Briefing

Cost of Developing a New Drug

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Innovation in the Pharmaceutical Industry: New Estimates of R&D Costs
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Agenda

- Main Finding
- Data and Methods
- Clinical approval rates, phase transition rates, and out-of-pocket costs per approved compound
- Development times, the discount rate, and capitalized costs per approved compound
- Post-approval cost estimates
- R&D cost growth rates
- Cost drivers
Main Finding:

The estimated average pre-tax industry cost per new prescription drug approval (inclusive of failures and capital costs) is:

$2,558 million
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

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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.
Clinical Approval Success Rates

Â 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.

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

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

Â 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.
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
Dataset of investigational compounds in the portfolios of top 50 firms (several commercial pipeline databases, published company pipelines, clinicaltrials.gov, web searches).

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*

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

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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

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Pre-human Cost Estimates

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

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

Â Based on development time data, we used a 5-year lag between median pre-human and median clinical expenditures.

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

Â Results are not very sensitive to assumed lag within reason (4 and 6-year lags applied in sensitivity analysis)
Nominal and Real Cost of Capital (COC) for the Biopharmaceutical Industry, 1994-2010

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

Implication: R&D costs were capitalized at a 10.5% real COC
Out-of-Pocket and Capitalized Cost per Approved New Compound

Out-of-Pocket Cost

- Pre-human: $430
- Clinical: $965
- Total: $1,395

Capitalized Cost

- Pre-human: $1,098
- Clinical: $1,460
- Total: $2,558

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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

Millions of 2013 $
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: 9.6%
- 1990s to early 2010s: 2.3%

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

Pre-human
- 1970s to 1980s: 10.6%
- 1980s to 1990s: 3.5%
- 1990s to early 2010s: 8.8%

Clinical
- 1970s to 1980s: 7.3%
- 1980s to 1990s: 7.4%
- 1990s to early 2010s: 12.2%

Total
- 1970s to 1980s: 9.4%
- 1980s to 1990s: 7.4%
- 1990s to early 2010s: 8.5%
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>
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<tbody>
<tr>
<td>Cash Outlays</td>
<td>Out-of-Pocket Clinical Phase Costs</td>
<td>82.5%</td>
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<tr>
<td></td>
<td>Pre-human/Clinical Cost Ratio</td>
<td>1.6%</td>
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<tr>
<td></td>
<td>Overall Out-of-Pocket Costs</td>
<td>85.5%</td>
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</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>
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</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>
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<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)
Summary

- Total capitalized cost per approved new compound grew at an 8.5% compound annual rate; out-of-pocket cost per approved new compound grew at a 9.3% annual rate.

- Clinical approval success rates have declined significantly.

- Increases in the cash outlays used to conduct clinical development and higher drug failure rates during clinical testing have contributed most to the estimated increase in R&D costs.

- Changes in the time to develop and get new drugs approved and in the cost of capital had modest moderating effects on the increase in total R&D cost.
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