Innovation in the Pharmaceutical Industry through Partnerships with Academia & Industry

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Drug Discovery

January 26th 2011
Annual Icelandic Medical Conference
Medical Research Symposium
Talk Plan

- Changing Landscape in the Pharma Industry
- Innovation in Pharmaceuticals
- The Future for Pharma & Healthcare
- Discovery Partnerships in Academia (DPAc)
- Concluding remarks
Changing Landscape in the Pharma Industry
Drug Development is a costly & risky business

- It takes up to 15 years to develop a new drug
- For every 5-10,000 molecules synthesised & screened for activity, only 250 reach pre-clinical development, only 5 reach clinical trials and only one reaches the market
- Cost to develop a drug in 2006: $1.318 billion
- Only 2 of 10 marketed drugs ever produce revenues that match or exceed R&D costs.
- Pharmaceuticals are generally cheap and easy to copy – generic companies enter mature markets developed by innovator with low entry costs
- These features are probably unique to the pharmaceutical industry

Estimated full cost of bringing a new chemical or biological entity to market ($ million – year 2005 $)

R&D Productivity decreases the innovation gap is getting wider
Pressures on the Pharma Industry

- R&D spend continues to rise
- The blockbuster model is unsustainable
- Drugs not being reimbursed in some countries if they are not sufficiently differentiated
- There are higher regulatory risks post-launch
- Pricing discussions continue
Over 6,000 compounds in development

Source: Adis R&D Insight Database, customized run (December 2007)
Competition in Therapeutic Innovation

• Many scientists seeking to solve same problems in different or similar ways from similar starting points at the same time

• The first to market is generally quickly followed by several others
  – >15 beta blockers
  – 9 protease inhibitors
  – 15 NSAIDs
  – >10 statins

• The first mover is rarely the most successful

• The period of exclusivity for first movers is shrinking & Pharma are becoming more conservative
The period of exclusivity for first entrants to a therapeutic class is decreasing (US data)

Compound differentiation

- New drugs tested against “gold standards”

- Patent competition drives improvements:
  
  - Increased Efficacy
  - Decreased Side-effects
  - Decreased ADRs
  - Decreased drug-drug interactions
  - Decreased dosing
  - Specialised drug delivery systems

- Patients benefit from a range of products with differing characteristics
Quarterly Enalapril sales in the UK

Source: IMS Health MIDAS database
The patent cliff:

Pfizer will lose $13bn of income when the Lipitor patent expires in 2011.

Eli Lilly will lose up to 75% of its revenue over the next 8 years unless it has new drugs to make up this loss.

- Forcing risk averse Pharma companies to diversify their approaches to R&D
Innovations in the Pharma Industry
Penicillins
Sulphonamides
Aspirin
Psychotropics
NSAIDS
H2-antagonists
Beta blockers
Lipid lowerers
ACE-inhibitors
Biotech drugs

Chronic degenerative disease associated with ageing, inflammation, cancer
Drugs against targets identified from disease genes

Natural products and derivatives
Serendipity
Receptors
Enzyme
H2-antagonists
ACE-inhibitors
Lipid lowerers

Genetic engineering
Cell pharmacology/molecular biology

Genomics/proteomics

Step Change Therapeutic Innovations

1st generation
2nd generation
3rd generation
Rapidly Changing Market
Biologics gaining market share
New drug product sales growth (2007-12)

Market Share %

% Sales Growth: CAGR 2007-2012
Emergent science drives new disease opportunities

Where science and unmet need converge

Core diseases

Opportunities in “new” diseases featured in the business plan

Key emergent areas of science

Lung repair
COPD, fibrotic lung diseases (IPF, ILD, CF)

Neuronal mechanisms
Rhinitis, asthma, COPD, cough

Immunomodulation
Asthma, allergic rhinitis

Unmet Need Index

US Population Prevalence/Incidence (Log Scale)
Changing Trends in Pharma/Biotech

• Management consultants, automation and HR:
  
  In the ’90s consulting companies offered their services to Pharma.
  
  – Robotics for screening 1,000,000 compounds/week.
  
  – Combinatorial Chemistry.
  
  – “me too” compounds.

• The rise of Biotech:

  Antibodies were validated as drugs, small innovative companies cash starved therefore ripe for take over (could solve Pharma’s pipeline problem). How do you copy a biotech product (no generics).

• Health Budgets are finite:

  The amount paid for healthcare is no more than 15% of GDP
  Drugs must offer value (NICE).
Biomedical innovation: The last 50 years

- new technologies:
  - applied pharmacology – agonists and antagonists
  - genetic engineering – therapeutic proteins, imaging, arrays and antibodies
  - bioengineering advances – hips and pacemakers

- but…
  - economic model is unsustainable
  - lacking productivity
  - US health reforms starting to bite

- & we cannot focus only on “developed nations”
Emerging Markets will outgrow Developed Markets by 2020

2020 Growth Profile:

BRIC countries, Mexico, South Korea & Turkey
12-13% growth p.a

Total sales $400 billion by 2020

Cf Mature markets (USA & Europe) low single digit growth
GSK turnover growth in 2009 despite decline in US Pharma

2009 Turnover £28.4bn (+3%)

CER growth rates
Rest of Pharma includes Stiefel sales of £248m
The Future for Pharma & Healthcare
The world today:

The population challenge

60% of the world's population is in Asia

Cf. 5% of the world population in N.America

N.America currently purchase almost 40% of the world's Pharmaceuticals.

This is unsustainable
Possible game changers looking out 20 years

- genomic medicine & epidemiology
- companion diagnostics
- pharmacogenetics
- stem cell therapeutics
- synthetic biology
- nanotechnology
- bioengineering
- computational sciences
- digital pathology
- decision support systems
- medical imaging
- neurology
- infectious disease
The changing face of biological innovation

- population (prevention)
- longevity (diabetes, neurological diseases, cancer)
- cost of healthcare (price, volume, companion diagnostics, efficacy)
- infectious disease (re-emergence of TB, influenza, potential for vaccines and therapeutics, drug resistance)
- counterfeiting
- understanding of genetics critical to human medicine.
Iceland’s Unique Offering:

“Genetic correction of Prostate Specific Antigen values using sequence variants associated with PSA levels”

Gudmundsson et al,
Science Translational Medicine 15th December 2010
The Future:

- Increased emphasis on in silico analysis

- Pulling disparate datasets together to create new knowledge

Genetic information
Species linkages – mouse, zebra fish, human
Spatial information – protein structures
Epidemiology
Screening data
Imaging data
Genomic medicine:
Treatment of metastatic malignant melanoma with selective inhibitor of BRAF V600E (Plexxicon 4032)

Before 15 days after

Courtesy of Dr Grant McArthur
Academic - Pharma Partnerships
Innovation through Partnership

Pharma
- Specific agonists & antagonists
  -- Biological reagents

Clinical academics
- Deeper understanding of physiological & pathological control mechanisms

Publications
**Q:** Why place Chemical Probes in the Public Domain?

**A:** Potent and selective small molecules provide complimentary (if not better) target validation to genetic methods as evidenced by their scientific impact.

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Data compiled from Google Scholar, October 5, 2007

**All compounds were made available by GSK to the Public Domain through commercial suppliers (Sigma-Aldrich and Tocris)**

**h-index:** a metric of scientific impact, combining quality and quantity of citations

**g index:** a modification of the h-index with more weight on highly-cited articles
Discovery Partnerships in Academia (DPAc)
DPAc aims to leverage the unique expertise of both academia and industry...

**Academia**
- In depth biological insight
- Target and pathway expertise
- In vivo disease models
- Clinical disease insight
- Key opinion leaders

**Industry**
- Hit generation & assay development
- Medicinal chemistry
- Quantitative biology
- Preclinical development
- Integrated discovery & development
- Regulatory & commercial infrastructure
GSK resource and expertise to progress project

- Large scale protein production
- HTS capacity 2 million compound set
- Medicinal chemistry and computational molecular design
- Selectivity screening
- PK-PD modelling

**Target Feasibility**
- Assay Development
- Lead Identification
- Early Lead Optimisation
- Late Lead Optimisation

- Flexible, high tech assay platforms
- Encoded Library technology >10million compounds
- Synthetic & analytical chemistry

Preclinical development (safety assessment, pharmacy, chemical development, DMPK)
DPAc focus on early drug discovery and future pathway options to launch

- Target Feasibility
- Assay Dev
- Lead ID
- Early LO
- Late LO

**DPAc Shared Project**
- Drug Discovery Initiated
- Screen Initiated
- Lead Identified In vitro
- Lead Identified In vivo
- Candidate Selection

**GSK Internal Project**
- CS to FTIH
- Phase I
- Phase IIa
- Phase IIb
- Phase III
- Registration

**AcDPU Shared Project**
- First dose human
- P III start
- Launch

DPAc project can transition at any stage but likely around CS.
Activities shared between academics and GSK

Drug Discovery Initiated
Screen Initiated
Lead identified in vitro
Lead identified in vivo
Candidate Selection

Typical GSK activities

Assay feasibility Tool generation
Assay development
Screening Chemistry
Screening Chemistry DMPK
Chemistry DMPK Safety Pharmacy

Typical academic activities

Reagent generation
Assay development
Physiological assays
Physiological assays In vitro and in vivo
Physiological assays In vivo models

Value of GSK contribution
Value research support & reward

£££££
£££££
£££££
£££££
£££££

+ downstream development milestones and/or royalty
DPAc looks for leading academics working on a target or pathway with high therapeutic potential

**DPAc Partnership Criteria**

<table>
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<th>Criteria</th>
<th>Description</th>
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<tr>
<td>Therapeutic hypothesis</td>
<td>Coherent and supportable hypothesis that modulation of target will produce an effect expected to be of therapeutic benefit</td>
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<tr>
<td>Target defined</td>
<td>Specific drug target identified, with some understanding of type of pharmacology desired</td>
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<tr>
<td>(Exclusive) enabling expertise</td>
<td>Academic partner has know-how, experience, expertise essential to progressing the target which is not (readily) found elsewhere</td>
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<tr>
<td>Tractability</td>
<td>A path to identification of a drug molecule can be defined. Target knowledge suggests that a drug-like molecule can be generated</td>
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<tr>
<td>Requirement for GSK contribution</td>
<td>GSK has capability which will help progress to the next milestone</td>
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Conclusions:

- GSK are keen to promote a more open culture for sharing ideas & data

- Traditional relationships between Academia and Industry are being re-defined

- Access to public funding will drive areas of science underpinning the Pharma industry

- Innovative partnership models allow both GSK & academics better access to science & technology
Thanks for listening
We are looking for innovation wherever it may originate.
DPAc is a differentiated approach to translating innovative academic research

**What DPAc is........**

- ✓ Access to GSK’s expertise and resource in early drug discovery
- ✓ The opportunity for academics to collaborate in drug discovery
- ✓ Milestone aligned resourcing

**What DPAc is not......**

- ✗ Funding of exploratory research
- ✗ Pulling projects into industry away from academics
- ✗ Fixed term research funding
DPAc offers a new approach to collaborative drug discovery

Discovery Partnerships with Academia

...looks for innovative academic science
...that may ultimately deliver differentiated medicines from across multiple therapeutic areas

...integrates with academic groups
...to provide resource and expertise to undertake early drug discovery in partnership with academics

...delivers quality development candidates
...through milestone driven collaborations, that can then progress through the GSK organisation
GSK profile of current global collaborations

GSK have more academic collaborations than any other UK company (all sectors)
GSK currently has >500 active research collaborations ongoing with UK Universities.

Two way exchange of knowledge & technology
## EUROPEAN ACTIVE AGREEMENTS BY COUNTRY

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GSK Agreements by State

January 2008 - April 2010

North Carolina NC
Maryland MD
Pennsylvania PA
Massachusetts MA
New York NY
California CA
Texas TX
Michigan MI
Missouri MO
Colorado CO
Connecticut CT
Virginia VA
Washington WA
Georgia GA
New Jersey NJ
Alabama AL
Arizona AZ
Delaware DE
Florida FL
Iowa IA
Nebraska NE
Oregon OR
Tennessee TN
GSK Academic Spend 2009
GSK funding to Harvard in 2009 was >£9m

- Immune Disease Institute
- Harvard Stem Cell Institute
- MGH
- Dana Farber Cancer Institute
- Brighmans & Womens
- MIT
How large Corporates are changing their business models to embrace Open Innovation
Data Sharing Agreements

GSK have collected bloods from clinical trials for more than a decade

Genetic analysis on cohorts of >20,000 patients

Need to combine datasets with other well phenotyped collections to find significant trends

e.g MRC £500k + GSK £500k

Nick Wareham (University of Cambridge) Obesity/Diabetes
Peter McGuffin (KCL) Bipolar disorder
Developing Chemical Probes for Epigenetics

No structures disclosed

Chemistry @ GSK

Assays @ Oxford

Data to GSK

Only GSK scientists can view data with compound structures

Structures disclosed

X-ray @ Oxford

Chemical Probe*

Public Domain

Sigma make probe available

1–5 Compounds meeting probe criteria for potency and selectivity:

* e.g. Potency <100nM, Selectivity >100, Cellular activity <1uM
A future model for Drug Discovery?
Wellcome Trust Epigenetics Collaboration

GSK-WT-SGC Partnership
Public Domain

Chemical Tractability
Chemical Probes
Enable Academic Target Validation

Open Access

Pharmaceutical Industry

Proprietary Target Validation
(Re)Screening
Lead optimization
Pharmacology
DMPK
Toxicology
Chemical development
Clinical development

Drug Discovery

No restrictions on use or publication

Chemistry (GSK)
Screening (WT-NIH)
Structure (SGC)
“Quality” of Journal Articles (2000):
Domains: Clinical Medicine, Biomedical Research, Biology

Average impact factor in subject area vs. Average citations in subject area

- Harvard
- Oxford
- Cambridge
- Imperial
- GlaxoSmithKline
- Southampton
- AstraZeneca
- Newcastle
The realities of having the best pipeline

Lehman Brothers Pharma Pipelines (Sept 2007)
Pharma Replacement Power – NPV

LB Method: \[ \text{NPV of recent launches (06-07)} + \text{NPV of pipeline opportunities from ‘08-’13} \] / \text{NPV of products marketed before 2006.}
Science base attracts R&D spend

Global Pharma sector

- UK market: 2.46%
- UK R&D: 0%
- US market: 37.64%
- US R&D: 50%

GlaxoSmithKline
MRC translational activities

Translational Research Support

- Developmental Pathway Funding Scheme
- Developmental Clinical Studies
- Translational Stem Cell Research Programme

Funding Scheme

- Targeted initiatives to alleviate bottlenecks
- Infrastructure/Resources
- Methodology
- Training

Capacity building

Continued commitment to basic lab, clinical and population research
Developmental Pathway Funding Scheme (DPFS)

- Cornerstone of the MRC’s Translational Strategy
- Launched at end of April 2008
- Planned expenditure of at least £25m over next 3 years
  - Guidance of £250k-750k; 1-2 years per project
  - Will consider larger scale proposals where justified
- Projects do not need to originate from MRC funded research
- Goal oriented rather than hypothesis-led
- Funding is milestone-based
  - Projects will be required to submit quarterly and milestones progress reports
  - Failure to meet a milestone may result in funding being terminated
Scope of the DPFS

- Examples of proposals:
  - Validating an association between a fundamental discovery & a preventive, diagnostic or disease process (target validation)
  - Developing candidate therapeutic entities - from discovery up to early evaluation in humans
  - Developing candidate diagnostics or medical devices - from prototype design up to early evaluation in humans
  - Developing a new research tool to overcome a bottleneck in the development of therapies or diagnostics
Drug Development Costs Escalate

INVESTMENT ESCALATION PER SUCCESSFUL COMPOUND

Exhibit 1

Investment required for one successful drug launch (discovery through launch)

- 1995-2000
  - Discovery: 0.5B
  - Phase I: 0.5B
  - Phase II: 0.5B
  - Phase III/File: 0.5B
  - Launch: 1.0B

- 2000-2002
  - Discovery: 0.5B
  - Phase I: 0.5B
  - Phase II: 0.5B
  - Phase III/File: 0.5B
  - Launch: 1.7B

Avg ROI %
- 1995-2000: 9%
- 2000-2002: 5%

Probability of reaching 12% ROI
- 1995-2000: 30%
- 2000-2002: 15%

SOURCE: Bain drug economics model, 2003
MRC translational activities

- Developmental Pathway Funding Scheme
- Developmental Clinical Studies
- Translational Stem Cell Research Programme

Translational Research Support

- Basic research
- Prototype discovery and design
- Pre-clinical development
- Early clinical trials
- Late clinical trials

Targeted initiatives to alleviate bottlenecks

- Infrastructure/Resources
- Methodology
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Capacity building
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MRC Industrial Collaboration Applications (MICAs)

- MICAs are aimed at encouraging & supporting collaborative research projects between academic researchers & industry.

- The key feature of this scheme is its flexibility, especially the level & nature of the industry contribution.
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Without patents there would be no innovation

- Given the costs & risks of drug development, without a period of exclusivity against copyists there would be no investment in pharmaceutical innovation
- Pharma do not seek therapeutic area exclusivity (anti-virals, antibiotics)

Patent protection promotes therapeutic & innovative competition
Changing Landscape of I.P

- More small companies owning & licensing basic IP
- Many companies not in manufacturing, only generating technology/IP
- More patent aggregators, who take on patents from universities & small companies
- Patents used as bargaining chips