Innovation in New Drug Development: Economic Factors

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Agenda

• Background results on economic factors associated with the incentives to develop new drugs (costs, risks, and time)

• Competitive development within pharmacologic classes

• New business models and emerging R&D strategies to deal with the growing challenges of new drug development
R&D Cost per Approved Drug
Out-of-Pocket and Capitalized Cost per Approved New Compound

<table>
<thead>
<tr>
<th>Pre-human</th>
<th>Clinical</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>430</td>
<td>965</td>
<td>1,395</td>
</tr>
<tr>
<td>1,098</td>
<td>1,460</td>
<td>2,558</td>
</tr>
</tbody>
</table>

Pre-approval, Post-approval and Total Lifecycle Cost per Approved New Compound

Out-of-Pocket

- Total: 1,861
- Pre-approval: 1,395
- Post-approval: 466

Capitalized

- Total: 2,870
- Pre-approval: 2,558
- Post-approval: 312

Growth in Capitalized R&D Costs per Approved New Compound

Sources: 1970s, Hansen (1979); 1980s, DiMasi et al. (1991); 1990s-early 2000s, DiMasi et al. (2003); 2000s-early 2010s, DiMasi et al. (2016)
Cost Drivers: Change in Capitalized Cost per Approved Compound by Factor (direct cash outlays)*

<table>
<thead>
<tr>
<th>Factor Category</th>
<th>Factor</th>
<th>Percentage Change in Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cash Outlays</td>
<td>Out-of-Pocket Clinical Phase Costs</td>
<td>82.5%</td>
</tr>
<tr>
<td></td>
<td>Pre-human/Clinical Cost Ratio</td>
<td>1.6%</td>
</tr>
<tr>
<td></td>
<td>Overall Out-of-Pocket Costs</td>
<td>85.5%</td>
</tr>
</tbody>
</table>

* Factor impact on current study cost relative to prior study cost ($1,044 million in 2013 dollars)

**Cost Drivers: Change in Capitalized Cost per Approved Compound by Factor (development risk)**

<table>
<thead>
<tr>
<th>Factor Category</th>
<th>Factor</th>
<th>Percentage Change in Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risk</td>
<td>Clinical Approval Success Rate with Prior Study Distribution of Failures</td>
<td>57.3%</td>
</tr>
<tr>
<td></td>
<td>Distribution of Failures with Prior Study Clinical Approval Success Rate</td>
<td>-6.0%</td>
</tr>
<tr>
<td></td>
<td>Overall Risk Profile: Clinical Approval Success Rate plus Distribution of Failures</td>
<td>47.3%</td>
</tr>
</tbody>
</table>

* Factor impact on current study cost relative to prior study cost ($1,044 million in 2013 dollars)

### Cost Drivers: Change in Capitalized Cost per Approved Compound by Factor (time and cost of capital)*

<table>
<thead>
<tr>
<th>Factor Category</th>
<th>Factor</th>
<th>Percentage Change in Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Time</strong></td>
<td>Pre-human Phase</td>
<td>-4.9%</td>
</tr>
<tr>
<td></td>
<td>Clinical Phase</td>
<td>0.2%</td>
</tr>
<tr>
<td></td>
<td>Regulatory Review</td>
<td>-3.0%</td>
</tr>
<tr>
<td></td>
<td>Overall Development Timeline</td>
<td>-5.6%</td>
</tr>
<tr>
<td><strong>Cost of Capital</strong></td>
<td>Discount Rate</td>
<td>-3.1%</td>
</tr>
</tbody>
</table>

*Factor impact on current study cost relative to prior study cost ($1,044 million in 2013 dollars)

Some Conjectures and Evidence Underlying Growth in Clinical Costs

- Increased clinical trial complexity: more procedures per patient (additional data gathered)
- Patient recruitment and retention
- Life sciences sector inflation (cost of inputs used in development)
- Testing against comparator drugs to meet market (payer) demands for comparative effectiveness
- Higher failure rates and more indications pursued
- Increased regulatory burden for some classes of compounds
## Procedures per Protocol

<table>
<thead>
<tr>
<th>Phase</th>
<th>Unique Procedures</th>
<th>Median Number (2005)</th>
<th>1999-2005 Annual Growth Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phase I</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Unique Procedures</td>
<td>40</td>
<td>6.1%</td>
</tr>
<tr>
<td></td>
<td>Total Procedures*</td>
<td>217</td>
<td>9.5%</td>
</tr>
<tr>
<td>Phase II</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Unique Procedures</td>
<td>35</td>
<td>5.8%</td>
</tr>
<tr>
<td></td>
<td>Total Procedures</td>
<td>195</td>
<td>12.1%</td>
</tr>
<tr>
<td>Phase III</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Unique Procedures</td>
<td>33</td>
<td>5.5%</td>
</tr>
<tr>
<td></td>
<td>Total Procedures</td>
<td>132</td>
<td>6.1%</td>
</tr>
<tr>
<td>Phase IV</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Unique Procedures</td>
<td>32</td>
<td>9.1%</td>
</tr>
<tr>
<td></td>
<td>Total Procedures</td>
<td>99</td>
<td>11.0%</td>
</tr>
</tbody>
</table>

* Defined as the number of unique procedures multiplied by their frequency during the duration of the study

Source: Getz et al., American Journal of Therapeutics 2008;15:450-457
Data Points Collected per Patient for a Typical Phase III Protocol

Number of Data Points

2002: 492,000
2012: 929,000

Source: Getz and Kaitin, Re-Engineering Clinical Trials 2015: ch 1; Medidata Solutions
Regulatory Change (Diabetes Drugs) and Impact on Drug Development Costs

- **Unexpected cardiovascular risks found for diabetes drug rosiglitazone (Avandia®)**

- **FDA issued guidance in Dec 2008** (*Guidance for Industry: Diabetes Mellitus – Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes*)

- **Number of randomized patients and patient-years increased more than 2.5 and 4.0 fold before and after guidance, respectively, for diabetes drugs approved 2005-2010** (*Viereck and Boudes, Contemporary Clinical Trials, 2011;32(3):324-332*)

- **Clinical costs (particularly for phase III) higher for diabetes drugs in cost sample**
Some Observations on the R&D Results

• Not the cost of developing a single drug and indication
  ➢ Links the costs of failures with the successes
  ➢ Includes R&D expenditures on all indications pursued (successful or not)
  ➢ Includes fixed costs (non-drug specific R&D, R&D management, cost of running an ongoing R&D organization, etc.) and CMC (chemistry, manufacturing and controls)

• It’s an estimate of industry cost per approved active ingredient for a specified period (in essence, total R&D expenditures divided by the number of approved NMEs and NBEs)

• Pricing paradox
  ➢ At a macro level, expected R&D costs, together with expected prices and non-R&D costs, jointly determine the incentive to invest in innovation
  ➢ At a micro level, individual prices not set according to R&D (sunk) costs
  ➢ Individual prices depend on perceived value to patients and payers, the competitive landscape, policies and practices of government and non-government payers
Development Within Pharmacologic Classes: Imitation or Racing?
A Fairly Common Viewpoint on Me-too Drug Development

“More often, me-too drugs are made by competing companies, who create their own versions of blockbuster drugs to cut into a market that has already proved both lucrative and expandable”

Marcia Angell, 2004, The Truth About the Drug Companies: How They Deceive Us and What to Do About It
Questions About “Me-Too” Drugs

- Perfect substitutes or product differentiation offering choice from diverse product profiles and varying individual responses?
- Is research duplicative, wasteful and after-the-fact (sequential development), or does the research mainly result from a multi-firm innovation race (parallel development) for clinical advances?
- What is the impact on pricing?
- How quickly does competition emerge?
- Is the first-in-class the best-in-class?
- When does the development of me-too drugs occur in relation to marketing of the first-in-class drug?
- Are me-too drugs less safe?
Share of Later-in-Class Drugs with Patent Filed or Development Phase Initiated Prior to First-in-Class Approval

First-in-class drugs approved from 2005 to 2011; later-in-class drugs approved from 2005 to 2015

Source: DiMasi and Chakravarthy, Clinical Pharmacology and Therapeutics 2016;100(6):754-760
Time from Patent Filed or Development Phase Initiated for Later-in-Class Drugs to First-in-Class Approval

First-in-class drugs approved from 2005 to 2011; later-in-class drugs approved from 2005 to 2015

Source: DiMasi and Chakravarthy, *Clinical Pharmacology and Therapeutics* 2016;100(6):754-760
Empirical Evidence on the Effects of M&A and Alliance Activity on Pharmaceutical Innovation

- Under-researched area

- Evidence mixed, but a number of studies suggest lower post-merger R&D spending, number of projects or patents, and productivity

- The studies, however, examine short-term impacts (two or three years post-merger) and outcomes are heterogeneous

- Some evidence that alliances and mergers can be complementary (i.e., alliances pre-merger can help predict which potential mergers will be successful)

- Some evidence that at an industry level, too much M&A activity can reduce industry innovation levels (fewer independent sources of innovation)
Summary

• New drug development is lengthy, risky, and costly

• R&D costs have continued to increase in an increasingly cost-conscious market

• Biopharmaceutical innovation is competitive, with development within pharmacologic classes occurring largely contemporaneously

• Biopharmaceutical firms have increasingly engaged in collaborative discovery and development to share risks and increase innovation
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