Innovation in the Pharmaceutical Industry: Trends in Time, Risks, and Costs
Agenda

• Background data on approvals and R&D expenditures
• New drug development and regulatory approval time trends
• Clinical approval and phase transition success rates for new oncology compounds
• New study of biopharmaceutical R&D costs: data and methods
• Pre-approval R&D cost per approved new drug
• Post-approval cost and total R&D lifecycle cost per approved new drug
• R&D cost growth rates
• Cost drivers
Background Data on New Drug Approvals
New Drug and Biologics Approvals and R&D Spending

R&D expenditures are adjusted for inflation; curve is a 3-year moving average for NME/NBEs
Sources: Tufts CSDD; PhRMA, 2014 Industry Profile
Trends in the Number of U.S. New Indication Approvals

New Indication Approvals

DiMasi, Clinical Therapeutics 2013;35(6):808-818

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Clinical Development and Approval Phase Times

Points are 3-year moving averages

Source: Tufts CSDD

Tufts Center for the Study of Drug Development

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Clinical Development Times Vary Across Therapeutic Classes, 2000-2013

- CNS: 8.5 years
- Antineoplastic: 7.5 years
- Endocrine: 6.5 years
- Immunologic: 6.2 years
- Antiinfective*: 6.1 years
- Cardiovascular: 5.8 years
- AIDS Antivirals: 5.3 years
- Anesthetic/Analgesic: 4.9 years

* excludes AIDS antivirals
Source: Tufts CSDD

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Regulatory Approval Times Vary Across Therapeutic Classes, 2000-2013

- CNS: 19.5 months
- Cardiovascular: 18.2 months
- Anesthetic/Analgesic: 17.0 months
- Immunologic: 16.6 months
- Antiinfective*: 15.1 months
- Endocrine: 14.9 months
- Antineoplastic: 10.0 months
- AIDS Antivirals: 7.7 months

* excludes AIDS antivirals
Source: Tufts CSDD

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Trends in Drug Development
Risk-Sharing
Trends in Collaborative and Risk-Sharing Arrangements

Source: DiMasi et al., Ther Innov Reg Sci, 2014;48(3):482-487

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Average Clinical, Approval, and Total Phase Times (2000-2011) and Shared Risk

<table>
<thead>
<tr>
<th>Clinical Phase*</th>
<th>Approval Phase**</th>
<th>Total Phase***</th>
</tr>
</thead>
<tbody>
<tr>
<td>Multi-firm clin dev</td>
<td>Single firm clin dev</td>
<td>All</td>
</tr>
<tr>
<td>74.9 months</td>
<td>66.0 months</td>
<td>70.2 months</td>
</tr>
<tr>
<td>17.0 months</td>
<td>15.8 months</td>
<td>16.4 months</td>
</tr>
<tr>
<td>91.5 months</td>
<td>82.0 months</td>
<td>86.5 months</td>
</tr>
</tbody>
</table>

*p=0.0131; **p=0.4147; ***p=0.0116

Multi-firm=licensed, co-developed, M&A

Source: DiMasi et al., Ther Innov Reg Sci, 2014;48(3):482-487

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Oncology Drug Development Risks
Phase Transition Probabilities for Cancer Drugs


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Phase Transition Probabilities for Cancer Drugs by Indication Number


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Phase Transition Probabilities for Cancer Drug Second Indications Conditional on Lead Indication Success or Failure


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R&D Cost Study Data and Methods
Outline of Study Cost Dataset

- 106 investigational new drugs and biologics from 10 firms first tested in humans anywhere in the world, 1995-2007
- Clinical period development cost data up to 2013
- Five compounds still active at the time of data collection.
- Compounds that lasted late in development oversampled to increase the amount of information for late development stages. Results then weighted to reflect the population distribution.
- Annual company biopharmaceutical R&D expenditures from 1990 to 2010 broken down in various ways (used to estimate pre-human R&D costs).
Elements Used to Determine Fully Allocated New Compound R&D Costs

- Out-of-pocket clinical costs (all indications, long-term animal testing, overhead, CMC during clinical testing and prior to first approval)
- Out-of-pocket discovery research and preclinical development costs
- Clinical approval success and phase attrition rates
- Development times
- Cost of capital
Out-of-Pocket Clinical Costs

- Survey data on costs by phase and year for a sample of investigational compounds.

- Oversampled compounds that proceeded to late-stage testing: stratified random sample.

- Weight survey response to reflect actual population distribution for strata.

- Calculate weighted average phase costs.
Out-of-Pocket Discovery and Preclinical Development Costs

• Cannot attribute all pre-human R&D costs to specific compounds.

• Use time series data on company annual aggregate spending on pre-human and clinical R&D.

• Apply lag structure on data based on gap between pre-human and clinical expenditures (difference in median phase times).

• Determine ratio of pre-human to clinical expenditures from lagged data.

• Apply ratio to clinical phase cost estimate to obtain a pre-human cost estimate.
Since many compounds fail in testing, phase costs must be weighted by the probability of entering the phase (expected costs) to obtain costs per investigational compound.

Overall clinical approval success rates used to translate cost per investigational compound to cost per approved compound.

Tufts CSDD database of investigational compounds used to estimate these probabilities (subset relevant to cost study sample period).

Other interesting results obtained: attrition rates and distribution of failures by phase.
Phase Development Times

- Use survey data to find average time in phase (across indications).

- Use survey data to find average time between start of one phase and beginning of the next phase.

- Average phase-to-phase times used to establish a representative development time profile from synthesis to approval.

- Representative time profile, along with average phase lengths, used to determine how expenditures are distributed over time.

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Cost of Capital and Capitalization

• Cost of capital is the expected return required by investors to get them to invest in drug development.

• Capital Asset Pricing Model (CAPM) applied to data on biopharmaceutical firms over relevant period to determine an industry cost of capital.

• Estimate is based on data on stock market returns and debt-equity ratios for a sample of biopharmaceutical firms.

• Used as the discount (interest) rate to capitalize R&D expenditures to marketing approval according to the estimated development timeline.
Results
# Out-of-Pocket Clinical Period Costs for Investigational Compounds (millions of 2013 dollars)

<table>
<thead>
<tr>
<th>Testing Phase</th>
<th>Mean</th>
<th>Median</th>
<th>Standard Deviation</th>
<th>N</th>
<th>Coeff of Variation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phase I</td>
<td>25.3</td>
<td>17.3</td>
<td>29.6</td>
<td>97</td>
<td>1.17</td>
</tr>
<tr>
<td>Phase II</td>
<td>58.6</td>
<td>44.8</td>
<td>50.8</td>
<td>78</td>
<td>0.87</td>
</tr>
<tr>
<td>Phase III</td>
<td>255.4</td>
<td>200.0</td>
<td>153.3</td>
<td>42</td>
<td>0.60</td>
</tr>
</tbody>
</table>
Coefficients of Variation by Clinical Phase for Prior* and Current Studies and for NPV of Lifetime Global Sales**

* DiMasi et al., J Health Econ 2003;22(3):151-185

** Berndt et al., Health Aff 2015;34(2):245-252
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### Number of Indications Pursued for Investigational Drugs During Pre-Approval Clinical Development

<table>
<thead>
<tr>
<th>Number of Indications</th>
<th>1st Quartile</th>
<th>Median</th>
<th>3rd Quartile</th>
<th>Mean</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unweighted</td>
<td>1.00</td>
<td>2.00</td>
<td>3.00</td>
<td>2.49</td>
</tr>
<tr>
<td>Weighted</td>
<td>1.00</td>
<td>1.00</td>
<td>2.00</td>
<td>2.02</td>
</tr>
</tbody>
</table>

Range: 1 - 19

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Mean Number of Indications Pursued for Investigational Drugs During Pre-Approval Clinical Development by Class and Type

Mean Number of Indications

- GI/Metabolism: 1.5 (Unweighted), 1.6 (Weighted)
- Cardiovascular: 1.7 (Unweighted), 1.4 (Weighted)
- CNS: 1.9 (Unweighted), 1.7 (Weighted)
- Antineoplastic: 5.1 (Unweighted), 3.8 (Weighted)
- Small Molecule: 2.5 (Unweighted), 2.0 (Weighted)
- Large Molecule: 2.5 (Unweighted), 2.4 (Weighted)

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Mean Number of Indications Pursued Prior to Research Termination or Original Approval for Investigational Drugs by Latest Clinical Phase Entered

<table>
<thead>
<tr>
<th>Phase</th>
<th>Mean Number of Indications</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phase I</td>
<td>1.41</td>
<td>1 - 19</td>
</tr>
<tr>
<td>Phase II</td>
<td>1.94</td>
<td></td>
</tr>
<tr>
<td>Phase III</td>
<td>3.44</td>
<td></td>
</tr>
</tbody>
</table>

Range: 1 - 19
Data for Phase Transition and Approval Success Rate Estimates

- Tufts CSDD dataset of investigational compounds in the portfolios of top 50 firms.

- Subset of self-originated compounds first tested in humans anywhere in the world from 1995 to 2007.

- 1,442 compounds met study inclusion criteria.

- Development status checked through end of 2013.

- For this set of compounds, 7.1% were approved, 80.3% had been discontinued in some phase, and 12.6% were still active in some phase.
Clinical Phase Transition Probabilities and Overall Clinical Approval Success Rate*

Transition Probability

<table>
<thead>
<tr>
<th>Phase I-II</th>
<th>Phase II-III</th>
<th>Phase III-ND/BLA Sub</th>
<th>NDA/BLA Sub-NDA/BLA App</th>
<th>Phase I - NDA/BLA App</th>
</tr>
</thead>
<tbody>
<tr>
<td>59.52%</td>
<td>35.52%</td>
<td>61.95%</td>
<td>90.35%</td>
<td>11.83%</td>
</tr>
</tbody>
</table>

*Therapeutic new molecular entities and new therapeutically significant biologic entities first tested in humans, 1995-2007

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New Drug Development Risks Have Increased Markedly

Clinical Approval Success Rate

- 1970s-early 1980s approvals: 12.0%
- 1980s-early 1990s approvals: 23.0%
- 1990s-early 2000s approvals: 21.5%
- 2000s-early 2010s approvals: 11.8%


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Distribution of Failures by Phase: Failing the Failures Faster

<table>
<thead>
<tr>
<th>Phase</th>
<th>Current Study</th>
<th>Prior Study*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phase I</td>
<td>45.9</td>
<td>36.9</td>
</tr>
<tr>
<td>Phase II</td>
<td>43.5</td>
<td>50.5</td>
</tr>
<tr>
<td>Phase III/RR</td>
<td>10.6</td>
<td>12.6</td>
</tr>
</tbody>
</table>

- DiMasi et al., *J Health Econ* 2003;22(3):151-185

* Do not distribute without speaker permission
## Expected Out-of-Pocket Clinical Period Cost per Investigational Compound (millions of 2013 dollars)

<table>
<thead>
<tr>
<th>Testing Phase</th>
<th>Mean Cost</th>
<th>Probability of Entering Phase</th>
<th>Expected Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phase I</td>
<td>25.3</td>
<td>100%</td>
<td>25.3</td>
</tr>
<tr>
<td>Phase II</td>
<td>58.6</td>
<td>59.5%</td>
<td>34.9</td>
</tr>
<tr>
<td>Phase III</td>
<td>255.4</td>
<td>21.1%</td>
<td>54.0</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td></td>
<td></td>
<td><strong>114.2</strong></td>
</tr>
</tbody>
</table>
# Expected Out-of-Pocket Clinical Period Cost per Approved Compound (millions of 2013 dollars)*

<table>
<thead>
<tr>
<th>Testing Phase</th>
<th>Mean Cost</th>
<th>Expected Cost per Investigational Compound</th>
<th>Expected Cost per Approved Compound</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phase I</td>
<td>25.3</td>
<td>25.3</td>
<td>213.9</td>
</tr>
<tr>
<td>Phase II</td>
<td>58.6</td>
<td>34.9</td>
<td>295.0</td>
</tr>
<tr>
<td>Phase III</td>
<td>255.4</td>
<td>54.0</td>
<td>456.6</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td></td>
<td></td>
<td>965.5</td>
</tr>
</tbody>
</table>

* Clinical approval success rate= 11.83%
Clinical Phase Cost per Investigational Compound by Whether the Compound Progressed to Next Phase

<table>
<thead>
<tr>
<th>Phase</th>
<th>Failed in phase (median)</th>
<th>Failed in phase (mean)</th>
<th>Succeeded in phase (median)</th>
<th>Succeeded in phase (mean)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phase I</td>
<td>21.4</td>
<td>16.7</td>
<td>22.4</td>
<td>27.7</td>
</tr>
<tr>
<td>Phase II</td>
<td>33.8</td>
<td>68.9</td>
<td>46.5</td>
<td>81.4</td>
</tr>
<tr>
<td>Phase III</td>
<td>109.1</td>
<td>287.9</td>
<td>184.2</td>
<td>336.6</td>
</tr>
</tbody>
</table>
Mean Total Clinical Phase Times (across indications)

- Phase I: 33.1 months
- Phase II: 37.9 months
- Phase III: 45.1 months

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Representative Development and Regulatory Review
Time Profile (synthesis to approval)

- **Synthesis — Approval**: 128.0 months
- **Clinical Start — Approval**: 96.8 months
- **Synthesis — Phase I**: 31.2 months
- **Phase I — II**: 19.8 months
- **Phase II — III**: 30.3 months
- **Phase III — NDA/BLA Submission**: 30.7 months
- **NDA/BLA Submission — Approval**: 16.0 months

*Months*
### Nominal and Real Cost of Capital (COC) for the Biopharmaceutical Industry, 1994-2010

<table>
<thead>
<tr>
<th>Year</th>
<th>Nominal COC</th>
<th>Inflation Rate</th>
<th>Real COC</th>
</tr>
</thead>
<tbody>
<tr>
<td>1994</td>
<td>14.2%</td>
<td>3.1%</td>
<td>11.1%</td>
</tr>
<tr>
<td>2000</td>
<td>14.9%</td>
<td>3.1%</td>
<td>11.8%</td>
</tr>
<tr>
<td>2005</td>
<td>13.3%</td>
<td>2.5%</td>
<td>10.8%</td>
</tr>
<tr>
<td>2010</td>
<td>11.4%</td>
<td>2.0%</td>
<td>9.4%</td>
</tr>
</tbody>
</table>

**Implication:** R&D costs were capitalized at a 10.5% real COC
# Capitalized Clinical Period Costs (millions of 2013 dollars)

<table>
<thead>
<tr>
<th>Testing Phase</th>
<th>Capitalized Mean Cost*</th>
<th>Capitalized Expected Cost per Investigational Compound</th>
<th>Capitalized Expected Cost per Approved Compound**</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phase I</td>
<td>49.6</td>
<td>49.6</td>
<td>419.3</td>
</tr>
<tr>
<td>Phase II</td>
<td>95.3</td>
<td>56.7</td>
<td>479.3</td>
</tr>
<tr>
<td>Phase III</td>
<td>314.0</td>
<td>66.4</td>
<td>561.3</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>172.7</td>
<td>1,460</td>
</tr>
</tbody>
</table>

*Discount rate=10.5%
**Clinical approval success rate=11.83%
Pre-human Cost Estimates

• Annual data on pre-human and clinical period company R&D expenditures on self-originated investigational compounds aggregated across companies.

• Need to impose a lag structure between pre-human and clinical expenditures.

• Based on development time data, assume a 5-year lag between median pre-human and median clinical expenditures.

• Implies that pre-human expenditures are 30.8% of costs per approved compound.

• Results are not very sensitive to assumed lag within reason (4 and 6-year lags applied in sensitivity analysis)
Out-of-Pocket and Capitalized Cost per Approved New Compound

Millions of 2013 $

Pre-human: Out-of-Pocket $430, Capitalized $1,098
Clinical: Out-of-Pocket $965, Capitalized $1,460
Total: Out-of-Pocket $1,395, Capitalized $2,558

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Capitalized Pre-human, Clinical, and Total Cost per Approved New Compound by Discount Rate

Discount Rate (%)

Millions of 2013 $
Monte Carlo Simulation Forecasts for Total Capitalized Cost per Approved New Compound
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

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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, Current Study

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Compound Annual Inflation-Adjusted Growth Rates for Out-of-Pocket R&D Costs

Pre-human
- 1970s to 1980s: 7.8%
- 1980s to 1990s: 2.3%
- 1990s to early 2010s: 9.6%

Clinical
- 1970s to 1980s: 6.1%
- 1980s to 1990s: 11.8%
- 1990s to early 2010s: 9.2%

Total
- 1970s to 1980s: 7.0%
- 1980s to 1990s: 7.6%
- 1990s to early 2010s: 9.3%

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Compound Annual Inflation-Adjusted Growth Rates for Capitalized R&D Costs

<table>
<thead>
<tr>
<th></th>
<th>Pre-human</th>
<th>Clinical</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>1970s to 1980s</td>
<td>3.5%</td>
<td>7.3%</td>
<td>9.4%</td>
</tr>
<tr>
<td>1980s to 1990s</td>
<td>10.6%</td>
<td>12.2%</td>
<td>9.4%</td>
</tr>
<tr>
<td>1990s to early 2010s</td>
<td>8.8%</td>
<td>7.4%</td>
<td>8.5%</td>
</tr>
</tbody>
</table>
### 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><strong>Cash Outlays</strong></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></td>
<td></td>
</tr>
<tr>
<td>Pre-human Phase</td>
<td>-4.9%</td>
<td></td>
</tr>
<tr>
<td>Clinical Phase</td>
<td>0.2%</td>
<td></td>
</tr>
<tr>
<td>Regulatory Review</td>
<td>-3.0%</td>
<td></td>
</tr>
<tr>
<td>Overall Development Timeline</td>
<td>-5.6%</td>
<td></td>
</tr>
<tr>
<td><strong>Cost of Capital</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Discount Rate</td>
<td>-3.1%</td>
<td></td>
</tr>
</tbody>
</table>

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

• Drug development have stabilized, but are still quite lengthy.

• Clinical approval success rates have declined significantly.

• R&D costs have continued to increase at high rates.

• Both clinical and pre-human R&D costs have risen substantially over the last decade or so.

• What can be done to “bend the R&D cost curve”?