Adapt and Survive. The Way Forward in Research IS

Dr. Wendy A. Warr
http://www.warr.com
The Long Road to a New Medicine

Full development

- Studies in 100-300 Patients (Phase II)
- Candidate Medicine Tested in 3-10,000 Patients (Phase III)
- Large Amounts of Candidate Medicine Synthesized

Exploratory development

- Studies in Healthy Volunteers Phase I
- Formulations Developed
- Extensive Safety Studies
- Early Safety Studies
- Project Team and Plans
- Synthesis of Compounds
- Screening
- IDEA

Registration

- Clinical Data Analysis

New Medicine

Source: Pfizer
Drug Discovery and Development

- Target discovery and validation
- Assays HTS
- Hit to lead
- Lead optimization
- IND
- Early stage research and discovery
- Preclinical development
- Clinical development
  - Phase I
  - Phase II
  - Phase III
- NCE approval

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From Concept to Product: 10-15 Years

<table>
<thead>
<tr>
<th>Process</th>
<th>Months/years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Target identification and validation</td>
<td>Months/years</td>
</tr>
<tr>
<td>Lead identification</td>
<td>4-6 months</td>
</tr>
<tr>
<td>Lead optimization</td>
<td>4-6 months</td>
</tr>
<tr>
<td>Preclinical development</td>
<td>4-6 months</td>
</tr>
<tr>
<td>Phase I</td>
<td>18 months</td>
</tr>
<tr>
<td>Phase II</td>
<td>12-24 months</td>
</tr>
<tr>
<td>Phase III</td>
<td>2-3 years</td>
</tr>
<tr>
<td>FDA review and scale up to manufacturing</td>
<td>6-24 months</td>
</tr>
</tbody>
</table>
## Attrition

<table>
<thead>
<tr>
<th>Stage</th>
<th>Compounds In</th>
<th>Compounds Out</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lead identification</td>
<td>Up to 50,000</td>
<td>100-200</td>
</tr>
<tr>
<td>Lead optimization</td>
<td>100-200</td>
<td>20</td>
</tr>
<tr>
<td>Preclinical</td>
<td>20</td>
<td>1-5</td>
</tr>
<tr>
<td>Phase I</td>
<td>1-5</td>
<td>1-3</td>
</tr>
<tr>
<td>Phase II</td>
<td>1-3</td>
<td>1-2</td>
</tr>
<tr>
<td>Phase III</td>
<td>1-2</td>
<td>1</td>
</tr>
</tbody>
</table>
The Cost

Source: DiMasi, Grabowski. *Managerial and Decision Economics* 2007, 28, 469-479

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Only Two in Ten Approved Drugs Produce Revenues That Exceed Average R&D Costs

R&D Spend

Source: PhRMA

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R&D Spend

Source: PhRMA
Number of New Molecular Entities Approved
Why the Fall in Numbers of NCEs?

- Easiest drugs already found
- Companies ultra-cautious about withdrawals
- Disruption from mergers
- Or is it just the normal cycle?
Number of New Molecular Entities Approved
Measuring Return from Investment in R&D

- 10/12 top pharma saw internal rate of return (IRR) fall from 11.8% in 2010 to 8.4% in 2011
- Cost of bringing a drug to market increased by 21%
- Number of compounds in late stage development decreased from 23 to 18

Source: Deloitte and Thomson Reuters
Measuring Return from Investment in R&D

- More value from product commercialization than lost from late-stage failures
- Non-R&D costs have declined; higher operating margin
- To combat high costs in future, R&D organizations will share capabilities in non-competitive R&D areas

Source: Deloitte and Thomson Reuters
Threats to the Industry

• CAGR in sales falling
• Generic competition (“the patent cliff”)
• Price pressures
• Crowded markets
• Increasing R&D budgets
• Declining productivity
The Solution?

- Mergers and acquisitions
- Cost cutting
- Restructuring
- Diversification
- In-licensing
- Alliances and outsourcing
- Target emerging markets
- Personalized medicine
- Portfolio management techniques
- Life cycle management
Drug Pipeline Databases

- Pharmaprojects/Citeline Pipeline
- R&D Focus
- R&D Insight
- Thomson Reuters Pharma
- Thomson Reuters Integrity
## BizInt Smart Charts: Drug Pipeline Report

<table>
<thead>
<tr>
<th>Product</th>
<th>Common Drug Name</th>
<th>Database</th>
<th>Originator</th>
<th>Highest Phase</th>
<th>Commercial Intro</th>
<th>Structure</th>
<th>Mechanism of Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>AC-480</td>
<td>AC 480</td>
<td>Thomson Pharma</td>
<td>Bristol-Myers Squibb Co</td>
<td>Phase 2 Clinical</td>
<td>Ambit Biosciences, under license from Bristol-Myers Squibb, is developing AC-480 (formerly BMS-599626), an orally active inhibitor of multiple HER tyrosine kinases, for the potential treatment of cancer (699937, 895412). In December 2008, it was reported that phase II trials for solid tumors had begun (929747).</td>
<td><img src="image" alt="Structure" /></td>
<td>Anticancer EGFR family tyrosine kinase receptor inhibitor</td>
</tr>
<tr>
<td>BMS 599626</td>
<td>AC 480</td>
<td>Adis R&amp;D Insight</td>
<td>Bristol-Myers Squibb  (Originator)</td>
<td>Phase II</td>
<td>Bristol-Myers Squibb and Ambit Biosciences Corporation are co-developing BMS 599626 for the treatment of cancer. The orally administered pyrrolidine compound is a dual inhibitor of both epidermal growth factor receptor (EGFR/HER1) and HER2 (ErbB2/HER2) protein tyrosine kinases. EGFR and HER2 have been found to be frequently overexpressed in a variety of tumor types. [CONT]</td>
<td><img src="image" alt="Structure" /></td>
<td>Epidermal growth factor receptor inhibitors, HER2 inhibitors</td>
</tr>
<tr>
<td>AC 480 (free base)</td>
<td>AC 480</td>
<td>Celgene Pipeline</td>
<td>Bristol-Myers Squibb</td>
<td>No Development Reported</td>
<td>BMS-599626 is a small molecule dual kinase inhibitor which targets the HER1 and HER2 receptors, which was under development by Bristol-Myers Squibb for the treatment of breast cancer (229th ACS (San Diego), 2005, MED 21).</td>
<td><img src="image" alt="Structure" /></td>
<td>ErbB-1 tyrosine kinase inhibitor ErbB-2 tyrosine kinase inhibitor Protein kinase inhibitor Tyrosine kinase inhibitor</td>
</tr>
<tr>
<td>AC 480</td>
<td>AC 480</td>
<td>Thomson Reuters Integrity Compounds</td>
<td>Bristol-Myers Squibb</td>
<td>Phase I</td>
<td>BMS-599626 is a small molecule inhibitor of the human epidermal growth factor receptor (HER) kinase family in early clinical trials at Bristol-Myers Squibb for the treatment of metastatic solid tumors. The drug candidate targets both the HER1 and the HER2 receptors, which are frequently co-expressed in a range of tumor types and possess the ability to form heterodimers. [CONT]</td>
<td><img src="image" alt="Structure" /></td>
<td>HER4 (erbB4) inhibitors EGFR (HER1 erbB1) inhibitors ErbB (erbB2) inhibitors</td>
</tr>
<tr>
<td>AC 480</td>
<td>AC 480</td>
<td>IMS R&amp;D Focus</td>
<td>Ambit (USA)</td>
<td>Phase II</td>
<td>Ambit is developing AC 480 (BMS 599626), an orally active pan-HER tyrosine kinase inhibitor, as a potential treatment for solid tumors. In August 2006, a phase II trial of the agent in the treatment of nonsmall cell lung cancer (NSCLC) was initiated in the USA. Ambit acquired rights to AC 480 from Bristol-Myers Squibb in November 2007. A phase II trial of AC 480 in the treatment of nonsmall cell lung cancer (NSCLC) has initiated in the USA (Ambit, AUG 2008) [CONT]</td>
<td><img src="image" alt="Structure" /></td>
<td>EGF receptor inhibitor Protein kinase inhibitor Tyrosine kinase inhibitor</td>
</tr>
</tbody>
</table>

**Source:** BizInt
Senior Management

Source: http://www.flickr.com/photos/yukariryu/

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M&As: the Impact on Productivity

• Rationalization needed after merger
  – TAs, research sites, conflicting informatics
• Disruption
• Momentum lost in research
• Entrenched camps develop
• Decision making loses objectivity
• Growth is largely from cost savings
• Benefits of scale not proven beyond a certain size
• M&As are self-limiting
Product Lifecycle Management

- New indications
- Reformulations
- Combination drugs
- Rx to OTC
- Branded generics
- Mergers and acquisitions
- Alliances
- Pricing

- Patent protection strategies
- New markets
- Refocusing R&D spend
- Reducing development time
- Branding and rebranding
Making R&D More Virtual

• Semantic technologies
• Computer-aided molecule design
• Predictive biosimulation
  – virtual cells, organs, animals
  – complete digital model of man

Source: Steve Arlington, Pricewaterhouse Coopers
Rational Drug Design

• Receptor structure unknown, ligand structures unknown
• Receptor known, ligand known
• Receptor known, ligand unknown
• Receptor unknown, ligands known
Rational Drug Design

- Receptor structure unknown, ligand structures unknown
- Receptor known, ligand known
- Receptor known, ligand unknown
- Receptor unknown, ligands known
Rational Drug Design

- Receptor structure unknown, ligand structures unknown
- Receptor known, ligand known
- Receptor known, ligand unknown
- Receptor unknown, ligands known
Docking a Ligand in a Protein

Source: Cambridge Crystallographic Data Centre

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Rational Drug Design

- Receptor structure unknown, ligand structures unknown
- Receptor known, ligand known
- Receptor known, ligand unknown
- Receptor unknown, ligands known
De novo Drug Design

Source: SimBioSys
Rational Drug Design

- Receptor structure unknown, ligand structures unknown
- Receptor known, ligand known
- Receptor known, ligand unknown
- Receptor unknown, ligands known
Pharmacophore Model

Source: Accelrys

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Quantitative Structure Activity Relationships (QSAR)

- Biological Activity
  - Physicochemical & Structural Properties
    - Calculated properties
    - Measured properties
  - Toxicology
  - Pharmacology

- Statistical Relationship
  - Validation

- QSAR

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Drug Discovery in the 1970s
Drug Discovery in the 1970s

- Unplanned innovation
- Serendipity
- Drugs based on natural products
- Chemists used intuition
- Random screening
- Linear workflow
- Informatics only peripheral
Advances of the 1990s

- The human genome project
- Genomics
- Proteomics
- Growth in knowledge of protein structures
  - X-ray crystallography
  - NMR
  - homology modeling
- High throughput screening (HTS)
- Combinatorialial chemistry
- Bioinformatics and cheminformatics
Drug Discovery Today

- Start with knowledge of a biological target
  - and maybe a known protein structure
- Screen the fewest compounds needed
- Vast quantities of data
- Informatics is of strategic importance
- Informatics supports decision making
- Multi-disciplinary teams share knowledge
- "Fail early": predict druglikeness
Changing strategies

- **Pharma 1.0**
  - Blockbuster model
  - Focus on top line

- **Pharma 2.0**
  - Strategies addressed in this talk
  - Focus on bottom line

- **Pharma 3.0**
  - Delivering health outcomes
  - Being customer-centric
  - Being payer-insightful

Source: Carolyn Buck Luce, Ernst & Young