The Economics of New Drug Development: Costs, Risks, and Returns

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The New England Drug Metabolism Group
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Agenda

- Drug development times
- Risks in new drug development
- R&D costs per approved new drug
- Returns to new drug development
- Improvements to the R&D process
- Development of “breakthrough” and “me-too” drugs
- Trends in new drug pipelines
Current Realities for Pharmaceutical Developers

- Drug development process is long, risky, expensive, and complex
- Industry is highly regulated
- Marketplace is competitive
- Market exclusivity periods have declined dramatically
- Public support has declined
FDA Amendments Act of 2007
Main Provisions

◆ Reauthorizes PDUFA and BPCA
◆ Drug safety: FDA authorized to…
  ▪ Require post-approval studies
  ▪ Require companies to develop REMs
  ▪ Order changes to drug labels
  ▪ Demand clinical transparency
  ▪ Levy substantial fines
◆ Other provisions
  ▪ PMS, AERs, clinical trial registries, DTC advertising
  ▪ Creation of Reagan-Udall Foundation (promote CPI)
Drug Development and Approval Times

Points are 3-year moving averages

Source: Tufts CSDD, 2007
Clinical and Approval Times Vary Across Therapeutic Classes, 2000-06

<table>
<thead>
<tr>
<th>Therapeutic Class</th>
<th>U.S. Clinical Phase</th>
<th>U.S. Approval Phase</th>
</tr>
</thead>
<tbody>
<tr>
<td>CNS</td>
<td>8.6</td>
<td>1.9</td>
</tr>
<tr>
<td>Antineoplastic</td>
<td>7.7</td>
<td>0.9</td>
</tr>
<tr>
<td>Endocrine</td>
<td>6.5</td>
<td>1.6</td>
</tr>
<tr>
<td>Antiinfective</td>
<td>6.2</td>
<td>1.5</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>5.9</td>
<td>2.1</td>
</tr>
<tr>
<td>AIDS Antivirals</td>
<td>5.5</td>
<td>0.5</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>5.2</td>
<td>1.5</td>
</tr>
<tr>
<td>Anesthetic/Analgesic</td>
<td>4.7</td>
<td>1.9</td>
</tr>
</tbody>
</table>

Source: Tufts CSDD, 2007
Pharmaceutical R&D Risks
Approval Success Rates for NCEs Also Vary by Therapeutic Class

- Antiinfective: 40.4%
- Oncology/Immunology: 27.2%
- Respiratory: 19.9%
- Cardiovascular: 15.2%
- Neuropharmacologic: 14.4%
- GI/Metabolism: 10.9%

Pharmaceutical R&D Costs
New Drug Approvals Are Not Keeping Pace with Rising R&D Spending

R&D expenditures are adjusted for inflation; curve is 3-year moving average for NMEs.

Source: Tufts CSDD, PhRMA, 2007
Recent Productivity Decline in the Drug Industry: Is this a Unique Phenomenon?

“In 1960 the trade press of the U.S. drug industry began to refer to the last few years as constituting a “research gap,” commenting that the flow of important new drug discoveries has for some inexplicable reason diminished.”

Opportunity Cost for Investments

◆ Consider two investment projects, A and B

◆ Both projects require the same out-of-pocket expenditure (say, $400 million)

◆ However, returns to A are realized immediately, but investors must wait 10 years before returns to B are realized

◆ Rational investors would conclude that B is effectively much costlier than A
Out-of-Pocket and Capitalized Costs per Approved Drug

Source: DiMasi et al., J Health Economics 2003;22(2):151-185
Pre-approval and Post-approval R&D Costs per Approved Drug

Source: DiMasi et al., J Health Economics 2003;22(2):151-185
Annual Growth Rates for Out-of-Pocket R&D Costs

Source: DiMasi et al., J Health Economics 2003;22(2):151-185
Clinical Cost per Approved New Drug Vary by Therapeutic Category

Source: DiMasi et al., Drug Information Journal, 2004;38(3):211-23
Mean Number of Subjects in NDAs for NMEs

<table>
<thead>
<tr>
<th>Approval Period</th>
<th>Subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td>1977-80</td>
<td>1,576</td>
</tr>
<tr>
<td>1981-84</td>
<td>1,321</td>
</tr>
<tr>
<td>1985-88</td>
<td>3,233</td>
</tr>
<tr>
<td>1990-92</td>
<td>3,567</td>
</tr>
<tr>
<td>1994-95</td>
<td>5,507</td>
</tr>
<tr>
<td>1998-01</td>
<td>5,621</td>
</tr>
</tbody>
</table>

Sources: Boston Consulting Group, 1993; Peck, Food and Drug Law J, 1997; PAREXEL, 2002
Clinical Trial Complexity Index (Phases I-III)

Source: DataEdge, 2002
Change in Protocol Eligibility Criteria

<table>
<thead>
<tr>
<th></th>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td>Inclusion</td>
<td>10</td>
<td>26</td>
</tr>
<tr>
<td>Exclusion</td>
<td>21</td>
<td>23</td>
</tr>
</tbody>
</table>

## 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>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.

Summary for R&D Costs

- R&D costs have grown substantially, even in inflation-adjusted terms
- The growth rate for discovery and preclinical development costs has decreased substantially
- Conversely, clinical costs have grown at a much more rapid rate
- New discovery and development technologies (e.g., genomics) hold the promise of lower costs in the long-run (but perhaps higher costs in the short-run)
Summary for R&D Costs (cont.)

- Evidence and conjectures regarding factors affecting growth in clinical costs
  - More clinical trial subjects
  - Increased complexity: more procedures per patient
  - Patient recruitment and retention
  - Treatments associated with chronic and degenerative diseases
  - Testing against comparator drugs
Biopharmaceutical R&D Costs
Pre-Approval Out-of-Pocket (cash outlay) and Time Costs per Approved New Biopharmaceutical*

* Based on a 30.2% clinical approval success rate

** All R&D costs (basic research and preclinical development) prior to initiation of clinical testing

Source: DiMasi and Grabowski, Managerial and Dec Econ 2007;28(4-5):469-479
Biopharmaceutical and Pharma R&D Costs Compared
Why Might Biopharma Cost Differ?

◆ Biotech firms may be more nimble and creative (different corporate culture)
◆ Replacement therapies may confront fewer safety issues (more relevant to early biotech era development)
◆ However, biotech firms have less experience in clinical development and in interacting with regulatory authorities
◆ Manufacturing process R&D and production of clinical supplies much more expensive for biopharmaceuticals
Pre-Approval Cash Outlays (out-of-pocket cost) per Approved New Molecule

* All R&D costs (basic research and preclinical development) prior to initiation of clinical testing
** Based on a 5-year shift and prior growth rates for the preclinical and clinical periods

Source: DiMasi and Grabowski, Managerial and Dec Econ 2007;28(4-5):469-479
Pre-Approval Capitalized Cost per Approved New Molecule

<table>
<thead>
<tr>
<th>Preclinical*</th>
<th>Clinical</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biotech</td>
<td>Pharma</td>
<td>Pharma (time-adjusted)**</td>
</tr>
<tr>
<td>$615</td>
<td>$439</td>
<td>$1,318</td>
</tr>
<tr>
<td>$376</td>
<td>$523</td>
<td>$899</td>
</tr>
<tr>
<td>$626</td>
<td>$879</td>
<td>$1,241</td>
</tr>
</tbody>
</table>

* All R&D costs (basic research and preclinical development) prior to initiation of clinical testing

** Based on a 5-year shift and prior growth rates for the preclinical and clinical periods

Source: DiMasi and Grabowski, Managerial and Dec Econ 2007;28(4-5):469-479
Returns to New Drug Development
Present Values of Net Sales and R&D Cost for New Drugs by Sales Decile (millions of 2000 $)

Source: Grabowski et al., PharmacoEconomics 2002; 20(Suppl 3):11-29
Productivity Improvements
Cost Reductions from Higher Clinical Success Rates

Cost Reductions from Simultaneous Percentage Decreases in All Phase Lengths

The Pace of Competitive Development
Market Exclusivity for First-in-Class has Declined: Mean Time to First Follow-on Approval

<table>
<thead>
<tr>
<th>Period of First-in-Class Approval</th>
<th>Years</th>
</tr>
</thead>
<tbody>
<tr>
<td>1970s</td>
<td>8.2</td>
</tr>
<tr>
<td>1980-84</td>
<td>5.9</td>
</tr>
<tr>
<td>1985-89</td>
<td>5.1</td>
</tr>
<tr>
<td>1990-94</td>
<td>2.8</td>
</tr>
<tr>
<td>1995-98</td>
<td>1.8</td>
</tr>
</tbody>
</table>

Source: DiMasi and Paquette, PharmacoEconomics 2004;22(Suppl 2):1-14
Percent of “Me-too” Drugs Reaching Clinical Milestone Prior to First-in-Class Drug Reaching Same Milestone

Source: DiMasi and Paquette, PharmacoEconomics 2004;22(Suppl 2):1-14
Clinical Options: Safety, Efficacy, and Convenience Trade-offs

- **Example:** beta interferons to treat multiple sclerosis (Betaseron®, Avonex®, and Rebif®)

- **Therapies differ in** relapse rates, injection site reactions, elevated liver function tests, leukopenia, rates at which neutralizing antibodies are developed, and frequency of injections.

- **Diversity in outcomes offers** individual choices that patients can make in consultation with their physicians.
Trends in Drug Development Pipelines
Clinical Testing Pipelines for Large Pharmaceutical Firms* Have Grown in Recent Years (Phase I Starts per year)

* Ten largest pharmaceutical firms

Trends in New Drug Development Pipelines* by Therapeutic Class

Percent of Phase I Pipeline

- **Antiinfective**: 7.9% (1993-97), 11.6% (1998-02), 13.7% (2003-05)
- **Cardiovascular**: 8.7% (1993-97), 9.1% (1998-02), 14.3% (2003-05)
- **CNS**: 10.7% (1993-97), 14.3% (1998-02), 20.6% (2003-05)
- **GI/Metabolism**: 4.3% (1993-97), 8.3% (1998-02), 20.2% (2003-05)
- **Oncology/Immunologic**: 9.1% (1993-97), 20.5% (1998-02), 27.2% (2003-05)
- **Respiratory**: 6.5% (1993-97), 4.8% (1998-02), 9.1% (2003-05)

* Ten largest pharmaceutical firms

Large Pharmaceutical Firms* are Increasingly Licensing-in New Drugs

* Ten largest pharmaceutical firms

Summary

- Drug development has been and still is costly, risky, and lengthy
- R&D costs have increased, but so have the returns to successful projects
- The potential payoffs for improvements in the development process are substantial
- Periods of marketing exclusivity have been shrinking for first-in-class drugs
- After a period of decline, more new drugs are now entering clinical testing pipelines