Industry strategies and biomarker business models

Arsia AMIR-ASLANI, PhD

OECD WORKSHOP ON POLICY ISSUES FOR THE DEVELOPMENT AND USE OF BIOMARKERS IN HEALTH

6&7 October, 2008

Wellcome Trust conference center, Hinxton, UK
Developments in biotechnology have allowed the drug discovery industry to move from serendipity-based research towards rational, evidence-based approaches. The wide range of technologies belong to one of the following fields:

- Informatics
- Chemistry
- Biology

A successful therapeutic compound needs to fulfill fundamental requirements, such as:

- Satisfies an unmet medical need
- Exhibits superiority over existing treatments
- Provides specific advantages in terms of pharmacokinetics and metabolism
- Safe with low adverse drug reactions
Value Chain of Drug Discovery Process
(Strategy based on target/ligand interaction for development of small molecule compounds)
Drug Discovery, Development and Approval Process

Research/Preclinical Testing
- Safety
- Biological activity
- Formulation

Phase I
- IND
- Safety
- Dosage
- Effectiveness

Phase II
- Side effects
- Effectiveness

Phase III
- Confirm
- Effectiveness
- Monitor
- Adverse reactions

NDA
- FDA

6.5 years
1.5 years
2 years
3.5 years
1.5 years

Biotechnology’s contribution to drug discovery

Genomics
- Bioinformatics

Functional Genomics
- Proteomic

Virtual Screening
- Structural Biology

HT ADME
- HTP

« Hit »
- HTS

Combinatorial Chemistry
- Preclinical Development

Lead Optimisation
- Pharmacogenomics

After n cycles

reiteration

Target Validation

Assay Development

Systems Biology

Lead Optimisation

HT ADME

HTP
Biotechnology and Drug Discovery and Development

Target Discovery | Drug Discovery | Drug Development

Target Identification | Target Validation | Lead Identification | Lead Optimisation

Genomics | Functional Genomics | Chemistry Enabled | Assay Capabilities

Screening | Profiling | Preclinical | Clinical

Est | Expression Arrays | Positional cloning | SNPs

Proteomics | Transcriptomes | Transgenes | Pathway Analysis | Animal models | Knock-out | Systems Biology

Chemogenomics | Structural Genomics | Homology Modeling

Comb.Chemistry | Chemical Libraries | Natural Products | In silico modeling

Micro technology | Robotics | Microassays | Detection Systems

Chemoinformatics | Molecular Modeling | Medicinal Chemistry

Toxicogenomics

Pharmacogenomics

Pharmacogenetics

Animal testing | Kinetics | Toxicity | Carcinogenicity

ADME/ Toxicology | High Throughput

7 years | 7 years
The need for data integration

Lack of R&D Productivity

- Genomics
- Expression Profiles
- Proteomics
- Pathway Analysis
- Computational biology
- In vivo Knock-out/Knock-in
- Animal Models

Increased R&D Productivity

- Genomics
- Expression Profiles
- Proteomics
- Pathway Analysis
- Computational biology
- In vivo Knock-out/Knock-in
- Animal Models
Major Biomarker-related benefits

1. A better understanding of the molecular mechanisms of diseases and drug response
2. A safer, faster and more efficient drug development process
3. A safer utilisation of therapeutic drugs
4. Increased efficiency
5. Better post marketing surveillance
6. Methods for differentiating competitors
7. New indications for new and existing therapeutic drugs
Integrating biomarkers into the drug discovery and development

**Product Risk**
- Discovery
- Preclinical
- Phase I
- Phase II
- Phase III
- FDA
- Phase IV Market

**Regulatory risk**

**Product risk**

**Market risk**

**Project prioritization**
- Improved decision making
- Mechanistic models

**Streamlining clinical trials**
- Mechanistic proof of concept
- Reduced populations
- Surrogate endpoints instead of traditional outcomes

**Risk Benefit analysis**

**Market Segmentation**
- Less ADRs
- Drug differentiation
- New indications
Drivers of diffusion

1. Nature of disease and intervention
2. Regulation
3. Value, coverage and reimbursement
4. Ability to integrate diagnostics and pharmaceuticals
Nature of disease and intervention

- Cancer
- Infectious Disease
### Examples of FDA approved of valid genomic biomarkers for approved drug labels (www.fda.gov).

<table>
<thead>
<tr>
<th>Biomarker</th>
<th>Test utilization</th>
<th>Drug</th>
<th>Drugs associated with this biomarker</th>
<th>Label</th>
</tr>
</thead>
<tbody>
<tr>
<td>C-KIT expression</td>
<td>Information</td>
<td>Imatinib</td>
<td>Omeprazole, pantoprazole, Esomerprazole, diazepam, nelfinavir, Rabeprazole</td>
<td>Gastrointestinal stromal tumor c-Kit expression.</td>
</tr>
<tr>
<td>CYP2C19 variants</td>
<td>Information</td>
<td>Voriconazole</td>
<td>Omeprazole, pantoprazole, Esomerprazole, diazepam, nelfinavir, Rabeprazole</td>
<td>Poor Metabolizers and Extensive Metabolizers with genetic defect leads to change in drug exposure.</td>
</tr>
<tr>
<td>CYP2C9 Variants</td>
<td>Information</td>
<td>Celecoxib</td>
<td>Warfarin</td>
<td>Poor Metabolizers and Extensive Metabolizers with genetic defect leads to change in drug exposure.</td>
</tr>
<tr>
<td>CYP2D6 variants</td>
<td>Information</td>
<td>Atomoxetine</td>
<td>Venlafaxine, Risperidone, Tiotropium bromide inhalation, Tamoxifen, Timolol Maleate</td>
<td>People with reduced activity in this pathway have higher plasma concentrations of atomoxetine compared with people with normal activity.</td>
</tr>
<tr>
<td>DPD Deficiency</td>
<td>Information</td>
<td>capecitabine</td>
<td>Fluorouracil</td>
<td>Unexpected, severe toxicity has been attributed to a deficiency of dihydropyrimidine dehydrogenase (DPD) activity.</td>
</tr>
<tr>
<td>EGFR expression with alternate Context</td>
<td>Required</td>
<td>Cetuximab</td>
<td>Gefitinib</td>
<td>Patients enrolled in the clinical studies were required to have immuno-histochemical evidence of positive EGFR expression using the DakoCytomation EGFR pharmDx™ test kit.”</td>
</tr>
<tr>
<td>Her2/neu Over-expression</td>
<td>Required</td>
<td>Trastuzumab</td>
<td></td>
<td>Detection of HER2 protein overexpression is necessary for selection of patients appropriate for Herceptin therapy</td>
</tr>
<tr>
<td>Protein C deficiencies</td>
<td>Recommended</td>
<td>Warfarin</td>
<td></td>
<td>Hereditary or acquired deficiencies of protein C or its cofactor, protein S, has been associated with tissue necrosis following warfarin administration.</td>
</tr>
<tr>
<td>TPMT variants</td>
<td>Recommended</td>
<td>Azathioprine</td>
<td>Thioguanine, Mercaptopurine</td>
<td>Thiopurine methyltransferase deficiency or lower activity due to mutation at increased risk of myelotoxicity.</td>
</tr>
<tr>
<td>UGT1A1 Variants</td>
<td>Recommended</td>
<td>Irinotecan</td>
<td></td>
<td>UGT1A1 mutation in patients, exposure to drug and hence their susceptibility to toxicity.</td>
</tr>
</tbody>
</table>
### Major drug withdrawals between 1997 and 2005

<table>
<thead>
<tr>
<th>Drug</th>
<th>Date of approval</th>
<th>Date of withdrawal</th>
<th>Adverse Drug Reactions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pondimin (Fenfluramine)</td>
<td>1973</td>
<td>1997</td>
<td>Risk of heart valve abnormalities</td>
</tr>
<tr>
<td>Redux (Dexfenfluramine)</td>
<td>1996</td>
<td>1997</td>
<td>Risk of heart valve abnormalities</td>
</tr>
<tr>
<td>Seldane (Terfenadine)</td>
<td>1985</td>
<td>1998</td>
<td>Risk of fatal heart rhythm abnormalities</td>
</tr>
<tr>
<td>Duract (Bromfenac)</td>
<td>1997</td>
<td>1998</td>
<td>Severe hepatic reactions, potentially fatal fulminant hepatitis and liver failure, with some cases requiring transplantation.</td>
</tr>
<tr>
<td>Posicor (Mibefradil)</td>
<td>1997</td>
<td>1998</td>
<td>Heart conditions including arrhythmias and low blood pressure.</td>
</tr>
<tr>
<td>Raxar (Grepafloxacin)</td>
<td>1997</td>
<td>1999</td>
<td>Severe cardiovascular events among patients</td>
</tr>
<tr>
<td>Hismanal (Astemizole)</td>
<td>1998</td>
<td>1999</td>
<td>Serious cardiac side effects, involving changes in heart rhythm</td>
</tr>
<tr>
<td>Lotronex (Alosetron)</td>
<td>2000</td>
<td>2000</td>
<td>Intestinal damage resulting from ischemic colitis, severely obstructed or ruptured bowels, and death.</td>
</tr>
<tr>
<td>Propulsid (Cisapride)</td>
<td>1993</td>
<td>2000</td>
<td>Heartbeat interruption and cause an arrhythmia</td>
</tr>
<tr>
<td>Rezulin (Troglitazone)</td>
<td>1997</td>
<td>2000</td>
<td>Severe liver toxicity has been known to occur</td>
</tr>
<tr>
<td>Baycol (Cerivastatin)</td>
<td>1997</td>
<td>2001</td>
<td>Fatal rhabdomyolysis, a severe muscle adverse reaction</td>
</tr>
<tr>
<td>Raplon (Rapacuronium)</td>
<td>1999</td>
<td>2001</td>
<td>An inability to breathe normally that can lead to permanent injury or death</td>
</tr>
<tr>
<td>Vioxx (Rofecoxib)</td>
<td>1999</td>
<td>2004</td>
<td>Increased risk of heart attack and stroke</td>
</tr>
<tr>
<td>Palladone (Hydromorphone)</td>
<td>2004</td>
<td>2005</td>
<td>Potential fatalities when taken with alcohol</td>
</tr>
<tr>
<td>Bextra (Valdecoxib)</td>
<td>2001</td>
<td>2005</td>
<td>Increased risk of heart attack and stroke</td>
</tr>
</tbody>
</table>
Assessing Value

• Cost-effective Analysis
• reimbursement
Ability to integrate diagnostics & Pharmaceuticals

- Herceptin
- CYP450
Defining a Business Model

A representation of a firm’s underlying core logic and strategic choices for creating and capturing value within a value network (Shafer et al., 2005)
Competitive Environment

• Healthcare companies manufacturing tests and analyzers
• Diagnostics/Pharmaceutical companies
• Molecular services businesses
• Companies developing drug discovery technologies
• Companies developing molecular diagnostics and genetics tests
• Companies developing POC and genetic tests
• Laboratory Services
• CROs
### Publicly listed companies with commercial interest in biomarkers (As of May 30, 2008)

<table>
<thead>
<tr>
<th>Company</th>
<th>Market Capitalization</th>
<th>Activity</th>
<th>Location</th>
<th>2007 Revenues</th>
</tr>
</thead>
<tbody>
<tr>
<td>Avalon</td>
<td>USD 28.8 M</td>
<td>Technology platform</td>
<td>USA</td>
<td>USD 0.81 M</td>
</tr>
<tr>
<td>Bio-reference labs</td>
<td>USD 337 M</td>
<td>Clinical and genetic testing</td>
<td>USA</td>
<td>USD 250 M</td>
</tr>
<tr>
<td>Clinical data</td>
<td>USD 393 M</td>
<td>Pharmacogenomics</td>
<td>USA</td>
<td>USD 63.7 M</td>
</tr>
<tr>
<td>Combimatrix</td>
<td>USD 58 M</td>
<td>Technology platform</td>
<td>USA</td>
<td>USD 6.03 M</td>
</tr>
<tr>
<td>Curidium</td>
<td>UK£ 47 M</td>
<td>Companion diagnostics</td>
<td>UK</td>
<td>No revenue</td>
</tr>
<tr>
<td>Diagnocure</td>
<td>CAN$ 98</td>
<td>Diagnostics and lab services</td>
<td>Canada</td>
<td>CAN$ 3.5 M</td>
</tr>
<tr>
<td>DNA Print genomics</td>
<td>USD &lt; 1M</td>
<td>Genetic testing, SNP analysis</td>
<td>USA</td>
<td>NA</td>
</tr>
<tr>
<td>Epigenomics</td>
<td>€ 54 M</td>
<td>DNA Methylation biomarkers</td>
<td>Germany</td>
<td>€ 2.6 M</td>
</tr>
<tr>
<td>Exact Sciences</td>
<td>USD 49 M</td>
<td>DNA testing</td>
<td>USA</td>
<td>USD 1.8 M</td>
</tr>
<tr>
<td>Gene News Ltd</td>
<td>CAN$ 55 M</td>
<td>Molecular diagnostics</td>
<td>Canada</td>
<td>CAN$ 2.17 M</td>
</tr>
<tr>
<td>Genomic Health</td>
<td>USD 487 M</td>
<td>Molecular diagnostics</td>
<td>USA</td>
<td>USD 64 M</td>
</tr>
<tr>
<td>Genetic Technologies</td>
<td>USD 38 M</td>
<td>Genetic testing and services</td>
<td>Australia</td>
<td>USD 11.7 M</td>
</tr>
<tr>
<td>Genoptix</td>
<td>USD 460 M</td>
<td>Laboratory service provider</td>
<td>USA</td>
<td>USD 59.3 M</td>
</tr>
<tr>
<td>Helicos Biosciences</td>
<td>USD 99 M</td>
<td>Genetic testing</td>
<td>USA</td>
<td>USD 0.58 M</td>
</tr>
<tr>
<td>IVAX Diagnostics</td>
<td>USD 20.8 M</td>
<td>Diagnostics</td>
<td>USA</td>
<td>USD 20 M</td>
</tr>
<tr>
<td>Imaging diagnostics systems</td>
<td>USD 13 M</td>
<td>Molecular imaging</td>
<td>USA</td>
<td>USD 0.07 M</td>
</tr>
</tbody>
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<th>Location</th>
<th>2007 Revenues</th>
</tr>
</thead>
<tbody>
<tr>
<td>Interleukin Genetics</td>
<td>USD 48 M</td>
<td>Genetic tests</td>
<td>USA</td>
<td>USD 9.7 M</td>
</tr>
<tr>
<td>Medtox</td>
<td>USD 129 M</td>
<td>Lab services and diagnostics</td>
<td>USA</td>
<td>USD 80 M</td>
</tr>
<tr>
<td>Monogram Biosciences</td>
<td>USD 155.6</td>
<td>Lab services and diagnostics</td>
<td>USA</td>
<td>USD 43.2 M</td>
</tr>
<tr>
<td>Nanogen</td>
<td>USD 24 M</td>
<td>Technology platform</td>
<td>USA</td>
<td>USD 38.2 M</td>
</tr>
<tr>
<td>Nanosphere</td>
<td>USD 211 M</td>
<td>Technology platform</td>
<td>USA</td>
<td>USD 1.2 M</td>
</tr>
<tr>
<td>Orchid Cellmark</td>
<td>USD 90.8 M</td>
<td>DNA testing</td>
<td>USA</td>
<td>USD 60 M</td>
</tr>
<tr>
<td>Ore Pharmaceuticals</td>
<td>USD 11 M</td>
<td>Drug repositioning</td>
<td>USA</td>
<td>USD 1.6 M</td>
</tr>
<tr>
<td>Oncomethylome</td>
<td>€ 112 M</td>
<td>Cancer detection tests</td>
<td>Belgium</td>
<td>€ 2.6 M</td>
</tr>
<tr>
<td>Pacific biometrics</td>
<td>USD 7.6 M</td>
<td>Lab service for clinical research</td>
<td>USA</td>
<td>USD 8.5 M</td>
</tr>
<tr>
<td>Radnet</td>
<td>USD 223 M</td>
<td>Diagnostics imaging</td>
<td>USD</td>
<td>USD 425 M</td>
</tr>
<tr>
<td>Rosetta Genomics</td>
<td>USD 52M</td>
<td>MicroRNA diagnostics</td>
<td>Israel</td>
<td>No revenue</td>
</tr>
<tr>
<td>Transgenic</td>
<td>USD 39 M</td>
<td>Genetic testing</td>
<td>USA</td>
<td>USD 23 M</td>
</tr>
<tr>
<td>Vermillion</td>
<td>USD 14 M</td>
<td>Diagnostics</td>
<td>USA</td>
<td>USD 0.04 M</td>
</tr>
</tbody>
</table>
Technology Uncertainty

Commerical Uncertainty

Business Model

Financial Uncertainty

Organizational Uncertainty
**Biotechnology R&D challenges**
- Increasing complexity
- Low R&D productivity
- High R&D expenditures
- Information over-load
- Technology integration
- New technologies

**Pharmaceutical industry dynamics**
- Mainly focused on small molecules
- Intense M&A activity
- Need for late-stage compounds
- Low innovative capability
- Management of numerous Strategic alliances

**Industry and capital market challenges**
- Decreasing number of Pharmaceutical partners
- Rising expectations from pharmaceutical partners
- Volatile financing through capital markets
- Increasing investor demand for value
- Favorable government policies
- Blockbuster model no longer valid
- High-patient expectations

**Organizational challenges**
- Ressource allocation
- Critical mass
- Organizational models
- Portfolio management
- Sustainable business model

**M&A driving forces**
<table>
<thead>
<tr>
<th>Acquirer</th>
<th>Target</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical Data</td>
<td>Genaissance Pharma Oct/05</td>
</tr>
<tr>
<td>Clinical Data</td>
<td>Icoria Dec/05</td>
</tr>
<tr>
<td>Clinical Data</td>
<td>Genome Express March/06</td>
</tr>
<tr>
<td>Clinical Data</td>
<td>Epidaurus Biotech Aug/07</td>
</tr>
<tr>
<td>Qiagen</td>
<td>Digene June/07</td>
</tr>
<tr>
<td>Qiagen</td>
<td>Genaco Oct/06</td>
</tr>
<tr>
<td>Siemens</td>
<td>Bayer Diagnostics Jun/06</td>
</tr>
<tr>
<td>Siemens</td>
<td>DiagnosticsProducts Apr/06</td>
</tr>
<tr>
<td>Quest Diag.</td>
<td>LabOne Aug/05</td>
</tr>
<tr>
<td>Quest Diag.</td>
<td>Focus Diagnostics May/06</td>
</tr>
<tr>
<td>Becton Dickson</td>
<td>GeneOhm Sciences Jan/06</td>
</tr>
<tr>
<td>Fisher Scientific</td>
<td>Athena Diagnostics Mar/06</td>
</tr>
<tr>
<td>Celera</td>
<td>Berkely Hearthlab Oct/07</td>
</tr>
<tr>
<td>Celera</td>
<td>Atria Genetics Oct/07</td>
</tr>
<tr>
<td>Sequenom</td>
<td>Michigan CLIA Sep/08</td>
</tr>
</tbody>
</table>
The benefits technology roadmapping in drug discovery and development
Thank You