Research, Regulation, Risk and Reward: The Strategic Environment for Pharmaceutical R&D

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Keynote address: Dutch Top Institute Spring Meeting Utrecht, 23 April 2009
The Impact of Advances in Technical Knowledge on Human Longevity, Disease Burden and Quality-of-Life

- public sanitation
- clean water
- improved nutrition
- education
- child labor laws
- workplace safety
- control of toxic waste and environmental spoilage
The Impact of Advances in Technical Knowledge on Human Longevity, Disease Burden and Quality-of-Life

**Broad Societal Programs**
- public sanitation
- clean water
- improved nutrition
- education
- child labor laws
- workplace safety
- control of toxic waste and environmental spoilage

**Pharmaceutical Innovation**
- control of parasitic and infectious diseases
- major reductions in CV, metabolic, musculo-skeletal and mental illness
- veterinary medicine and improved productivity and safety of food supply
Health Matters:
Healthcare R&D Occupies a Unique Position in Societal Expectations

- **public expectancy:** the entitlement mentality
  - ever faster innovation but at no risk and cost paid by others

- **political expediency:** control of escalating costs
  - governments court ‘high-tech’ corporate R&D investment but set efficacy barriers and pricing policies that hinder innovation/investment
Health Matters: Healthcare R&D Occupies a Unique Position in Societal Expectations

- free market forces or a public good?
  - distrust/rejection of profit-motive
  - media portrayal of corporate ‘greed’ at expense of the ill
- global equity and distributive justice
  - the “90:10” challenge
- negative industry image
  - profiteers rather than innovators
  - lack of public/political awareness of massive R&D investments and time, cost and complexity of Rx development
The Mega-Project Industries: Masters of Complexity
“Mega-Projects”

- very high R&D investment per project ($1 billion plus)
- extended R&D cycles (10-25 years)
- multi-disciplinary integration of diverse specialized skills
- multi-national scope
- high uncertainty, high risk
  - technical failure
  - financial risk
  - product risk
- impact of government and market policies that can change significantly in project lifetime
R&D Investments by Different Industries

- Pharmaceutical and biotechnology
- Technology hardware and equipment
- Automobile and parts
- Electronic and electrical equipment
- Software and computer services
- Chemicals
- Aerospace and defense
- Leisure goods
- Industrial engineering
- General industrials

<table>
<thead>
<tr>
<th>Industry</th>
<th>R&amp;D Investment ($ million)</th>
<th>Change from previous year (percent)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pharmaceutical and biotechnology</td>
<td>$93,069.9</td>
<td>15.7%</td>
</tr>
<tr>
<td>Technology hardware and equipment</td>
<td>$85,162.2</td>
<td>13.1%</td>
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<tr>
<td>Automobile and parts</td>
<td>$80,247.1</td>
<td>1.5%</td>
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<tr>
<td>Electronic and electrical equipment</td>
<td>$35,815.2</td>
<td>4.9%</td>
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<tr>
<td>Software and computer services</td>
<td>$22,680.4</td>
<td>13.2%</td>
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<tr>
<td>Chemicals</td>
<td>$21,680.4</td>
<td>9.6%</td>
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<tr>
<td>Aerospace and defense</td>
<td>$21,103.7</td>
<td>12.4%</td>
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<tr>
<td>Leisure goods</td>
<td>$18,751.1</td>
<td>11.5%</td>
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<tr>
<td>Industrial engineering</td>
<td>$12,298.7</td>
<td>8.0%</td>
</tr>
<tr>
<td>General industrials</td>
<td>$11,702.6</td>
<td>-10%</td>
</tr>
</tbody>
</table>
Innovation Gap: R&D Investments Versus New Drug Approvals

Pharma Innovation Gap

*Estimated
Source: Burrill & Company
COST, CONSERVATISM AND RESISTANCE TO CHANGE
The Strategic Environment for Healthcare

- escalating costs without major gains in quality
- focus on late-stage disease detection/intervention
  - high cost
  - low reversibility of chronic diseases
- demographic trends and additional costs of chronic disease in the aged
- fragmented and uncoordinated care
• unacceptable levels of misdiagnosis/error
• highly variable patterns of clinical care
• massive waste and inefficiency by lack of real-time, comprehensive electronic medical medical records
• illness versus wellness
• inadequate social and economic incentives for wellness
0.5% patients consume 25% of healthcare budget
1% consume 35%
5% consume 60%
10% consume 70%
75% of cost is for patients with chronic diseases

Source: Healthcare Reform Now
G. Halvorson, Chairman and CEO
Kaiser Foundation Health Plan and Hospitals
Wiley, NY 2007 p.2
Managing the Economic and Clinical Impact of Aging Demographics and Complex, Chronic Conditions
Global Health: Understanding the Implications of Major Economic and Environmental Dislocations
The Strategic Future of Healthcare

Economic Unsustainability or Reform and Rational Care

Confronting the Imbalance Between Infinite Demand and Finite Resources
Reasonable Expectations for Rational Healthcare

- what works
- why it works
- who it works for
- what works best
- when should it be used optimally

- validated evidence
- mechanism of action
- personalized medicine
- comparative effectiveness
- best practice guidelines, standard-of-care and malpractice

VALUE
Defining New Value Propositions for Healthcare Delivery

- Social and economic value of reducing disease burden will rise
  - Earlier disease detection and mitigation
  - Rational Rx and guaranteed outcomes
  - Integrated care management of complex chronic diseases
  - Extension of working life
Urgent Priorities for Improvements in Clinical Practice and Healthcare Delivery

- from empirical diagnosis (symptoms) to definitive profiling (molecular pathology) of causal disease mechanisms
  - personalized medicine and rational therapy
- earlier detection of disease (pre-symptomatic) or disease progression
- routine monitoring of individual health status
- instant access to patient information
  - anytime, any place, any patient
Convergence
The Three Forces Shaping the Evolution of Healthcare

- Molecular medicine and personalized medicine
- Access, cost and quality of care
- Proficient use of information (e.health)

Demonstrating Value
Convergence

- Molecular medicine
- Engineering-based medicine
- Information-based medicine
Molecular Diagnostics and Biomarkers: The Fundamental Technology Platforms For Molecular Medicine and the Future Healthcare Value Chain
Ignoring The Obvious in Clinical Practice

- diseases are not uniform
- patients are not uniform
- a “one-size fits all” Rx approach cannot continue

- inefficiency and waste of empirical Rx
- cost of futile therapy
- medical error and AEs
“If it were not for the great variability among individuals, medicine might be a science, not an art”
Sir William Osler (1892)

“Because of the great variability among individuals, medicine **must** finally become a science, not an art”
Rational Therapeutics and Personalized medicine: Key Drivers

Science

Policy

Cost and Outcomes
Drug-Target Networks for FDA Approved Rx
Disease Subtyping: Next-Generation Molecular Diagnostics (MDx) and A New Molecular Taxonomy of Disease

B1 skin, B2, melanocytes, B3, melanoma, B4 and 5 metastatic melanoma

From: C. Haqq et al. (2005) 102, 6092

**Dx Platforms**

- massive parallelism
- miniaturization
- automation
- rapid
- POC

**RIGHT Rx for RIGHT DISEASE SUBTYPE**
Molecular Diagnostics and Disease Subtyping

“Riches in the Niches”

- right diagnosis, the first time
- right Rx selection, the first time
- rise of Dx-Rx combination
- Rx approval and labeling
- reimbursement only with obligate Dx?
Molecular Diagnostics and Targeted Therapeutics

- premium pricing for predictable Rx outcomes
- pay-for-performance (P4P)

Logos of Johnson & Johnson, Celgene, VELCADE, and Revlimid.
K-RAS Profiling and Anti-EGFR Monoclonal Antibody Therapy

- greater response in patients with K-RAS versus mutant-
- estimated $604 million/year savings (ASCO)

regulatory demand
clinical guidelines

- regulatory inertia
- payor adoption
Personalized Medicine
The Initial Era: Targeted Rx

- opening era in linking disease molecular pathology to rational Rx
- increasing payor, regulatory and public pressures for reliable ID of Rx-responsive patients
- demand for Dx-Rx combinations will intensify
- Dx-Rx combination will become an obligate element of NDA/BLA submission and product labeling
- development of Dx-Rx combinations as intrinsic components of R&D programs for investigational Rx
Pharmacogenetic Predisposition to Adverse Drug Reactions

- 1.5 to 3 million annual hospitalizations (US)
- 80 to 140 thousand annual deaths (US)
- Est. cost of $30-50 billion
## REMS: Risk Evaluation and Mitigation Strategies

<table>
<thead>
<tr>
<th>Product</th>
<th>Manufacturer</th>
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<tbody>
<tr>
<td>Plenaxis (abarelix) * for prostate cancer</td>
<td>Praecis</td>
</tr>
<tr>
<td>Lotronex (alosetron) for irritable bowel syndrome</td>
<td>Prometheus</td>
</tr>
<tr>
<td>Letairis (ambrisentan) for pulmonary arterial hypertension</td>
<td>Gilead</td>
</tr>
<tr>
<td>Tracleer (bosentan) for pulmonary arterial hypertension</td>
<td>Actelion</td>
</tr>
<tr>
<td>Clozaril (clozapine), Fazaclo ODT (clozapine) for schizophrenia</td>
<td>Novartis, Azur and generics</td>
</tr>
<tr>
<td>Tikosyn (dofetilide) for atrial fibrillation/atrial flutter</td>
<td>Pfizer</td>
</tr>
<tr>
<td>Soliris (exulizumab) for paroxysmal nocturnal hemoglobinuria</td>
<td>Alexion</td>
</tr>
<tr>
<td>Ionsys (fentanyl hydrochloride)*, Actiq (fentanyl citrate) for pain</td>
<td>Alza, Cephalon</td>
</tr>
<tr>
<td>Accutane (isotretinoin) for acne</td>
<td>Roche and generics</td>
</tr>
<tr>
<td>Revlimid (lenalidomide) for myelodysplastic syndromes and multiple myeloma</td>
<td>Celgene</td>
</tr>
<tr>
<td>Mifeprex (mifepristone) for pregnancy termination</td>
<td>Danco</td>
</tr>
<tr>
<td>Tysabri (natalizumab) for multiple sclerosis and Crohn’s disease</td>
<td>Biogen Idec/Elan</td>
</tr>
<tr>
<td>ACAM2000 (smallpox vaccine, live)</td>
<td>Acambis</td>
</tr>
<tr>
<td>Xyrem (sodium oxybate) for daytime sleepiness and cataplexy</td>
<td>Jazz</td>
</tr>
<tr>
<td>Thalomid (thalidomide) for multiple myeloma and leprosy</td>
<td>Celgene</td>
</tr>
</tbody>
</table>

* Plenaxis and Ionsys are currently not marketed in U.S.
- Update labeling for Abacavir (Ziagen) to require pre-therapy screening for HLA-B*5701 allele to avoid fatal hypersensitivity.

Table of Valid Genomic Biomarkers in the Context of Approved Drug Labels

http://www.fda.gov/cder/genomics/genomic_biomarkers_table.htm
From Pharmaceuticals to Pharmasuitables

Disease Subtyping:
Right Rx for Right Disease

Individual Variation and AE risk
Right Rx for Right Patient
Identification and Validation of Disease-Associated Biomarkers: Obligate Need for a Systems-Based Approaches

Biospecimens and Molecular Pathway Analysis

Biomarker Validation and Multiplex Assays

Instrumentation and Informatics

Clinical Impact and Patient Monitoring
# Development of Molecular Diagnostics and Biomarkers for Personalized Medicine: The Need for End-to-End R&D Solutions

## Complex Biosignature Profiling

<table>
<thead>
<tr>
<th>genomics</th>
<th>proteomics</th>
<th>immunosignatures</th>
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<tbody>
<tr>
<td>![Genomics Image]</td>
<td>![Proteomics Image]</td>
<td>![Immunosignatures Image]</td>
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</table>

## Signature Detection, Deconvolution and Multivariate Analysis

<table>
<thead>
<tr>
<th>multiplex assays</th>
<th>novel test devices (POC)</th>
<th>new algorithms</th>
</tr>
</thead>
<tbody>
<tr>
<td>![Multiplex Assays Image]</td>
<td>![POC Device Image]</td>
<td>![New Algorithms Image]</td>
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</tbody>
</table>
Identification of Biosignatures and Multiplex Molecular Profiling

Detection of Multiplex Biosignatures in Clinically Relevant Formats

Actionable Information

Profile

Life Sciences and Mathematical/Statistical Tools for Complex Signal Analysis

Sense

Miniaturization Engineering and Materials Science

Act

Large Scale Informatics and Information Architectures
Nanoscale Systems and Targeting Materials to Specific Body Locations

Application

- next-generation body imaging for resolution of specific cell types/metabolic activities (versus current whole organ profiling)

- advanced drug and gene delivery systems for target specific localization and release
Personalized Medicine: Disease Predisposition Profiling
Disease Predisposition Risk Profiling for Common, Multigenic Late-Onset Disorders

- slower evolution than many predict
- cost complexity and poor replication of Genome-Wide Association Studies (GWAS)
- substantial ambiguities regarding probabilistic risk of future disease
  - combinations of multiple low penetrance alleles
  - epistasis
  - epigenetics
  - environmental confounders
Personalized Medicine: Challenges for Clinicians

- sustained awareness of relevant conceptual advances and new products/services
- timing and training for adoption into routine practice
- accurate identification of relevant patients for use of MDx profiling and targeted Rx selection
- new malpractice risks
Health Status Monitoring and the Promotion of Wellness
On Body: In Body Sensors/Devices
For Real Time and Remote Monitoring of Individual Health Status
“Savings from broad-band remote monitoring for all chronically ill patients are potentially quite remarkable. ....as much as 30 percent of all hospital, out-patient and drug expenses”

Robert Litan
Kaufman Foundation December 2005

Objective

- remote monitoring of health status

Applications

- multi-feature monitoring and broadband wireless networks
  - ubiquitous sensing
- enhanced autonomy for in-home aged
- proactive alerting and intervention to mitigate health incidents
- monitoring of patient compliance
- coupled linkage to remote Rx dispensing for efficient disease management
The Costs of Non-Compliance with Rx Regimens

- $177 billion projected cost
- 20 million workdays/year lost (IHPM)
- 40% of nursing home admissions
- Projected 45-75% non-compliance (WHO)
- 50-60% depressed patients (IHPM)
- 50% chronic care Rx (WHO)
Challenges in the Management of Complex Chronic Conditions and Co-Morbidities

- Multiple conditions
- Multiple providers
- Multiple treatments
- Multiple coding and reimbursement policies
- Multiple medications
How Much New Technology Can We Afford?
Key Questions

• what is the role of technology innovation in healthcare?
• do current public and private strategies support innovation and disruptive technologies?
• how should the ‘value’ of new technologies be assessed?
• how should dissemination of new value-added technologies be supported?
CONNECTIVITY AND INTEGRATED CARE
Information-Based Medicine

HELL IS THE PLACE WHERE NOTHING CONNECTS — T.S. ELIOT
The Unacceptable Failure to Establish Comprehensive Electronic Medical Records
Paper Kills!

The Inefficiencies and Patient Risks Imposed by Sustained Dependency on Paper Health Records
The Unacceptable Cost of Unconnected Healthcare

- extravagant waste via excessive duplication of tests/procedures
- error via lack of crucial data
- lack of data capture for outcomes analysis and individual physician performance
- failure to capture population-based disease parameters
  - sentinel public health/national security
  - meta-analysis of outcomes
  - drug and device safety and recall
CONSUMERS
“Until the person receiving the product is responsible in some fashion for the costs, there will be no incentive to spend responsibly”

Scott Serota
CEO, BCBS Association of Chicago
Chief Executive Magazine, March 2007 p. 50
After a Short Stay in America, Michelangelo's David Returned to Europe
The shape of things to come

Diabetes

POP 20,870,000
• cost-shifting to consumers

• clinical and economic benefits of coordinated care of complex chronic conditions

• lifestyle and disease risk mitigation

• new information intermediaries

• cost-driven transitions from ‘passive patient’ to ‘engaged consumer’
Telecommunications and Media Industry Convergence: Implications for Healthcare
The Changing Nature of Social Interaction

Herd Behavior: 1951
1.3 Million Bathers, Coney Island, NY

Herd Behavior: 2008
Social Networks and Virtual Communities
Consumer-Directed Healthcare: The Wellness Premium

- leveraging social and peer networks
- increased role of fitness industry and entertainment in healthcare
  - “success via distraction”
- “virtual touch”
  - web-based consultation and diagnostic algorithms
  - emerging generational gap in need for direct physical interaction with physician
- evolution of ‘near-patient’ health status profiling
  - POC and in-home Dx
  - OBIBs
AORTA: Always on Real-Time Access: Interactive, Distributed and Customized Datasets
Healthcare Information Networks: AORTA: Always On Real Time Access

- end-to-end continuity in use of internet and wireless technologies
- from routine remote monitoring of health status to advanced critical care

- comprehensive connectivity
  plus
- collapsing time
  plus
- global networks
The Evolution of In-Home POC Diagnostic and Compliance Monitoring Systems
A New Healthcare Ecosystem Arising From Technology and Market Convergence

Integrated Technology Platforms

Dx/Devices

Rx

Hlx

passive/active data collection
analytics and network architecture
EMR/PMR
performance and outcomes analysis
Data Mining and Integration Services

Increasingly Targeted Care and Efficient Use of Finite Resources

patients

consumers

services for integrated care
“Managing Mega-Data”

volume

scale

Visualization and Collaboratories

Heterogeneity and Context

Cognitive Systems for Optimum Decisions
The Rise of Open-Source Networks and Consortia
Privacy and Information

- 2010: 15 Petabits \((10^{16})\) / $250,000

- Human Genome: 10 Gigabits \((10^{11})\)

For a few million dollars, one could store the complete genome of every American and European.

...for several more, could add credit card records, telephone logs, travel history,...
Personalized Medicine: Progressive Evolution
Based on Increasingly Comprehensive Profiling of Disease Risk and Health Status

- Targeted Care
  - rational Rx based on profiling of underlying molecular pathology
  - MDx and disease subtyping

- Personalized Care
  - rational Rx based on comprehensive molecular profiling of individuals
    - disease subtypes and optimum Rx
    - Rx AE risk
    - disease predisposition risk and mitigation

- Individualized Care
  - integrated framework of longitudinal data on individual health status
  - real time remote health status monitoring
  - transition to disease prediction and preemption
The Coming Convergence in Healthcare Delivery

Technologies

- biotechnology, medicine, engineering, computing

Clinical Practice

- molecular medicine and increasingly customized care
- diagnostic, drug and device combinations
- POC testing and remote monitoring
- reduced error and improved compliance
- improved clinical and economic outcomes

Realigned Incentives

- integrated care for complex chronic diseases
- earlier disease detection and risk reduction
- wellness versus illness
- health status monitoring
The Coming Convergence in Healthcare Delivery

**Consumers**
- increased personal responsibility for health
- new incentives for wellness/compliance
- health status monitoring

**Connectivity**
- integrated care networks for chronic disease
- improved outcomes and effectiveness
- social networks and informed consumers
- new supplier networks of specialized turnkey expertise
- value added ‘content’ services for clinical data mining
The Urgent Imperative for New Drivers of Efficiency and Equity in Healthcare Delivery

- Earlier detection and prevention of disease episodes
- Wellness versus Illness
- Rational Therapeutics and Personalized Medicine
- Optimum Use of Costly Resources
- Proficient use of information: anytime, anywhere
- Molecular profiling of patients and their diseases
Building an Integrated Framework for Personalized Medicine

- earlier detection and prevention of disease episodes
- optimum Rx selection and outcomes
- customized information for optimum decisions

- molecular profiling of patients and their diseases

Patients
Payors
(Bio)Pharm. Cos.

VALUE

Rx
Dx
Devices
Ix
Aspiration and Engagement with Grand Challenges