New Ecosystems for Innovation – Networked R&D

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February 11, 2013

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Pharma's Productivity Problem

SPECTRUM A Service

Discovery and Innovation: Technologies, Strate

Barbara M. Bolten, M.S., M.B.A., Senior Program Manage

Rethinking Pharmaceutical R&D: Will New Strategies Yield a Pipeline

Barbara M. Bolten, M.S., M.B.A.

Decision Resources

"Pharmaceutical companies must rapidly reform R&D to meet pressing challenges facing the industry. However, restructuring and shrinking R&D units is not enough to increase R&D productivity: companies must identify the right targets and efficiently implement new technology to discover novel, innovative drugs."

Morgan Stanley

February 5, 2010

Industry View
Attractive

Pharmaceuticals

Research shrinkage. Even faster than we envisaged

Quick Comment – Impact on our views: Recent presentations at FY09 results by GSK and AZN support our recent industry thesis anticipating a much-accelerated shrinkage of significant parts of the small molecule research infrastructure, we believe. Given GSK and AZN comments, we expect Sanofi Aventis to outline a similar strategy at their results next week. We reiterate our thesis that small molecule

Morgan Stanley

January 20, 2010

Industry View
Attractive

Pharmaceuticals

Exit Research and Create Value

Still significant value in Pharma – we see material upside to ROIC, earnings and multiples as Pharma withdraws from most internal small molecule research and reallocates capital to in-licensing and other non-pharma assets. Worsening generic pressure

ANALYSIS

Lessons from 60 years of pharmaceutical innovation

nvestment in pharmaceutical research and development
proved by the US Food and Drug Administration (FDA)
s conundrum, this article investigates the record of
ysing data on the companies that introduced the
pproved by the FDA since 1950. This analysis shows that
eutical companies in this period has essentially been
e attempts to increase it. This suggests that, contrary to
output is not depressed, but may simply reflect the
L The implications of these findings and options to
aceutical industry are discussed.

REUTERS

Special Report: Big Pharma's stalled R&D machine

Wed, Jun 16 2010

By Ben Hirschler and Kate Kelland

LONDON (Reuters) - At just 28, Duncan Casey has already been from the university science bench to the world of Big Pharma research and back again. Now working in an Imperial College lab tucked behind London's famous Science Museum, he has no illusions about the prospects for researchers in the pharmaceutical industry.

"The unit I used to work in -- GlaxoSmithKline's place in Harlow -- has been closed down now," says Casey, dressed in signature protective goggles and white coat as he works on synthetic chemistry. "It used to be a job for life. Now it's a job until the next restructuring."

Across the western world, Big Pharma is cutting back on the number of scientists it employs in its labs and the money it spends on research and development. The hunt for new drugs continues, but the men and women in white coats -- traditionally viewed as the lifeblood of the industry -- are not as untouchable as they once were.

Pfizer

February 2010; doi:10.1038/nrd3078

ANALYSIS

How to improve R&D productivity: the pharmaceutical industry's grand challenge

Steven M. Paul, Daniel S. Mytelka, Christopher T. Dunwiddie, Charles C. Persinger, Bernard H. Munos, Stacy R. Lindborg and Aaron L. Schacht

Abstract | The pharmaceutical industry is under growing pressure from a range of environmental issues, including major losses of revenue owing to patent expirations,

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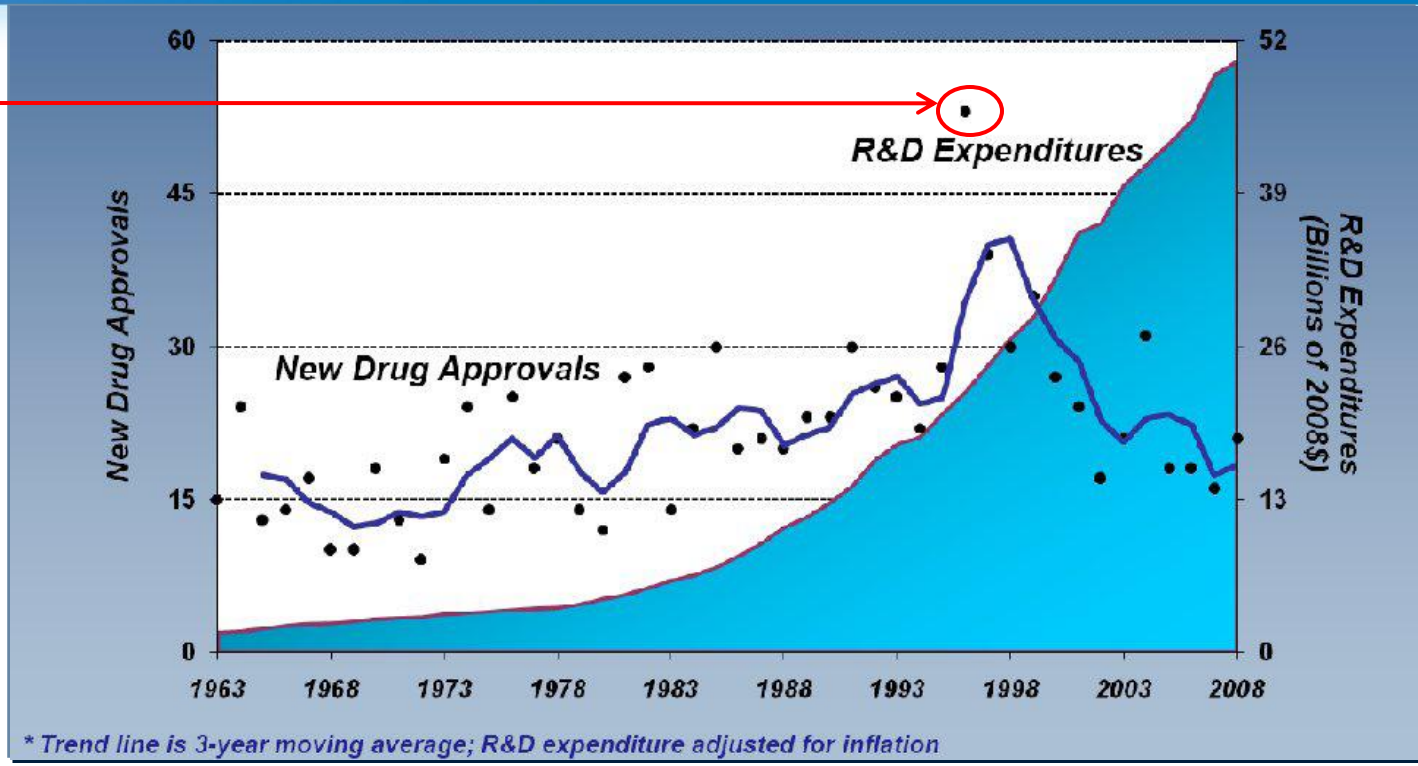
What got us here #1? R&D output hasn't really changed…….it just costs a lot more

1996 was an anomaly and peak was due to PDUFA backlog

- **Ave. approvals per year remains steady at 18-25**
- ***NUMBER INCREASED TO ~30 IN 2012 POINTING TO TURNING POINT***



- ✓ **Escalating costs and inefficiencies contribute to industry productivity problem; strategies focused on operational efficiency**
- ✓ **Focus on complex diseases; biological pathways undefined biological**
- ✓ **Increasing Regulatory and Payor hurdles**

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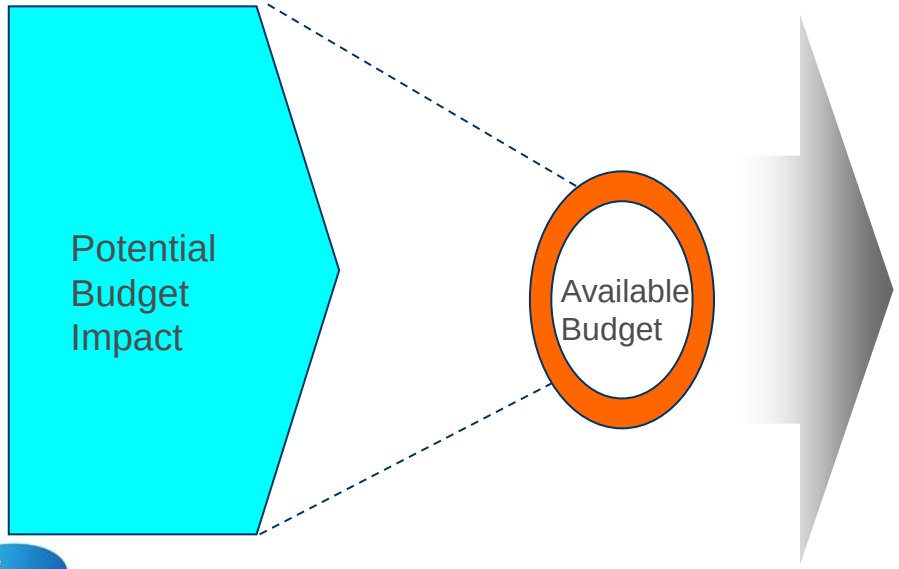
What got us here #2? Payer Perspective on New Product Value

In addition to the usual considerations:

1. Is it safe? **(safety)**
2. Does it work? **(efficacy)**
3. Is it good quality? **(quality)**

The new questions that are being asked include:



4. Is it worth it? **(value for money)**
5. Can we afford it? **(budget impact)**
6. Is this disease a priority? **(political sensitivity)**

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What got us here #3? Inflexible Approaches to External Partnerships

- Standard licenses and sponsored research agreements
- Pharma concern re controlling all aspects of products
  - Emphasis on owning as much IP as possible, and
  - Directing prosecution of related IP
- Attempts to limit publication/presentation of results
  - Loss of patent rights due to premature disclosure
  - Industry patents late; academics patent early
- Less emphasis on understanding disease biology & mechanisms of action
  - Belief that explosion in genomics info would lead to increased NMEs
- Not Invented Here syndrome
  - Perception/sometimes reality that non-pharma research less reliable
  - Led to “Valley of Death” for many academic discoveries

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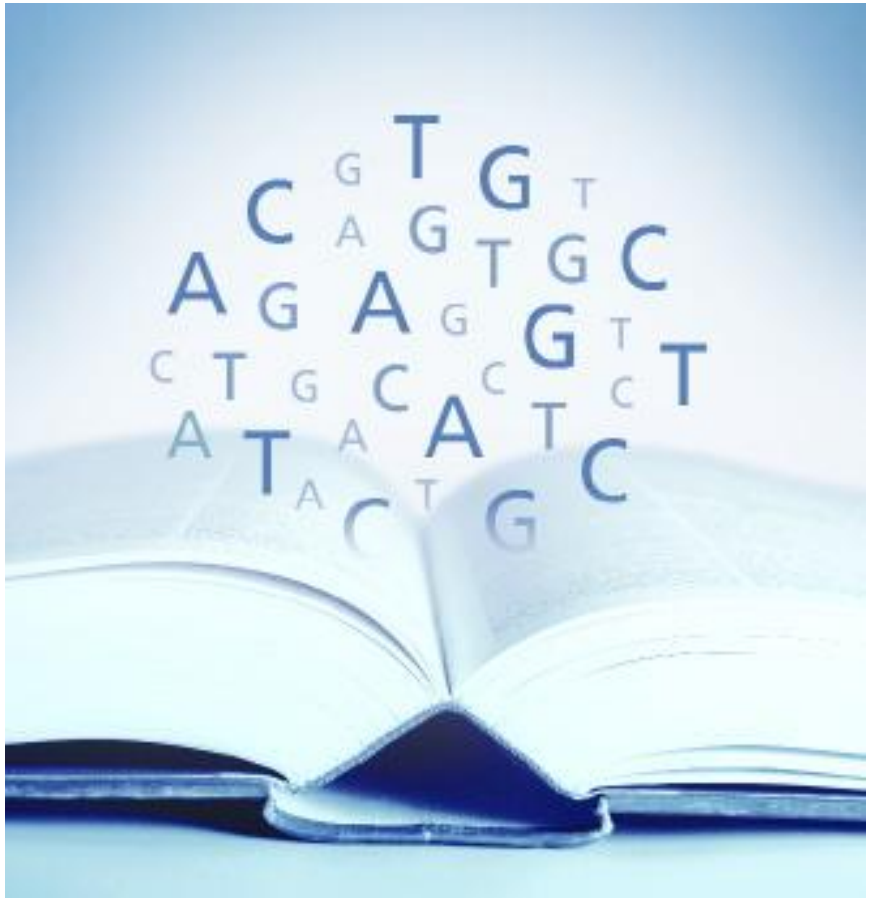
What Will Lead Us Out?

- Pre-competitive Consortia with Other Pharmas (E.G., Critical Path Institute)
- Shared Funding and Risk (E.G., CROs as VCs)
- Non-exclusivity for Research Tools (E.G., Ablexis Consortium)



- Joint Ventures with Other Pharma –(E.G., Viiv)
- Pooling of Research Knowledge –(E.G., BBMRI)
- Clinical Trial Transparency re. HCP Payments, Results, Etc.

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Opening the Door – "Pre-Competitive" Consortia

- **What are they?**
  - projects in which R&D activities will be conducted by several parties
  - Output shared by all parties to further advance their own R&D efforts
- **Who participates?**
  - Can be any combinations of parties from industry, academia and gov't
  - varying responsibilities, obligations, and funding commitments
- **What are the benefits?**
  - Develop collective research knowledge ('wisdom of the crowd')
  - shared funding and risk
  - robust research plans
- **Are they really pre-competitive?**

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Pre-Competitive Consortia – Recent Examples

TransCelerate BioPharma

- formation of non-profit entity by 10 leading biopharma companies
- goal to solve common drug development challenges to improve the quality of clinical studies

Target Validation Consortium

- NIH-led effort to identify and validate the in vivo relevance of potential therapeutic targets
- Oncology, Alzheimer's Disease, Schizophrenia, Type II diabetes, and/or immune-mediated disorders.

The Biomarkers Consortium

- public-private biomedical research partnership managed by the NIH
- attempting to discover, develop, and qualify biological markers (biomarkers) to support new drug development, preventive medicine, and medical diagnostics
- focus on four disease areas (oncology, immunity & inflammation, metabolic disorders and neuroscience)

Innovative Medicines Initiative (IMI)

- world's largest public-private partnership in drug research
- linking industry, academia, regulators and patients' organizations with work groups
- activities include finding new biomarkers, educating researchers and using electronic health records for research purposes

Alzheimer's Disease Neuroimaging Initiative (ADNI)

- originally funded by the NIH with contributions from industry, foundations and the UCSF
- designed to validate the use of biomarkers for AD clinical trials and diagnosis

Mass Life Sciences Center Neuroscience Consortium (MLSC)

- fund for pre-clinical neuroscience research at Massachusetts academic and research institutions work to identify and validate targets in the areas of AD, Multiple Sclerosis, neuropathic pain and Parkinson's Disease

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Navigating IP Issues in Consortia Agreements

- background (pre-existing) technology
- foreground (new) technology
- compensation for the use of technology
- downstream benefits
- IP disputes
- proprietary information
- material transfer
- patent prosecution logistics
- publication
- consider funding sources

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Other risks that must be addressed

- project execution and managing multiple participants
- ‘free rider’ problems
- potential joint and several liabilities
- potential violations of anti-trust regulations
- intellectual property issues
- shared decision-making
- misuse and disclosure of confidential information
- bad consortium participant behavior

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Top Ten List of Up Front Issues

1. Gain Early Alignment among Participants
2. Manage Antitrust Considerations
3. Gain Clarity Around Joining/Exiting
4. Develop a Robust Research Plan
5. Determine the Participants' Contributions
6. Clearly Articulate Governance Requirements
7. Discuss Confidentiality and IP Concerns
8. Address Data Privacy & Use, and a Publication Strategy
9. Spell-out Termination and Exiting Rights/Obligations
10. Think About Liability, Dispute Resolution and Law

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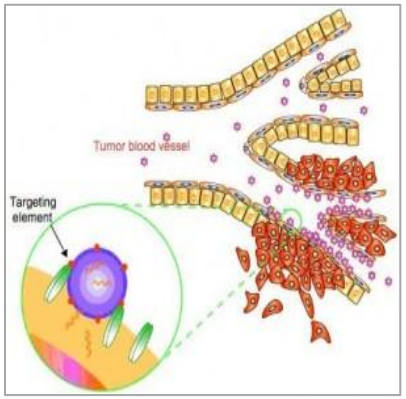
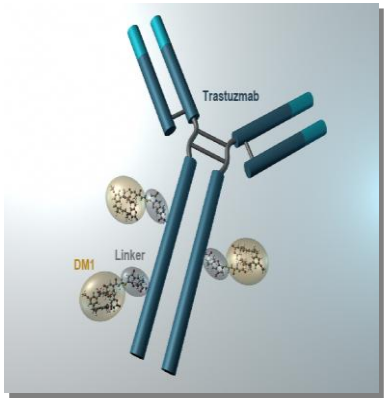
What will lead us out?
Precision Medicine Approaches

Right Target	Right Drug (or Combinations)	Right Patient
		
Genetic validation; Rare phenotypes	*Selective design and delivery; Combinations for complex diseases*	*Phenotyping and Genotyping*

***Precision Medicine** – an approach toward discovering & developing medicines*

***Personalized Medicine** – medical practice of tailoring treatment to individual characteristics of each patient*

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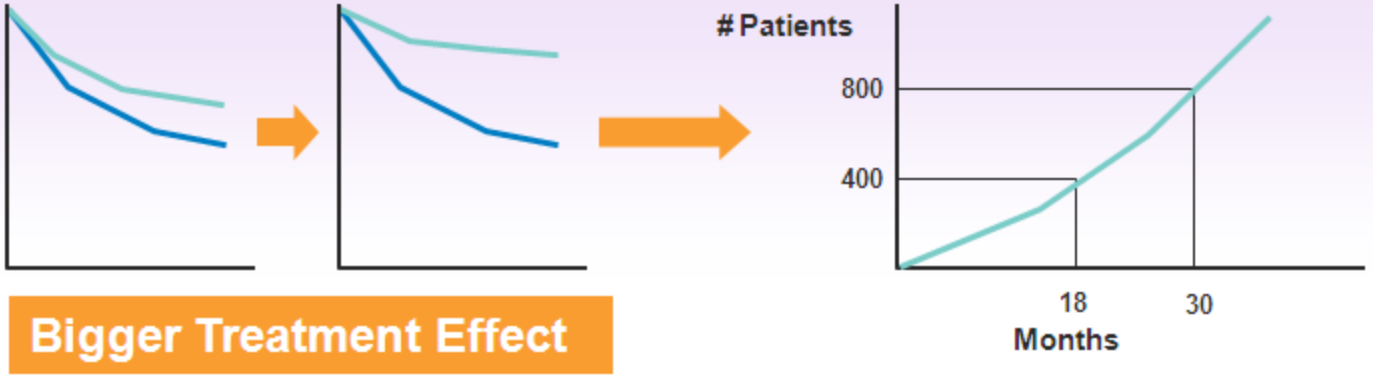
Precision Medicine – Value Proposition

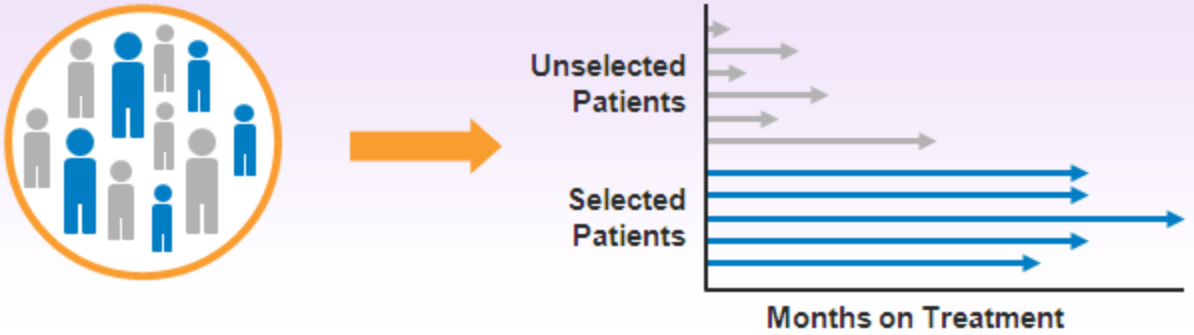
Clinical Development



Bigger Treatment Effect

Smaller Clinical Trials + Less Costly, Faster Trial Completion

Commercial Benefits



Patients Treated More Likely to Benefit

Longer Time on Treatment

Earlier Regulatory Submission + Earlier Launch

More Dramatic Effect in Treated Patients ➡ Value of Treatment Easier to Demonstrate to Payers

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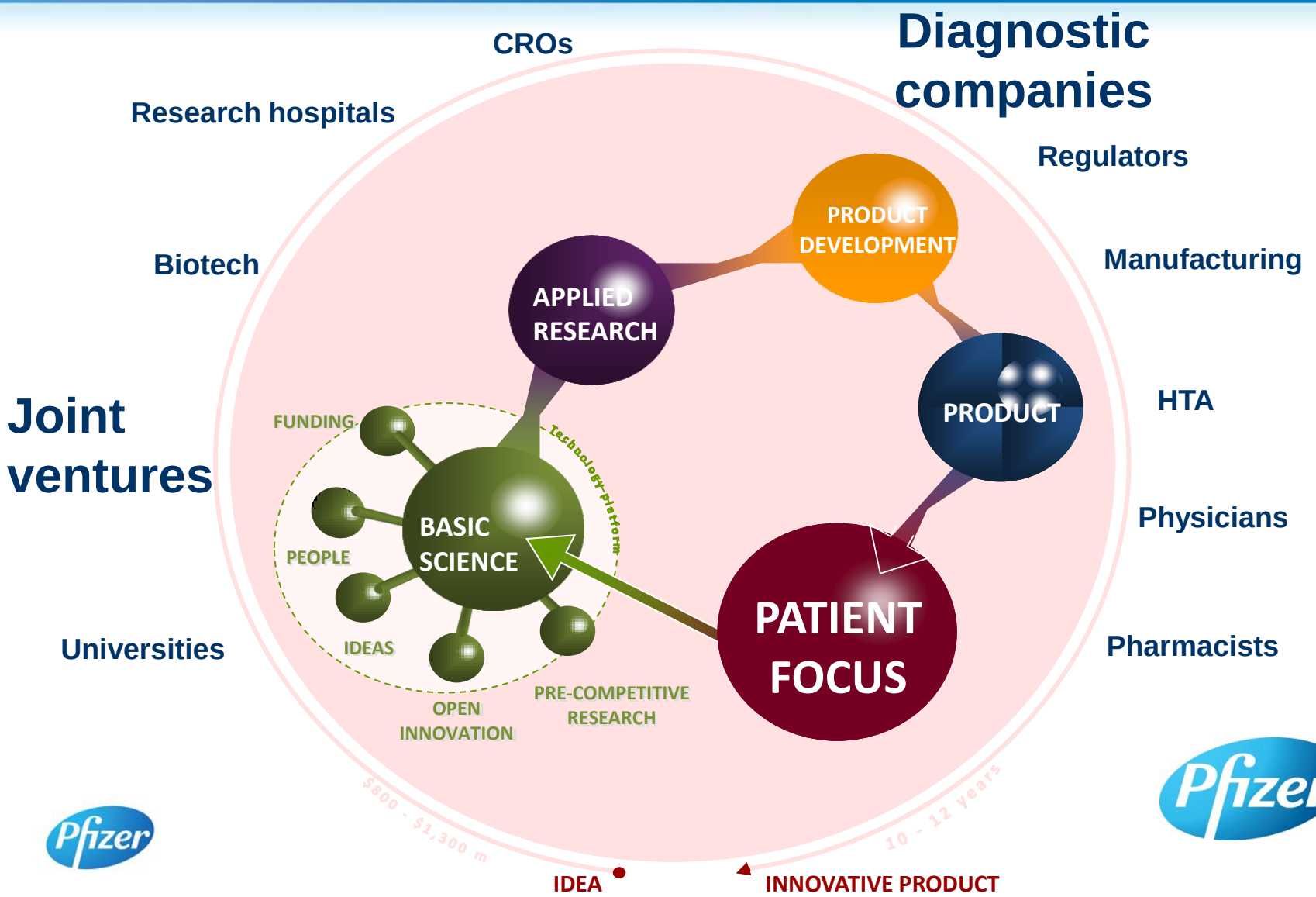
Diagnostics and Collaboration are critical to Precision Medicine



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Evolving Legal Landscape

PM Strategy	• Precision Medicine has the potential to increase R&D productivity, provided we follow best practices for clinical trials, IT services and companion diagnostic development
Privacy in PM	• The Privacy landscape is rapidly evolving, particularly in what is considered “identifiable” data. Unique opportunity, especially in Europe and the US, to help shape evolving laws to better support research needs
US Case Law is Quickly Evolving	• Based on recent court decisions, diagnostic patents will likely be harder to obtain – will need to narrowly tailor claims to avoid “pre-emption of natural law”
IP Access is Critical	• A critical consideration in a precision medicine program strategy is the ownership of diagnostic IP required to develop a companion diagnostic to ensure access to the new drug

–Pfizer Confidential Information

IP Landscape - Mayo and *Myriad*

- **In March 2012, in *Mayo vs. Prometheus*, the Supreme Court invalidated Prometheus' patent for methods of treating a patient by assessing the level of a drug metabolite.**
- **In 2013, the Supreme Court will decide *Ass'n for Molecular Pathology (AMP) vs. Myriad Genetics*, relating to identification and diagnostic use of two genes predictive of increased risk of breast and ovarian cancer.**
- **The sole question taken up by the Supreme Court in *Myriad* on *certiorari* is: "Are human genes patentable?"**
  - **The Supreme Court declined to review the Federal Circuit Court's decision that most of *Myriad's* diagnostic methods using those gene sequences were not patentable.**

Where does this leave the field of companion diagnostics? What is impact on Precision Medicine?

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What will lead us out? Novel Models of Collaboration and Open Innovation

▪Biopharmaceutical companies are evolving into more open, collaborative and distributed organizations

New Ecosystem of Networked Relationships:

- **Laboratories in innovation "hot-spots"**
  - PFE, NVS and GSK
  - Much recent movement by Pharma to Asia-Pacific corridors
- **Novel Open Source/Innovation Platforms**
  - Centers for Therapeutic Innovation
  - Lilly PD² and TargetD²
- **Inter-industry partnering**
  - Risk Sharing of Late Stage Development
  - Joint ventures, spin outs
- **Government collaborations**
  - AZN, PFE, Lilly collaboration with NIH re: New indications discovery
  - Genentech and NIH re: early diagnosis of Alzheimer's Disease
- **Venture capital investments**
  - Warp Drive Bio (Sanofi and Third Rock)
  - Lilly Mirror portfolio
  - MPM Capital SideCar Funds (NVS)
- **Patient Groups/NGOs**
  - Michael J. Fox Foundation

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What does Networked R&D look like?

	Enterprise R&D	Collaborative R&D	Networked R&D
Innovation sourcing	Internally focused	Internal focus plus some external collaborations	An innovation network that extends beyond the enterprise
Processes	Managed by functions	Managed by therapeutic areas	Managed by projects
Organization	Fixed functional *(Chemistry, toxicity, etc.)*	Fixed therapeutic areas *Plus supporting functions*	Flexible project teams *Plus select large-scale support functions*
Culture	"We are the world."	"We are part of the world."	"The world is our laboratory."
Investment criteria	Internal hurdles	Science driven internal hurdles	Science driven external comparative hurdles
Licensing	Traditional in- and out-licensing *Small function*	Empowered in-licensing *Large function*	Embedded in the organization *Small orchestrating function*
Mergers and aquisitions	Ingest and transform	Ingest and co-exist	Integrate into the network

Source: 2010 Biopartnering Survey. IBM Institute for Business Value and Silico Research.

Figure 6: **Biopharmaceutical R&D will become increasingly networked.**
By Stuart Henderson, Salima Lin, Heather Fraser, Per Lindell and Tiffany Yu

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New Approaches to Partnerships: Centers for Therapeutic Innovation (CTI)

Idea Generation

Academic Medical Center (AMC)

PIs

Ideas →

PIs capture idea in non-confidential pre-proposal and confidential proposal forms

Idea Adoption

Joint Steering Committee approval

PFE internal review

Projects →

Joint development of Statement of Work

Idea Execution

Centers for Therapeutic Innovation

CTI Head

AMC Physicians

AMC Scientists

CTI Lab Team

Work together on biology, screening of Pfizer library, antibody and protein generation to deliver Lead

Benefits :

- Additional ideas
- Broad IP provided by pioneer PIs from AMCs
- Access to pre-existing AMC materials
- Opportunity for other research groups for additional interface and progression
- Delivery of Candidate drugs
- Proof of mechanism
- Completion of First in Human studies

***Overall goal*: Identification of programs that can translate to hypothesis and mechanism in humans**

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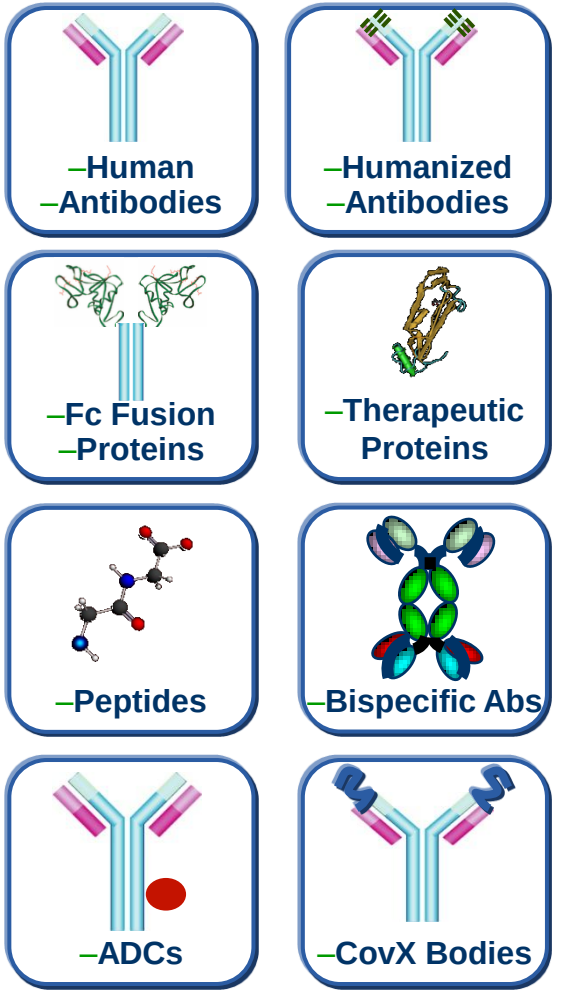
Core Elements of the CTI Model

- Focused on Biologics
- From Discovery to Phase I – POM
- Standard Form License Agreement
- Equity in Core Provisions (Publication, IP)
- Pre-negotiated Milestones; Royalty Range
- Post-doc Support Program; co-location
- Leverage Pfizer libraries, reagents and technology



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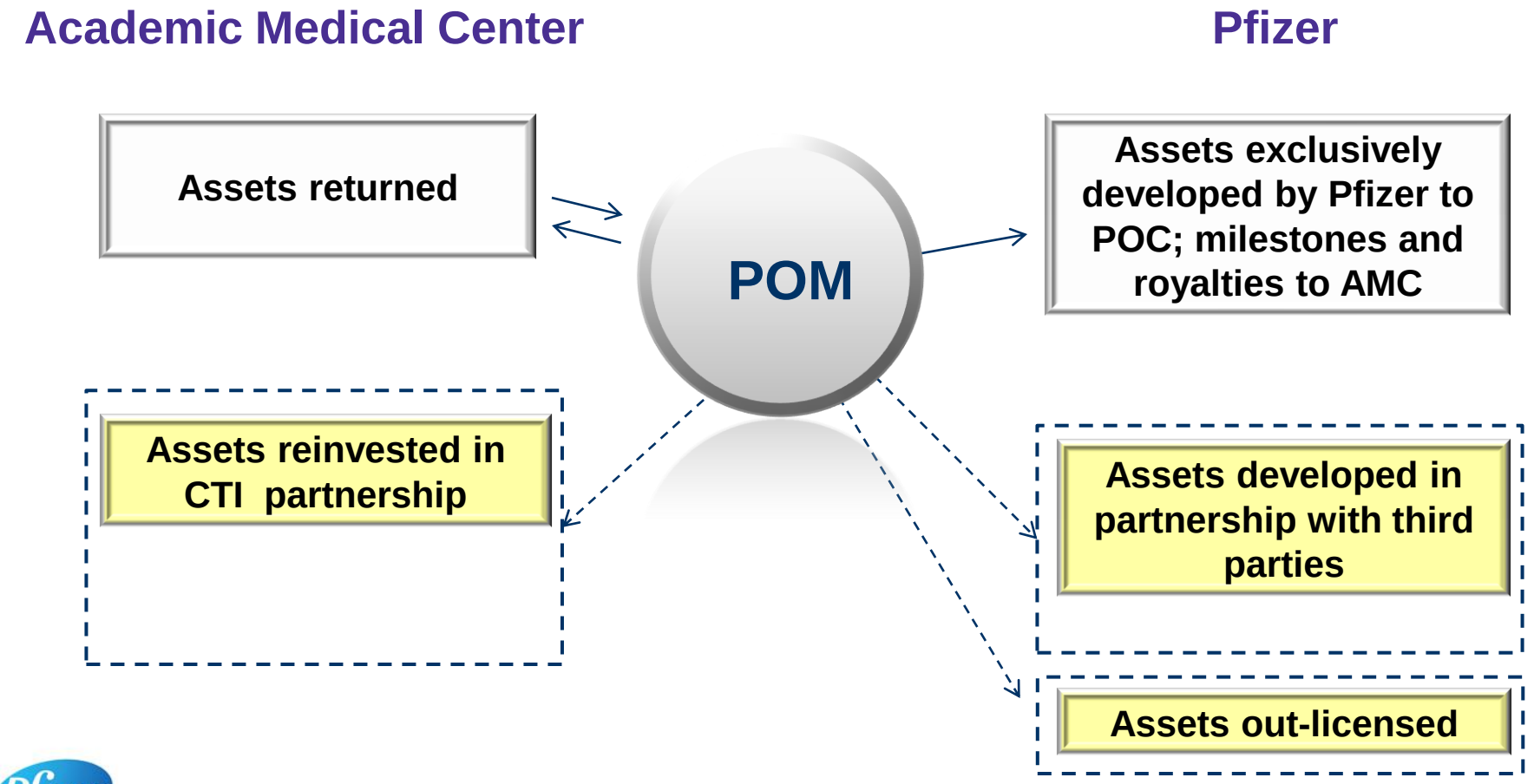
Centers for Therapeutic Innovation: Value Creation Possibilities

Various monetization scenarios



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NIH Principles Embedded in CTI Initiative

Principle	NIH	CTI
Respect the existing proprietary rights of each party (background IP)	✓	✓
Maintain the confidentiality of proprietary information	✓	✓
U.S. law governs inventorship	✓	✓
Each party owns the inventions made by its employees, including joint ownership if inventors of both parties are involved	✓	✓
Publication is encouraged, without revealing confidential information of the other party; opportunity to review and comment on manuscripts	✓	✓
Conduct only agreed studies (remedy for unauthorized use of materials)	✓	✓
Pre-negotiated license framework and royalty rate range	✓	✓
Retained right to grant not-for-profit institutions a royalty-free NEL for research use to sole AMC inventions subject to an exclusive license option	✓	✓

Pfizer

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Centers for Therapeutic Innovation – CTI Network

CTI-Boston

Beth Israel Deaconess Medical Center

Children's Hospital Boston

BRIGHAM AND WOMEN'S HOSPITAL

MASSACHUSETTS GENERAL HOSPITAL

Tufts Medical Center

BOSTON UNIVERSITY

Harvard University

Tufts UNIVERSITY

UMASS

CTI-New York

ALBERT EINSTEIN COLLEGE OF MEDICINE of Yeshiva University

The Rockefeller University 1901

MOUNT SINAI SCHOOL OF MEDICINE

COLUMBIA UNIVERSITY

CTI-California

UCSF University of California San Francisco

UCSD

Sanford Burnham Medical Research Institute

New Approaches To Partnerships: From St. Louis to Washington DC

Indications Discovery unit

- **Formed to discover new indications for existing compounds**
- **Relocated adjacent to Wash U Med School**

Wash U Collaboration

- **Joint WU / PFE proposals**
- **IP ownership follows inventorship**
- **Pfizer has perpetual research license; option to exclusive commercial license**
- **Pfizer pays patent costs only if option exercised**
- **If no agreement on license, 1-year ROFR**

NCATs Collaboration

- **Department within NIH ncats.nih.gov**
- **Catalyze new methods and technologies to speed and improve development and testing of diagnostics and therapeutics**

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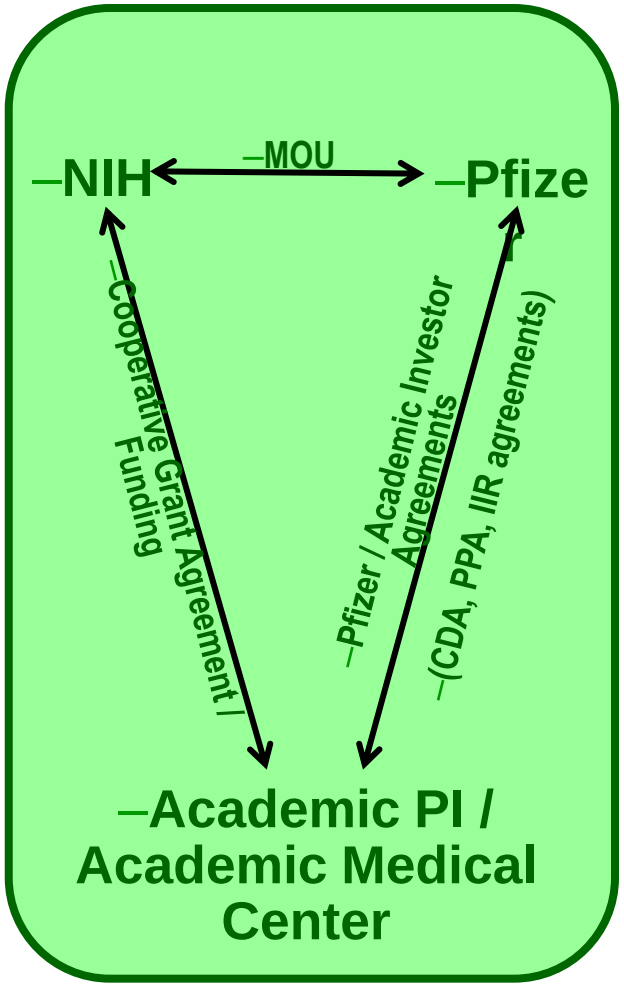
New Paradigm – Gov't-Academia-Industry "Drug Rescue" Partnership

Key Elements of Program:

- **Virtual Med Cabinet**
  - Ca. 25 shelved compounds
  - All Phase I or later
  - LOE varies
- **Pfizer-NIH MOU sets expectations for the program**
  - NIH initially screens grant applicants
  - PFE decides whether to participate
- **Pfizer-AMC agreements**
  - Collaborative research agreement
  - CDA
  - IIR Agreement
- **NIH-AMC Grant Agreement**



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Putting it Together – The MOU

- **Five-year term**
- **NIH Activities**
  - Proposal and Application Processes
  - Peer Reviews
  - Funding
- **Pfizer Activities**
  - CRA
  - Materials/Technology Transfer
  - Collaboration in Preparation of Full Proposal
  - Potentially Other Research Support

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Putting it Together – The Collaborative Research Agreement

- **Many standard CRA terms: Steering Committee, Confidentiality, MTA**
- **Inventions**
  - Each party owns its background IP
  - Foreground IP ownership follows inventorship
- **Patents**
  - AMC Files on AMC's inventions and consults with PFE on countries of filing
  - PFE right to file on Joint Inventions
- **Licenses**
  - Perpetual cross-research licenses on foreground IP
  - PFE has exclusive option on exclusive commercial license
- **Either party may terminate at will**

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Status

- **MOU was executed May 1, 2012**
- **Seven other Pharmas**
  Used MOU which Pfizer negotiated
- **Timeline:**
  Awards Made: May 2013
  Contingent upon CRA execution
  Projects conducted: 2-3 years

New Partnerships - Private Foundations / Patient Advocacy Organizations

- Private Foundations and Patient Advocacy groups increasing moving into drug development space
- Singular focus on bringing medicines to market
- The "Value Equation" – when done correctly, a win-win relationship is created:

  Value Creation for the Foundation/Advocacy Organization :

  - Access to vast technical and scientific resources
  - Ability to partner with entity that has rich drug development expertise and established clinical development networks
  - Ability to serve as a source of inspiration/encouragement to scientists

  - Value Creation for the Pharmaceutical Partner:
    - Financial Risk Sharing
    - Introductions to key scientific advisors and opinion leaders
    - When appropriate, access to established and focused patient networks

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The Path Forward – Networked R&D

- **Development of methodologies that allow for safe sharing of data between health care providers, industry and regulatory authorities**
- **Strong collaborative relationships between government agencies, industry and academia to drive application of science to drug discovery**
- **Flexible policies and practices that enable collaboration and leverage value of contributors**
  - E.g. IP policies, publications, tax free bond status, etc.
- **Advancement of regulatory and legislative policy agendas that encourages innovation, protects patients, and accelerates new medicines to market**
  - Uncertainty and ambiguity creates barriers to innovation and risk taking

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The next evolution of model?

Motion Picture Industry:

A TimeWarner Co. film

produced by

New Line Cinema

in association with

Castle Rock Entertainment

Pharmaceutical Industry:

A Pfizer pharmaceutical compound

developed in association with

Private Foundation

discovered together with

Harvard and UCSF

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