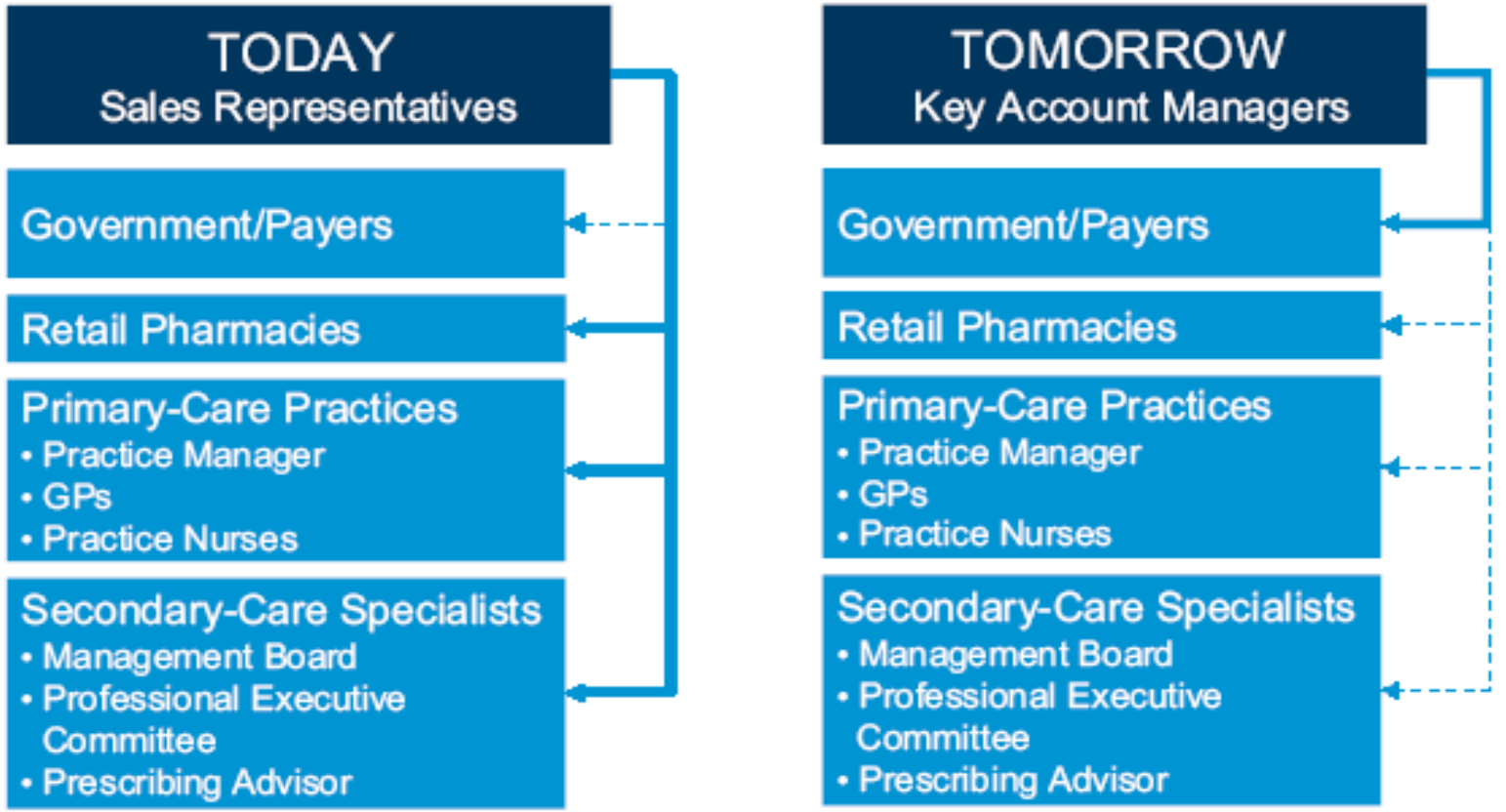
THE INCREASING IMPACT OF THE PAYER ON PRODUCT DEVELOPMENT, PRICING, AND SALES



Source: PricewaterhouseCoopers

GENERIC COMPETITION IS INCREASING

PhRMA Analysis of National Prescription Audit data from IMS Health™, data through 3rd Quarter of 2007.

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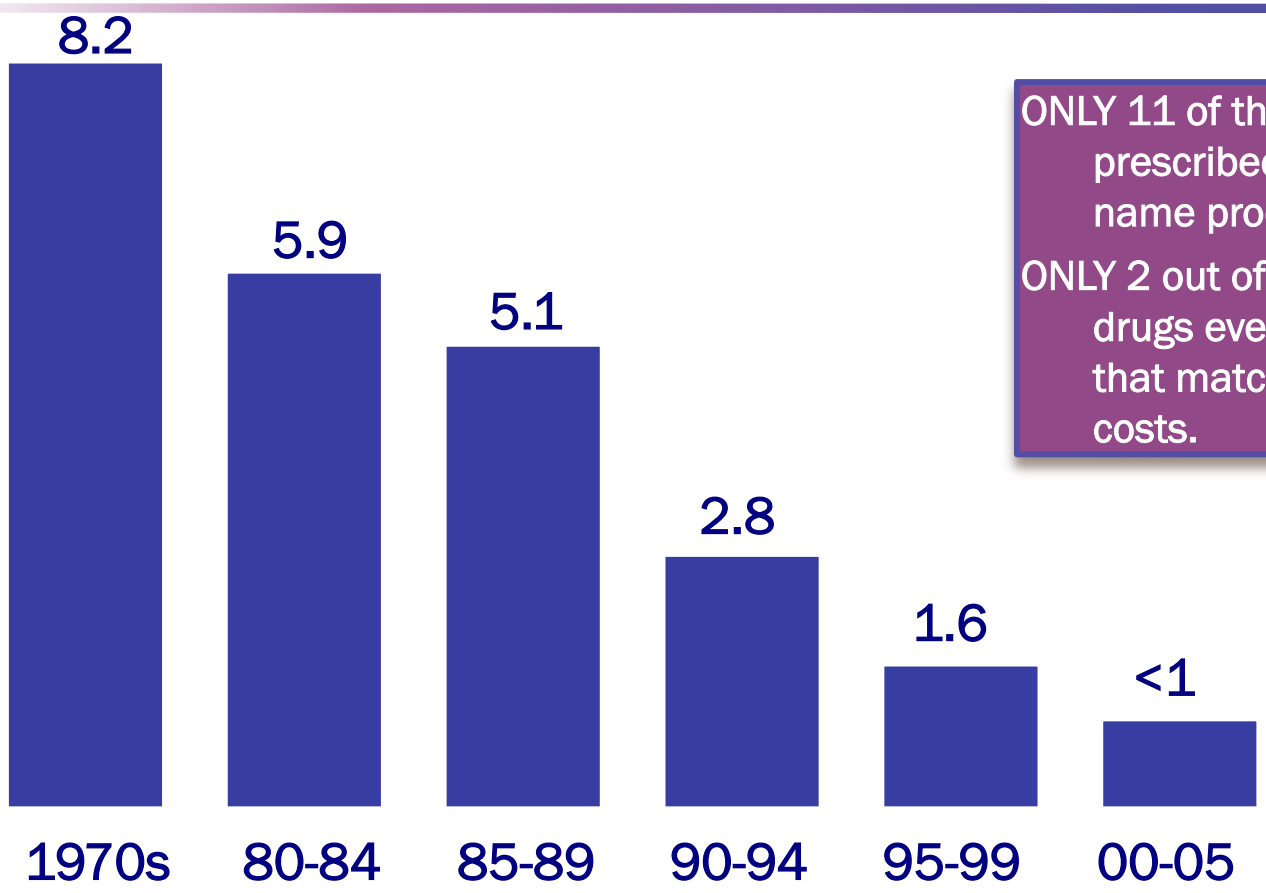
INNOVATOR PRODUCT REVENUES ERODE RAPIDLY ONCE PATENTS EXPIRE



ONLY 11 of the top 50 most prescribed drugs are brand name products.

ONLY 2 out of 10 marketed drugs ever return revenues that match or exceed R&D costs.

Source: FDA; The Pink Street; Morgan Stanley; DiMasi; Paquette; Pharmacoeconomics 2004, 22 (Suppl 2): 1-14; IMS; team analysis IMS Health, National Sales Perspectives, National Prescription Audit, March 2009 AARP, The 50 Most Prescribed Drugs, October 2009.

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TAKING A TOLL ON JOBS AND INTERNAL CAPABILITIES

Company	Announced Job Cuts	Reason
Merck	16,000	Merger with Schering-Plough
Pfizer	19,500	Merger with Wyeth
Roche	1,500	Full ownership of Genentech
Johnson & Johnson	8,000	Increase competitiveness
Eli Lilly	5,500	Increase competitiveness
GlaxoSmithKline	6,000	Increase competitiveness
Total:	56,500	

Loss of seasoned development veterans and technical skill sets

From "The Pharmaceutical R&D Model is Broken. Here's How to Fix It" by Stewart Lyman. Published on 3/5/10.
http://www.xconomy.com/seattle/2010/03/05/the-pharmaceutical-rd-model-is-broken-heres-how-to-fix-it/?single_page=true

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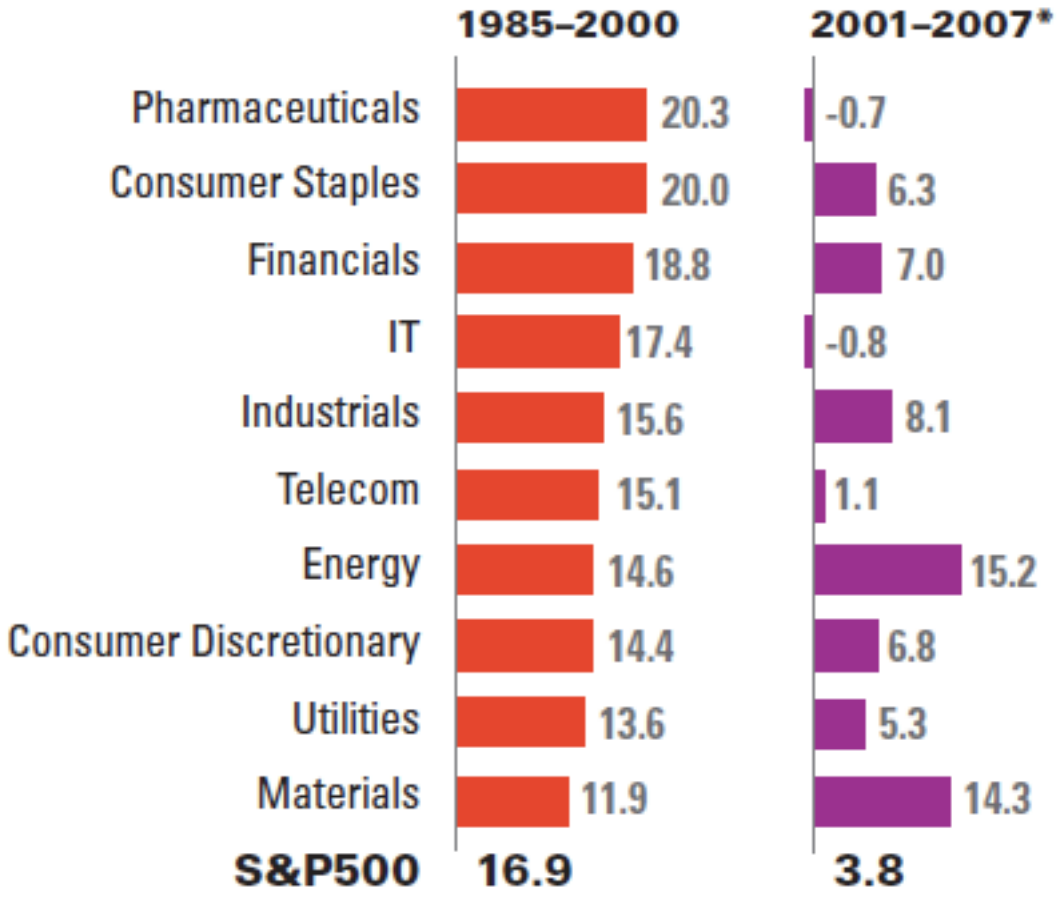
AND IMPACTING PHARMA R&D PRODUCTIVITY



*Data as of June 30, 2007. All U.S. publicly traded companies with revenues of $500M or more, adjusted for inflation.

Jean-Pierre ***Garnier, "Rebuilding the R&D Engine in Big Pharma", Harvard Business Review May*** *2008 pg 70*

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BIG PHARMA REPUTATION – PATIENT VIEW 2009

Category	Top Company in 2009	Most Improved Company since 2008	Largest Falling in Rankings since 2008
Understanding Patients Needs	Novartis (Swiss), Pfizer (US), Roche	Roche (Swiss)	Merck (US)
Relationship with Patient Groups	Sanofi-Aventis (France)	Sanofi-Aventis (France)	Merck (US)
Trustworthiness	Novartis (Swiss)	Roche (Swiss)	J&J (US) and Merck (US)
Availability of Patient Information	Astra-Zeneca (Anglo-Swedish)	Astra-Zeneca and Sanofi-Aventis	Merck (US)

Decrease in reputation of US-based Big Pharma Companies

http://www.thepharmaletter.com/file/31533d33bd87229b7bdc99eed1013023/big-pharma-still-not-very-trusted-by-patients-groups-but-european-drugmakers-viewed-more-favorably-than-others.html *Published 3/15/10.*

BIG PHARMA REPUTATION – PATIENT VIEW 2009: TRUSTWORTHINESS

Rank	Company	Total Score	Change from 2008
1	Sanofi-Aventis	3	↑ 8 places
2	Novartis	6	↓ 1 place
3	AstraZeneca	8	↑ 5 places
4	Pfizer (with Wyeth)	10	↓ 2 places
5	Roche (with Genentech)	10	↑ 1 place
6	Abbott Labs	11	↑ 4 places
7	Johnson & Johnson	11	↓ 3 places
8	Amgen	12	Not included
9	GSK	14	↓ 5 places
10	Bayer	15	Not included
11	Eli Lilly	20	↓ 6 places
12	Merck	22	↓ 7 places
13	Bristol Meyers Squib	26	Not included
14	Baxter	28	Not included

http://www.thepharmaletter.com/file/31533d33bd87229b7bdc99eed1013023/big-pharma-still-not-very-trusted-by-patients-groups-but-european-drugmakers-viewed-more-favorably-than-others.html *Published 3/15/10.*

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PHARMA INDUSTRY CHALLENGES ARE NUMEROUS AND ARE CHALLENGING BOTH INNOVATION AND PRODUCTIVITY

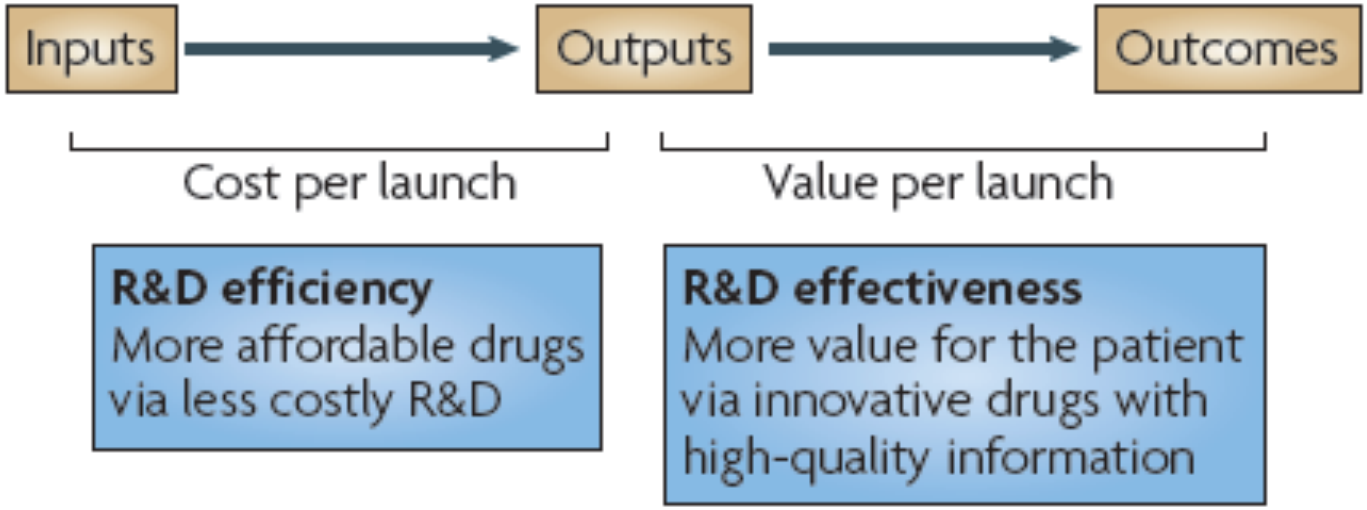
- Increasing R&D costs and reduced productivity
- Challenging product portfolios and pipelines
- Inability to recoup R&D costs for innovator products
- Aggressive generic competition
- Pricing and marketing pressures from insurance companies
- Loss of internal skill sets and technical capabilities
- Lowered public reputation and trust

ENHANCING PRODUCTIVITY IN PHARMA

Response to the Current Challenges:

M&As, In-licensing, Fast to Fail POCs, and Distributed Development Approaches

R&D PRODUCTIVITY COMPONENTS



Value = delivering innovative products (differentiated and needed by patients) with high quality information

In this model, productivity is the relationship between value created ($ and patient benefit) and investment.

Steven Paul, et. al., "How to Improve R&D Productivity: the pharmaceutical industry's grand challenge" Nature Reviews Drug Discovery, March 2010, 203-214.

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CURRENT THINKING: BUSINESS MODELS FOR INCREASED PRODUCTIVITY

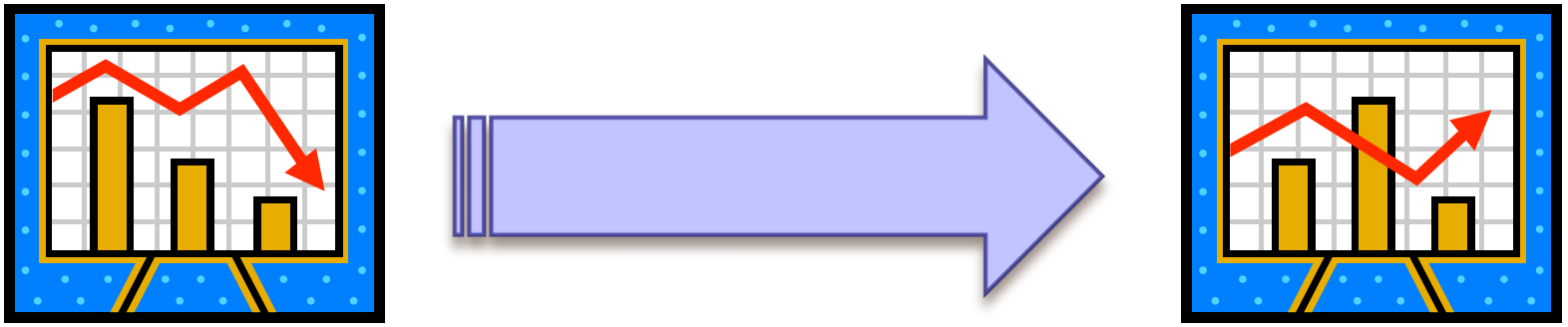
- Shift from conventional integrated to virtual or distributed product development
  - Large Pharma companies should abandon their own early stage drug development programs, and switch to a less costly in-licensing model
  - Small, more nimble and innovative biotech companies should discover drugs
  - Partner with academic institutions for discovery
  - Off-shoring research and development to reduce costs
  - Utilize CROs to compensate for limited internal resources and expertise

This model would result in "higher success rates, lower costs, and triple returns"
– Financial Times

MERGERS AND ACQUISITIONS

"Mergers are a defensive response to internal weakness, particularly innovation deficit and managerial concerns about R&D efficiency and productivity."

– *J. Mittra*



J Mittra, "Life Science Innovation and the Restructuring of the Pharmaceutical Industry: Merger, Acquisition and Strategic Alliance Behaviour of Large Firms," Technology Analysis & Strategic Management 19(3), May 2007, 279-301.

MAJOR PHARMA M&AS: 1990 - 2004

Year	Purchaser	Target	Cost of target (US$ billion)	Name of merged entity
2004	Sanofi	Aventis	63.0	Sanofi-Aventis
2003	Pfizer	Pharmacia	60.0	Pfizer
2001	Bristol Myers Squibb	Dupont Pharma	7.8	Bristol Myers Squibb
2000	Johnson & Johnson	Alza	10.8	Johnson & Johnson
2000	Shire	Biochem Pharma	4.0	Shire
2000	Abbott	Knoll (BASF Pharma)	6.9	Abbott
2000	Glaxo Wellcome	SmithKline Beecham	76.0	GlaxoSmithKline
2000	Pfizer	Warner-Lambert	89.2	Pfizer
1999	Pharmacia Upjohn	Monsanto	26.9	Pharmacia
1998	Rhone-Poulenc Rorer	Hoechst AG	21.2	Aventis
1998	Sanofi	Synthelabo	11.1	Sanofi-Synthelabo
1998	Zeneca	Astra	34.6	AstraZeneca
1997	Hoffmann-La Roche	Boehringer Mannheim	11.0	Roche
1996	Sandoz	Ciba-Geigy	60.0 (value of merged entity)	Novartis
1995	Glaxo	Burroughs Wellcome	20.0	Glaxo Wellcome
1995	Hoechst-Roussel	Marion Merrell Dow	7.1	Hoechst Marion Roussel
1995	Pharmacia	Upjohn	13.0	Pharmacia & Upjohn
1995	Rhone-Poulenc Rorer	Fisons	2.7	Rhone-Poulenc Rorer
1995	American Home Products	American Cyanamid	9.2	American Home Products
1995	Hoffmann-La Roche	Syntex	5.3	Hoffmann-La Roche
1994	Sanofi	Sterling (prescription drugs)	1.9	Pharmacia
1990	Beecham	SmithKline Beckman	6.5	SmithKline Beecham

Source: PhRMA/Reuters, Wood Mackenzie and Company Websites.

$548.2B invested over 14 years

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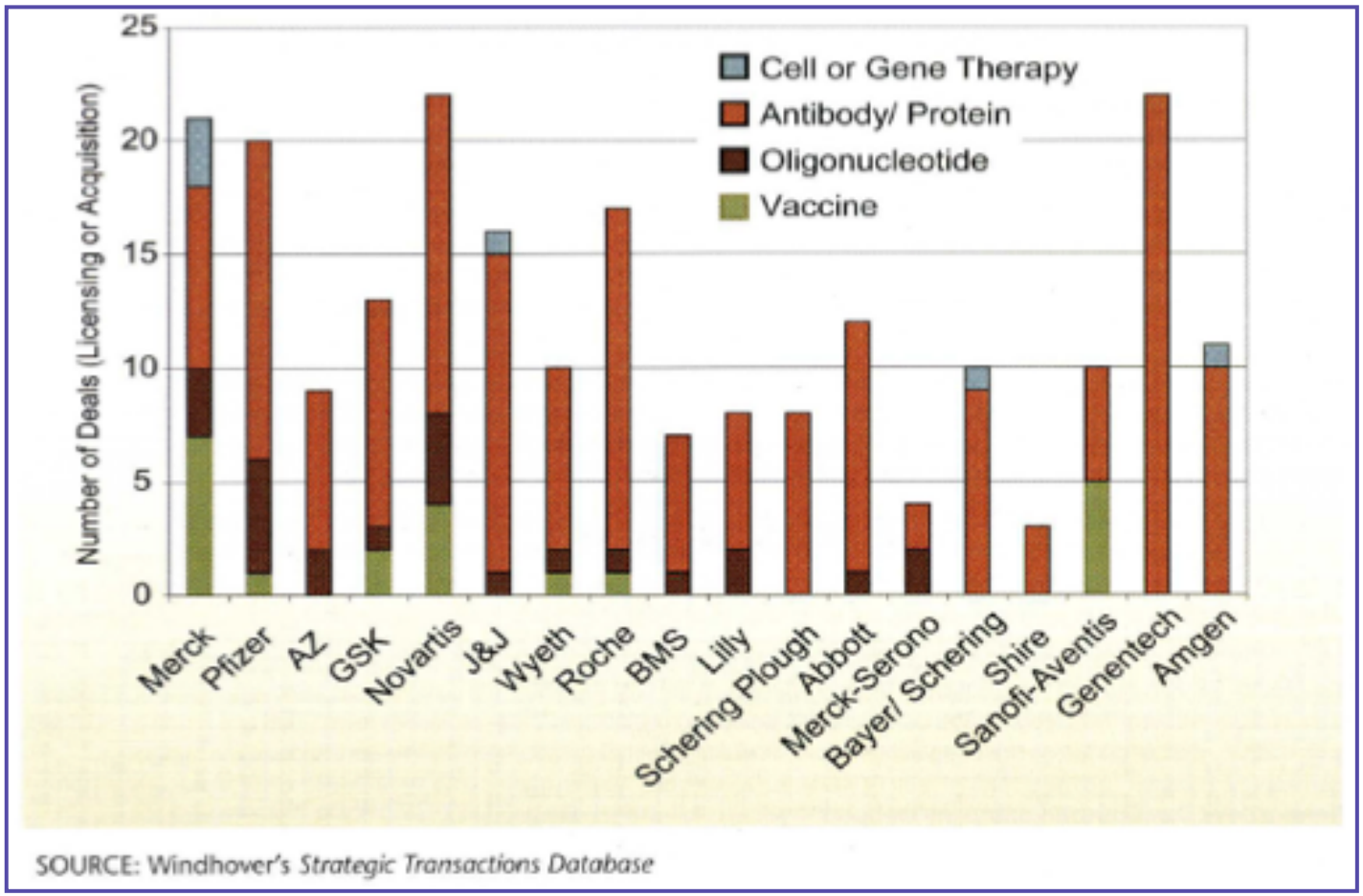
IN-LICENSING: BIOLOGICS ACTIVITY 2003 - 2007



- Roche, Novartis, GSK and Aventis account for more than 50% of the licensing deals between 2002 and 2004.

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BIOTECH PARTNERSHIP DEALS: 1995 - 2004

Year	Biotech–biotech deals	Pharma-biotech deals
1995–1996	198	577
1997–1998	352	645
1999–2000	485	631
2001–2002	777	641
2003–2004	894	813

Source: Recombinant Capital.

Pharma has initiated >3300 alliances/deals with biotech companies between 1995 and 2004

J Mittra, "Life Science Innovation and the Restructuring of the Pharmaceutical Industry: Merger, Acquisition and Strategic Alliance Behaviour of Large Firms," Technology Analysis & Strategic Management 19(3), May 2007, 279-301.

EU PHARMA R&D PIPELINES CONTAIN AT LEAST 20% EXTERNAL CANDIDATES

Table 8. European drugs sector mid/late-stage R&D pipelines

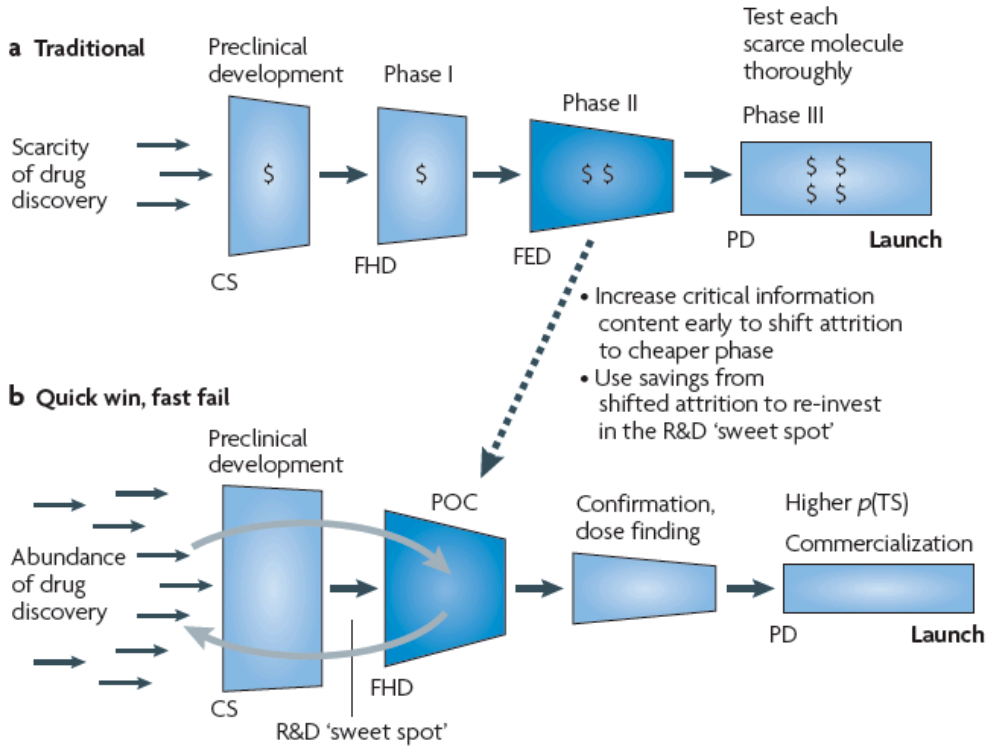
Company	Phase 2	Phase 3	Filed	Internal candidates	External candidates	% External
GSK	34	4	5	31	12	28
Sanofi-Aventis	20	11	7	30	8	21
Novartis	15	9	3	17	10	37
Roche	9	4	10	13	10	43
AstraZeneca	8	2	2	9	3	25

Source: Deutsche Bank AG estimates and company information (phase 1 not included due to limited data and high attrition rate).

- Licensing *versus* M&A strategies:
  - The pharma company can "cherry pick" desirable compounds from external sources without having to acquire the whole organization
  - For many pharma companies licensing has become a core business development strategy

J Mittra, "Life Science Innovation and the Restructuring of the Pharmaceutical Industry: Merger, Acquisition and Strategic Alliance Behaviour of Large Firms," Technology Analysis & Strategic Management 19(3), May 2007, 279-301.

DEVELOPMENT APPROACHES: QUICK WIN, FAST FAIL VERSUS TRADITIONAL



- Although the "fast to fail" approach makes sense, it requires access to large drug discovery pipelines and front loads the development costs.

Steven Paul, et. al., "How to Improve R&D Productivity: the pharmaceutical industry's grand challenge" Nature Reviews Drug Discovery, March 2010, 203-214.

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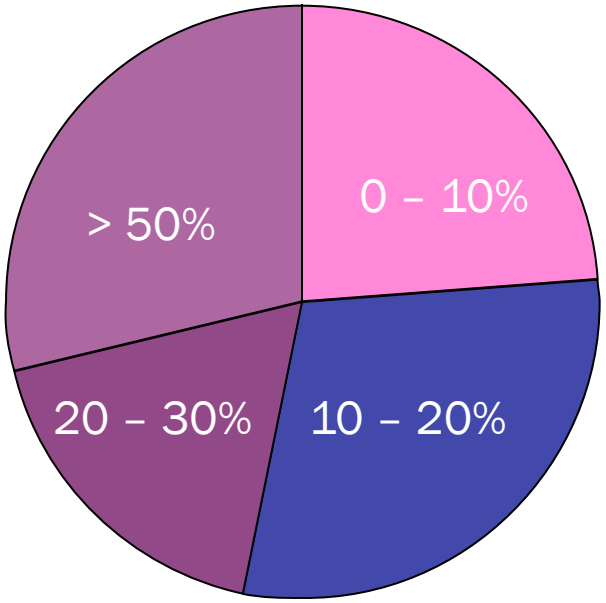
OUTSOURCING: PHARMA RELIANCE ON DELIVERY, BIOTECH, AND SPECIALTY PLAYERS FOR PRODUCT DEVELOPMENT

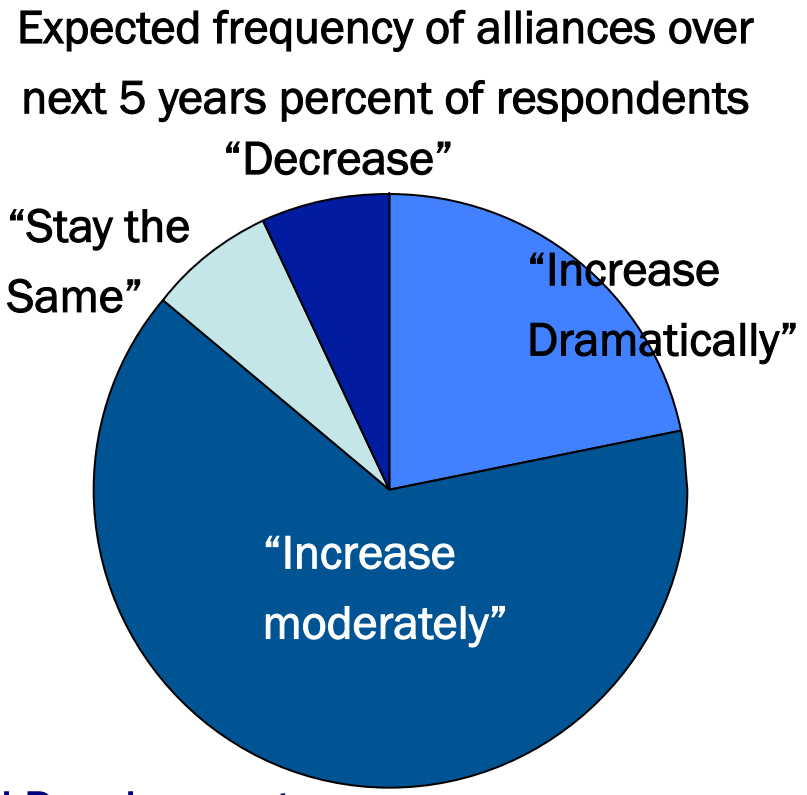
Nearly 50% of respondents attributed at least 20% of revenue to alliances...

...and an overwhelming majority expect the frequency of alliances to increase

Estimated percent of revenue from Alliances percent of respondents



Expected frequency of alliances over next 5 years percent of respondents



The Advent of Distributed Development

Source: McKinsey Pharmaceutical and Biotechnology Alliances Survey

THE CHALLENGES ASSOCIATED WITH DISTRIBUTED DEVELOPMENT

"firms rarely fail because of an inability to master a new field of technology, but because they do not succeed in managing the firm's systems of coordination and control to the nature of the available technological opportunities"

– K. Pavitt

J Mittra, "Life Science Innovation and the Restructuring of the Pharmaceutical Industry: Merger, Acquisition and Strategic Alliance
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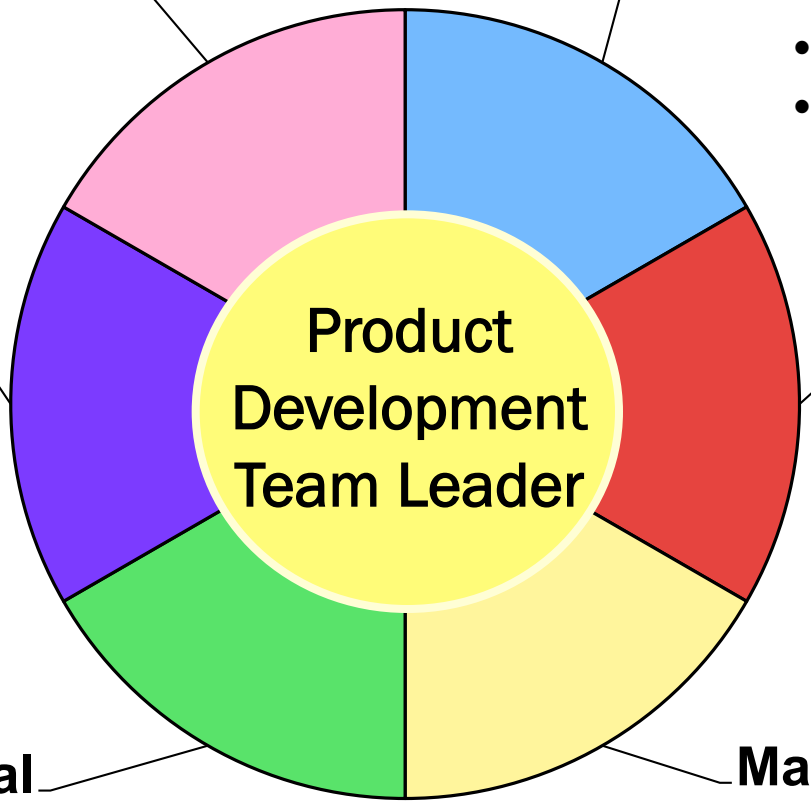
TRADITIONAL PRODUCT DEVELOPMENT TEAM



Project Management

- Project Planning
- Finance

Clinical

- Clinical Research
- Biostats
- Clinical Pharmacology
- Safety

CM&C

- Analytical
- Engineering
- Formulation
- Manufacturing
- Supply Chain
- Process Chemistry
- Preformulation
- Quality

Regulatory

- Operations
- Device
- Drug

Nonclinical

- Toxicology
- Biology
- Pharmacology

Marketing

- Market Research
- NPP
- Reimbursement

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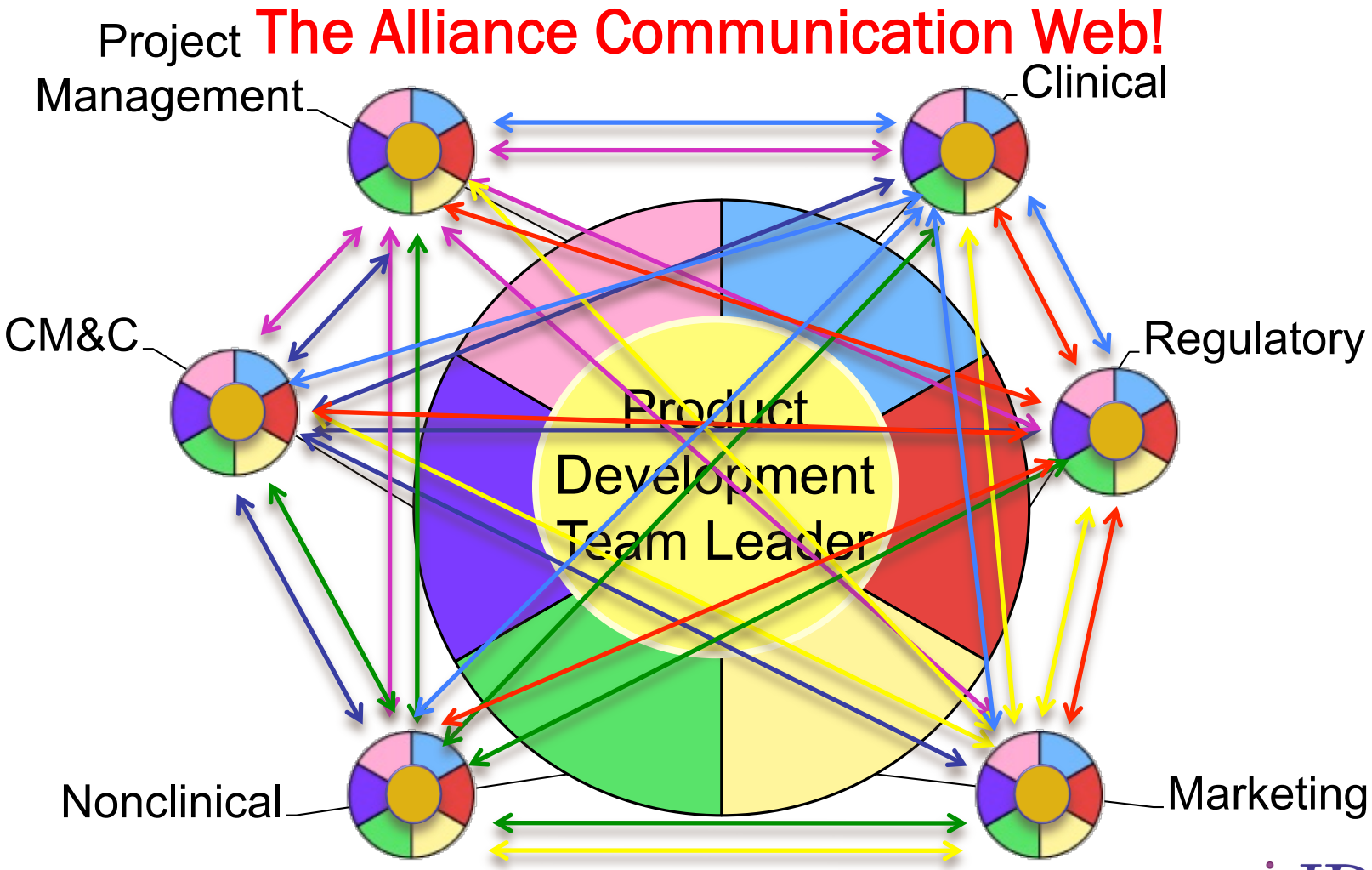
VIRTUAL DEVELOPMENT MODEL



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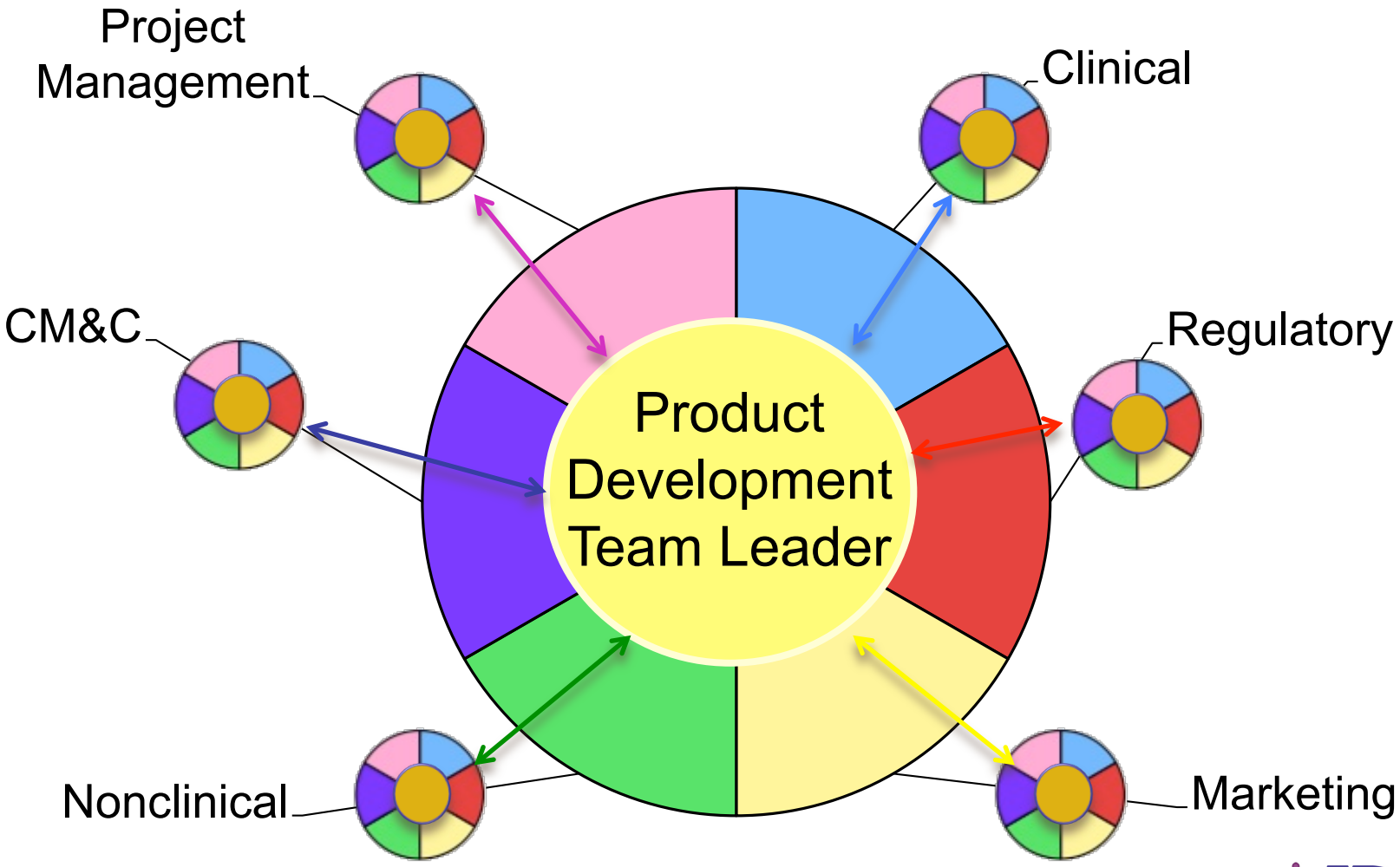
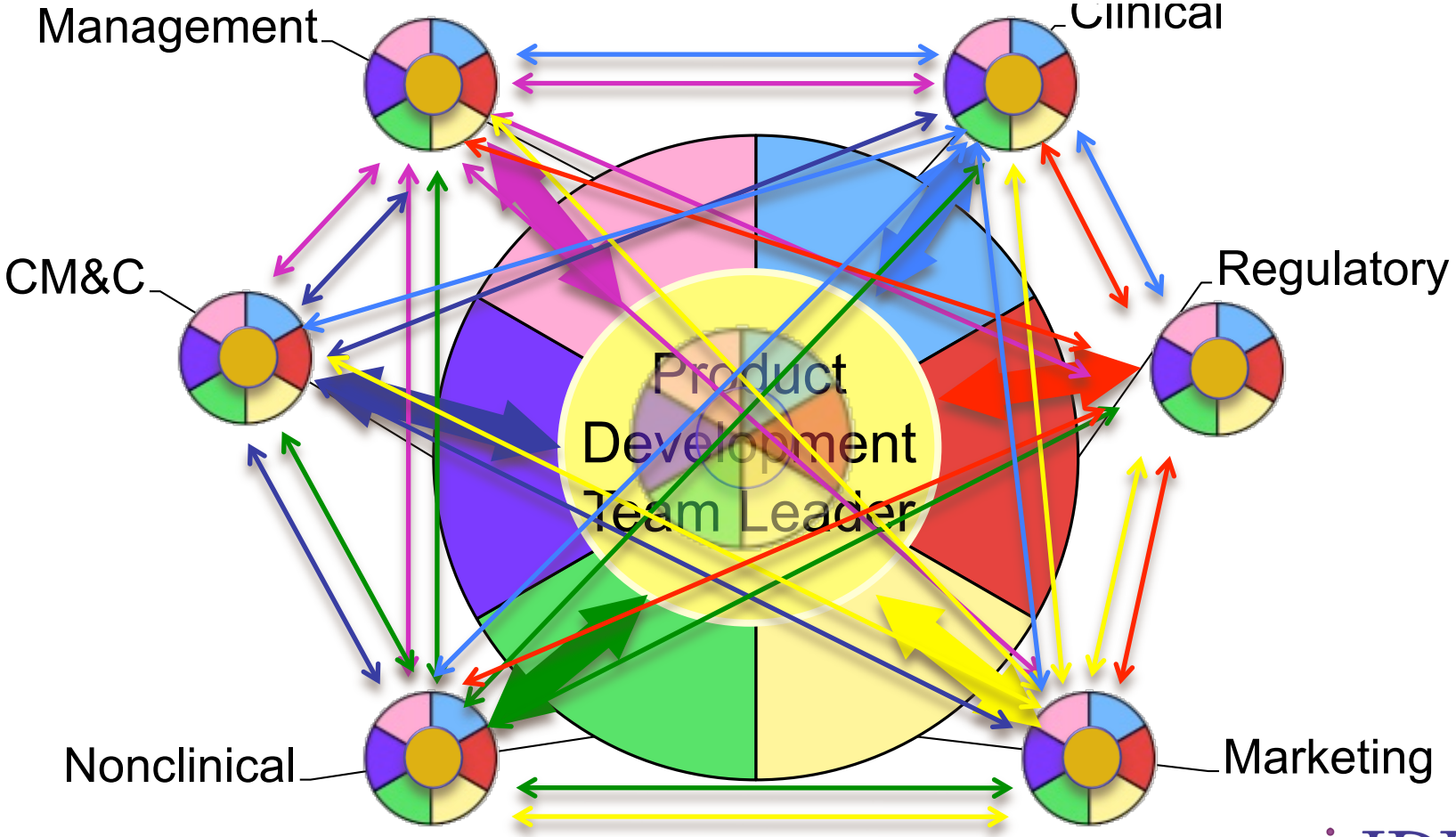


VIRTUAL DEVELOPMENT MODEL

The Alliance Communication Pressure Cooker!



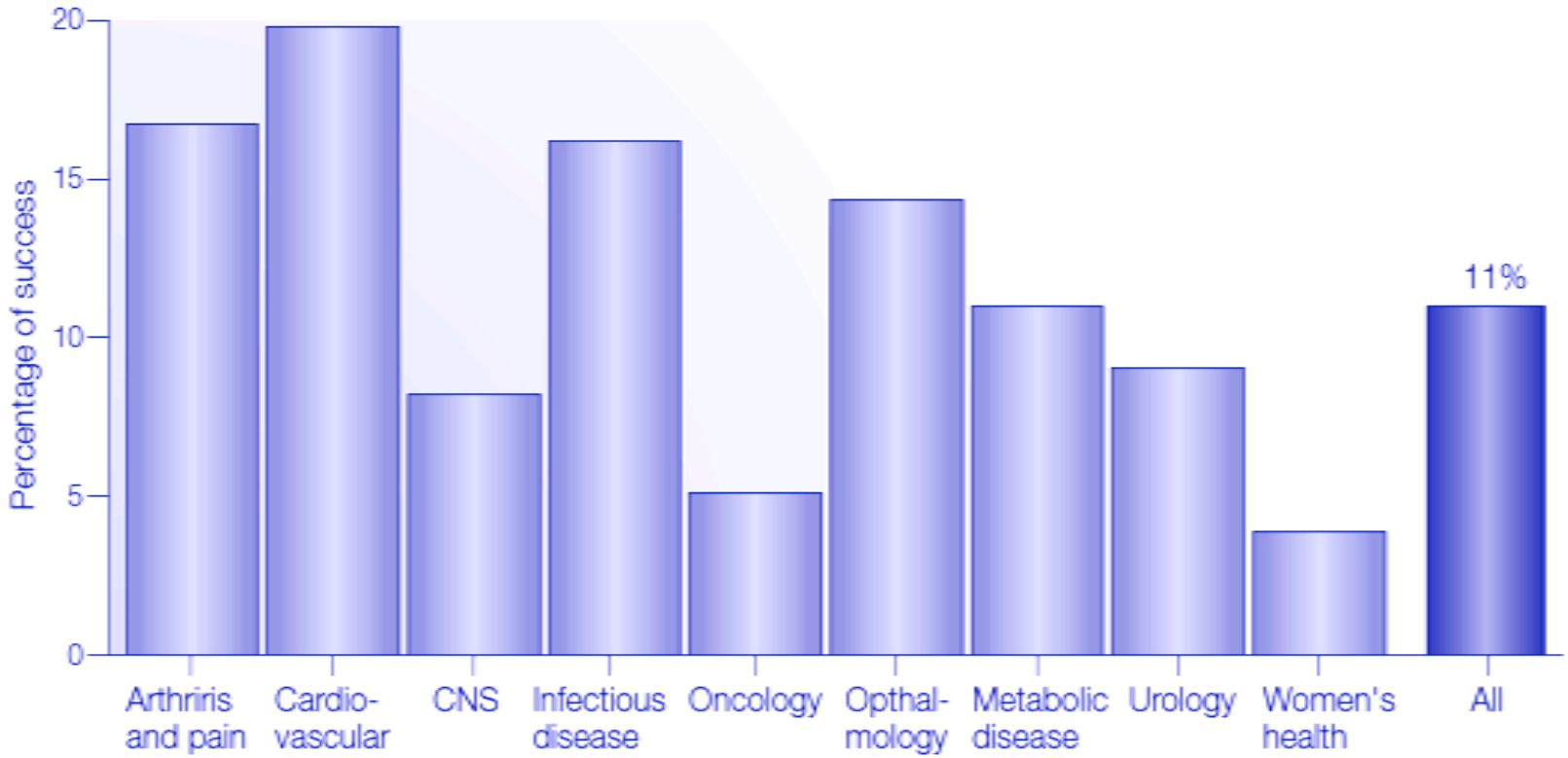
KEY LEARNINGS: THE WAY WE DO DEVELOPMENT IS CHANGING

- In-licensing from small biotech and pharma companies allows large pharma to "cherry pick" their molecules
  - Timing: After POC is established to reduce development risk
- Reduce CMC effort until after POC is established
  - "Fast to Fail" approaches reduce up front investment and missed opportunity costs
- Outsource technical expertise and capabilities
  - Utilize external CROs and CDMOs and distributed development approaches instead of internal resources and integrated development approaches
  - Successful alliances require elevated levels of program management (collaboration and communication) and an understanding of the external technology

WHY DO DRUGS FAIL?

Evaluating the Common Failure Modes and the Science Needed

SUCCESS RATES BY THERAPEUTIC AREA: FROM FIM TO REGISTRATION



I. Kola, J. Landis; "Can the Pharmaceutical Industry Reduce Attrition Rates?", Nature Review; Drug Discovery, Aug 2004, pg. 711.
Data provided by Datamonitor in the Pharmaceutical Benchmarking Study

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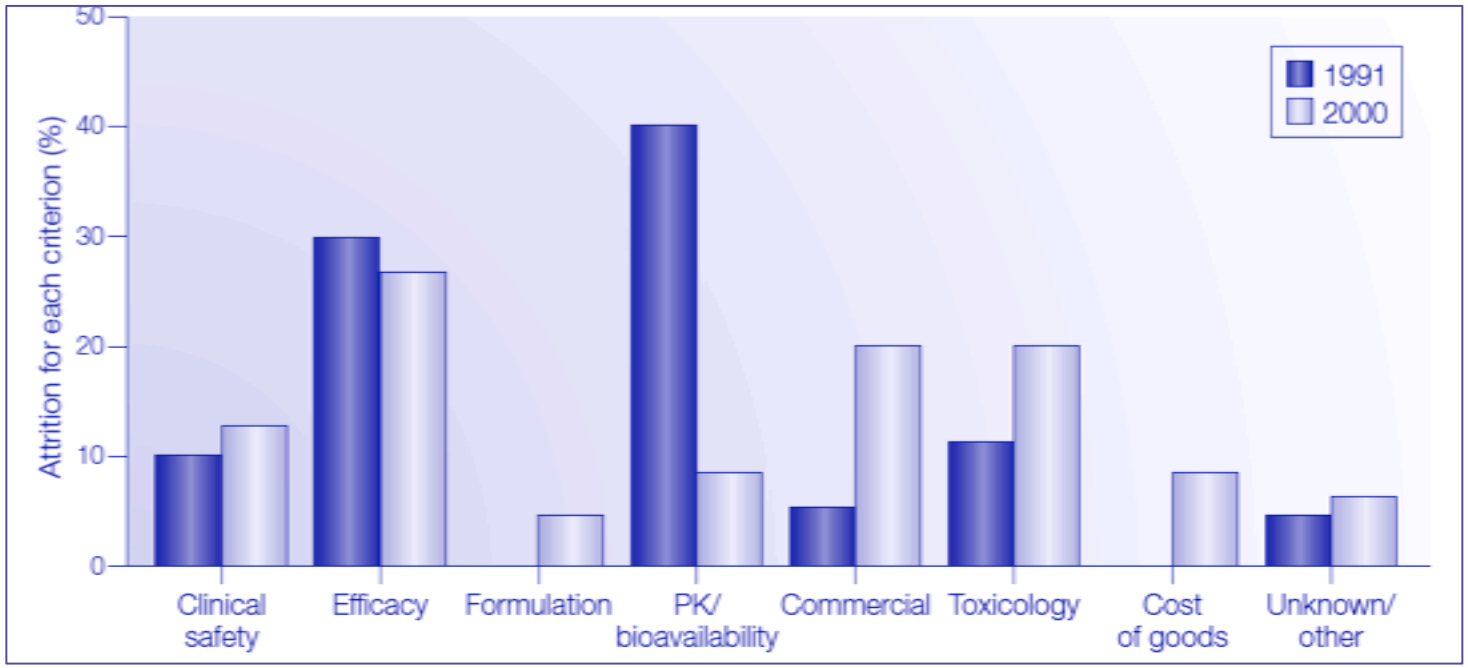
CAUSES FOR PHARMA PRODUCT ATTRITION: 1991 - 2000



- Currently highest attrition is due to lack of efficacy, followed by toxicology and commercial issues
- Attrition due to Formulation/CMC is low
- Lesson: cost of goods and commercial strategies need to be well thought out early on. Must be able to differentiate the commercial product.

I. Kola, J. Landis; "Can the Pharmaceutical Industry Reduce Attrition Rates?", Nature Review; Drug Discovery, Aug 2004, pg. 711.

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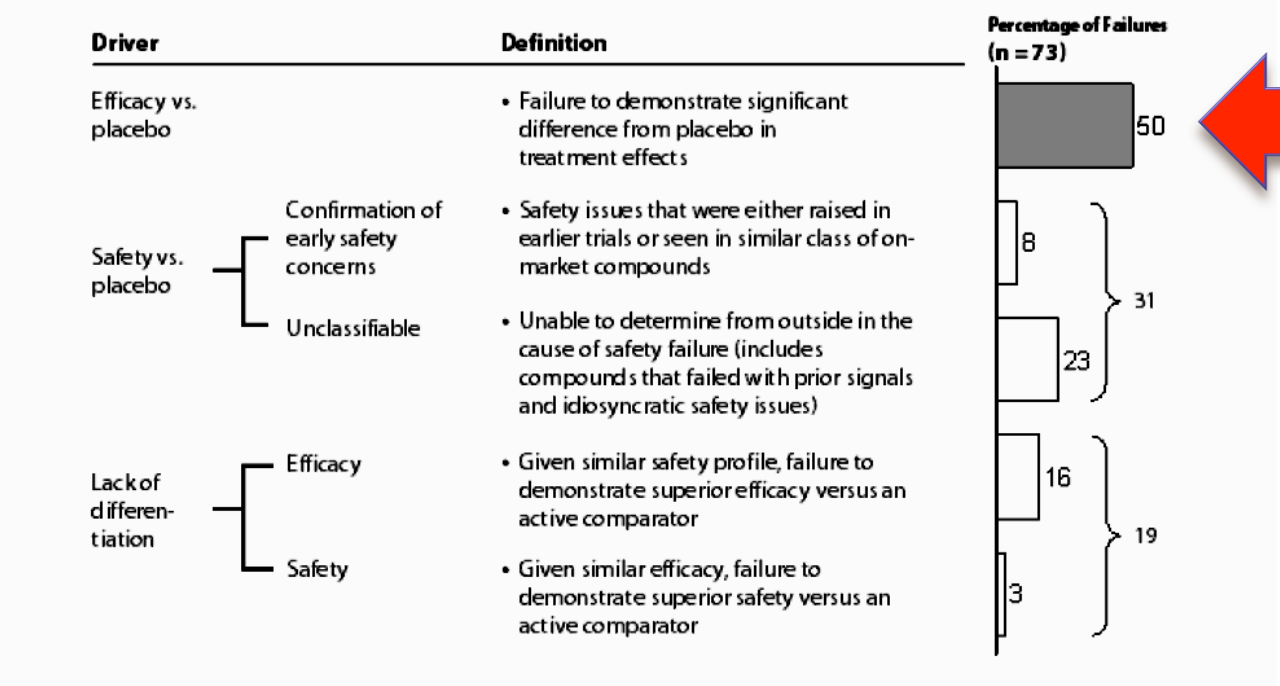
ROOT CAUSE OF 50% PHASE III CLINICAL TRIAL FAILURES RATES



- Reasons for failures:
  - *Lack of objective trial endpoints*
  - *Novel mechanism of action*
- If both are combined: results in a 70% failure rate compared to 25% for drugs with validated mechanisms and objective endpoints
- Lesson: Make the tough decisions based on well-designed Phase 2 studies

T Elias, et al., "Why products fail in Phase III," In Vivo, Apr 2006

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LACK OF EFFICACY IS NOT A NEW EVENT FOR MARKETED PRODUCTS

	Efficacy rate (%)
Alzheimer's:	30
Analgesics (Cox-2):	80
Asthma:	60
Cardiac Arrhythmias:	60
Depression (SSRI):	62
Diabetes:	57
Hepatitis C (HCV):	47
Incontinence:	40
Migraine (acute):	52
Migraine (prophylaxis)	50
Oncology:	25
Rheumatoid arthritis	50
Schizophrenia:	60

"Vast majority of drugs (>90%) only work on 30-50% of patients."*

*Dr. Allen Roses, VP Genetics, GSK, Dec 2003
http://www.independent.co.uk/news/science/glaxo-chief-our-drugs-do-not-work-on-most-patients-575942.html

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KEY LEARNINGS: FAILURES ARE MAINLY DUE TO LACK OF EFFICACY

- Compounds with novel mechanisms and/or difficult clinical endpoints/biomarkers carry higher risks of failure
- What about CMC issues:
  - Can lack of efficacy be linked to formulation design and/or product performance?
    - YES!
  - Are there examples of products that have been recalled, never launched, or simply pulled from the market due to technical design issues?
    - YES!
  - Can potential Phase 3 failures be mitigated during POC?
    - YES!

CONCLUSIONS: DEVELOPMENT STRATEGIES, POC, SCIENCE, AND THE PATIENT

- Product development strategies to increase productivity only work when the path is understood and the science is good
  - Determine "fast to fail" versus "fast to market" approach early on
  - Distributed development or integrated development?
    - Collaboration and relationship building = PARTNERING instead of contract development and manufacturing
    - Clarity of roles and responsibilities and great project management are essential to success

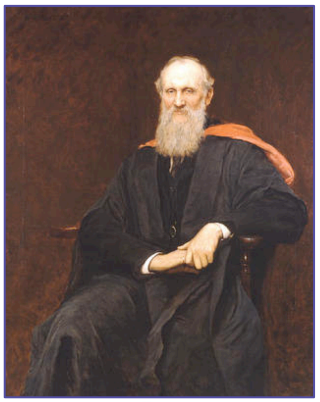
- Well-designed POC studies add value to the product throughout the development cycle
  - Conduct POC studies using the right science in support of the longer term product goal/vision
    - Target product profile will evolve with the product development
  - Make tough decisions early – well-designed Phase 2 studies
- Understand the technology and the science required to differentiate the product
  - Applicable to both internal *and* external development strategies
- Design products with an understanding of how the patient will interact with them

GOALS FOR THE WEEK

1. Identify the pros and cons of integrated *versus* distributed product development approaches
2. Learn how to incorporate good science in a distributed development model
3. Identify development risks and mitigation approaches best suited for POC studies
4. Determine what new skill sets are needed in order to be successful in distributed POC approaches
5. Determine how these strategies can be utilized to add value throughout the product development cycle

"I often say that when you can measure what you are speaking about, and express it in numbers, you know something about it; but when you cannot measure it, when you cannot express it in numbers, your knowledge is of a meagre and unsatisfactory kind; it may be the beginning of knowledge, but you have scarcely in your thoughts advanced to the state of Science, whatever the matter may be."

Lord Kelvin, 1883



http://www.atmos.washington.edu/~robwood/teaching/451/Lord_Kelvin_quote.pdf

THANK YOU