R&D Productivity

SPECTRUM
Discovery and Innovation: Technologies, Strategies
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Rethinking Pharmaceutical R&D: Will New Strategies Yield a Pipeline
Barbara M. Bolton, M.S., M.B.A.

"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."

Pharmaceuticals
Research shrinkage. Even faster than we envisaged
February 5, 2010

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 lessons from 60 years of pharmaceutical innovation

REUTERS
Special Report: Big Pharma's stalled R&D machine
Wed, Jun 15 2011
By Ben Hirschler and Kate Kelland

LONDON (Reuters) - At just 26, 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 Harrow — 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.

Morgan Stanley
January 20, 2010
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

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

Steven M. Paul, Daniel S. Mytelka, Christopher T. Dunwald, Charles C. Persinger, Bernard H. Munos, Stacy R. Lundberg 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,
R&D Output Across The Industry Is Flat, Despite Increasing Investment Over The Last 20 Years

Source: Pharmaceutical Research and Manufacturers of America, PhRMA Annual Membership Survey, 2008; CDER
Cost To Launch Is Driven By Attrition

Cost Of One Program To Market

Portfolio Cost Of One Program, Including Attrited Projects

>$100 Million

Single Program

>$1 Billion

Attrited Programs
Evolution of the R&D Organization

2003-2007

21 sites in 10 countries
14 layers from CEO to bench scientists
56 committees
Complex, numerous “activity” & CAN output goals
Numerous Research projects
  - Multiple portfolio review processes
  - 38 Disease Areas
Large Research groups up to 1000 scientists responsible only to First-in-Human
4 levels of review, approval for decisions
No formal external science advisory body
>90% science conducted in house

2010

4 major R&D sites
8 or fewer layers from CEO to bench scientists
11 committees
New value-based goals that rewards positive POC
Focus on Research projects with strong human disease correlation
  - In-depth portfolio review prioritization
  - 29 Disease Areas
Smaller Research Groups driving to POC
Fully empowered Chief Scientific Officers
Six Scientific Advisory Panels
30% of science conducted externally
Utilizing Independent Research Units Conveys Significant Benefits

- Clarity of objectives
- Colleagues identify and connect with their projects
- Small size allows robust interactions and timely decisions
- Entrepreneurial spirit
- Concentration of expertise to share best practices and problem solve
- Strategy to optimize all aspects of the unit’s operations
  - Focus on identifying new opportunities and emerging Science and Technology
  - Deep understanding of the options at each stage of development
- Specific funding earmarked for the unit’s needs

Focus  Alignment  Nimbleness
Smaller Research Units Headed By An Accountable CSO

Enabled By

- Pain
- CV & Metabolic
- Inflammation
- Oncology
- Neuroscience
- Antivirals
- Antibacterials
- Allergy & Respiratory
- Genitourinary
- Vaccines
- Regenerative Medicine
- Indications Discovery
- Medicinal Chemistry
- Clinical
- Biotherapeutics
- Comparative Medicine
- *PDM
- Centers of Emphasis
- Research Portfolio

*Pharmacokinetics, Pharmacodynamics & Metabolism
New Operating Model

Nine Diverse Businesses Supported by an Integrated Research & Development Organization

Biopharmaceutical Businesses
- Primary Care
- Specialty Care
- Oncology
- Established Products
- Emerging Markets

Diversified Businesses
- Animal Health
- Capsugel
- Consumer Healthcare
- Nutrition

Worldwide Research & Development Including: PharmaTherapeutics, BioTherapeutics, Vaccines and Biotech units

Business Units Including: Development, Medical, Sales & Marketing

Manufacturing

Enabling Functions

Customer Focused
Traditional Drug Discovery Paradigm...

Druggable Protein Classes

Validation in Animal Models

Small Molecule Chemistry

Phase I, Phase II Trials

Pick A Target

Pick A Molecule

Clinical Test

Human Genome ~30,000

Druggable Genome ~3,000

Drug Targets ~600-1500

Disease-Modifying Genes ~3,000

The Emerging Paradigm: In Depth Knowledge Of Targets And Pathways

- The Best Target
- The Best *Small or Large* Molecule
- Clinical Learning Loop

- *Human Biology Target Validation*
- Pathway Expansion
- Expanding Target Tractability
- Definitively Testing Mechanism

![Diagram showing the relationship between the human genome, small molecule druggable genome, and disease-modifying genes.](Diagram)

- Human Genome ~30,000
- Small molecule Druggable Genome ~3,000
- Disease-Modifying Genes ~3,000
Human Genetics & Cell Biology Are Revolutionizing Target Selection

- Molecular Profiling
- Stem Cells
- Systems Biology
- Human Genetics
- Bioimaging
Innovative Therapies In Key Areas Of Unmet Medical Need

- Neuroscience/Pain
- Inflammation/Immunology
- Infectious Diseases
- Oncology
- CV/Metabolic

Focus is on High Priority Disease Areas Using Various Modalities

- Vaccines
- Small Molecules
- Biologics
Patient Segmentation Has Potential To Improve Clinical Outcomes

- **Research**
  - Patient segment understanding seeds new research
  - Disease understanding drives more informed target selection

- **Development**
  - Higher probability of success
  - Fast termination of projects that are going to fail
  - Cheaper and potentially faster to patients

- **Regulatory, Payers, and Market**
  - Greater assurance for payers on outcome for spend
  - More confidence in risk/benefit ratio
  - System benefits of healthier population

- **Patients**
  - Get drugs that work better, with less risk
  - Won't waste valuable time on drugs that won't work
  - Improved compliance resulting from greater efficacy
Highly effective therapy
Overall response rate = 65%
Disease control rate = 84% at a median of ~24 weeks

Accelerated clinical activities
Initiated Phase 3 trial based on Phase 1 results, bypassing Phase 2 and accelerating development timeline

Crizotinib: A potent and selective oral inhibitor of MET and ALK

... initially being developed for MET mechanism

Academic discovery of new patient segment redefined lung cancer
10-15\%\(^1\) of non small cell lung cancer (NSCLC) patients with fusion oncogene ELM4-ALK\(^2\) are unresponsive to conventional EGFR inhibitor\(^1\) treatment

New Phase I trial targeting advanced NSCLC patients harboring ALK rearrangement

Note: Patients in trial composed of 2nd to 4th line. 1st line response to Standard of Care: ~50%, 2nd line: ~10%, 3rd line: 3-5%
Loss Of Function of PCSK9 Result In Reduced LDL-C And CHD Events

No Nonsense Mutation (N=3278) 50th Percentile

Plasma LDL Cholesterol in Black Subjects (mg/dl)

28% in LDLc

28% in LDLc

No Ab:  
- PCSK9  
- LDLr  
- LDL

With Ab:  
- PCSK9  
- LDLr  
- LDL

88% in CHD events in 15 yrs
Characterization Of RN316

• **Anti-PSCK9 antibody (RN316; PF-04950615)**
  Humanized monoclonal antibody
  Binds to LDLR binding domain of PCSK9
  Specific to human (5pM), mouse, rat and cynomolgus PCSK9
  Completely blocks PCSK9 function in binding and cell base assays

• **Efficacy and safety in animals**
  Reduces cholesterol in rodents
  Selectively reduces LDL-c by 80% in NHP, without significant effects on HDL-c
  LDL lowering effect is additive with a statin in hypercholesterolemia NHP
  No drug related toxicity observed in rodents and NHP
Significant Limitations For Meaningful Patient Segmentation

- Our disease understanding lags our desire to match mechanisms and targets with patient and disease subsets, *a priori*
- Lack of translational cell / animal models and tools needed to predict human segments and select therapeutic targets
- Few biomarkers clinically validated to support patient segmentation, predisposition to disease and therapeutic response
## Challenges

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<tr>
<th>Challenges</th>
<th>Examples</th>
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<tr>
<td>Develop and qualify biomarkers for early disease modification</td>
<td>Cerebral spinal fluid Aß for Alzheimer’s</td>
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<td>Synchronize biomarker and drug development, including approval of biomarker as diagnostic at launch</td>
<td>KRAS not identified as biomarker for EGFR inhibitors until post-marketing</td>
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<td>Partner with payers for clinical translation of biomarkers, conduct of clinical trials and reimbursement of diagnostics</td>
<td>PBMs conducting clinical trials on diagnostic-drug pairs for private payer industry in US</td>
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<td>Engage patient groups for support in biomarker development and biomarker-driven clinical trials</td>
<td>Alzheimer’s Association quality control program to standardize cerebrospinal fluid biomarker measurement</td>
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<td>Develop better models to assess biomarker-driven drug development costs and market fragmentation by biomarkers/diagnostics</td>
<td>MIT stratified medicine model</td>
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Understanding Disease Biology Is Not A Competitive Activity

Major U.S. Drugmakers Form Asian Research Center

NEW YORK (AP) -- Three major U.S. drugmakers, Eli Lilly and Co., Merck & Co. and Pfizer Inc., said Tuesday they have formed a not-for-profit company in Asia to focus on cancer research and treatments.

The companies said they formed the Asian Cancer Research Group to focus on the most commonly diagnosed cancers in Asia, including lung and gastric cancers.

They did not say in a news release how much funding they were committing to the project.

Over the next two years, Lilly, Merck and Pfizer said they will create an extensive database that will be made available to researchers.

“The goal of the Asian Cancer Research Group is to improve the knowledge of cancers prevalent in Asia and to accelerate drug discovery efforts by freely sharing the resulting data with the scientific community,” the companies said.

They said as many as 40 percent of patients with lung cancer in Asia demonstrate a mutation that is relatively rare in Western patients, suggesting a different research approach is needed for developing treatments.
Open Innovation: Industry – Academy Partnerships

- Unprecedented access via a confidential web portal to more than 500 Pfizer compounds
- Enables new discoveries with existing compounds
• Identifying human gene variants that protect diabetics from heart-attacks, and people from becoming diabetic

• Collaboration focus is on understanding this complicated disease, identifying novel therapeutic pathways and targets, and developing genetic risk models to guide clinical study patient selection

• Daily, no-holds barred scientific exchange exemplifies the collaboration
New Drug Design Platforms Are Emerging

Proven technologies to deliver high impact medicines

- Peptides
- ADCs
- Vaccines
- Antibodies
- Therapeutic Proteins

Emerging drug design technologies

- Shark IgNARs
- CovX Bodies
- Bifunct CovX Peptibodies
- Scorpions
- Tandem Approaches
- Lobsters
- scFv Multimers
- Shark Jaws
- SMIPs*
- Nanobodies

*SMIP™ Trubion Pharmaceuticals

The Right Molecule for Every Patient
Four Imperatives For Success

Be Right About Targets

Select the Right Patients

Design Molecules That Survive

Move Faster, Better Patient Outcomes