Economic Challenges of Antibacterial Drug Development

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DISCLAIMER
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Presentation Outline

- ERG study for HHS ASPE*
  - Objectives
  - Model framework
  - Key findings
  - Limitations

- Implications for incentive choices designed to stimulate antibacterial drug development

Available at:
http://aspe.hhs.gov/sp/reports/2014/antibacterials/rpt_antibacterials.cfm
### Fostering Antibacterial Drug Development

#### Analytical Framework

- **Policy Questions**: What are the incentives? At what level(s) should they be provided?
- **Economic Questions**: What are the private and social value of antibacterial drugs?
Study Objective

- Develop an analytic framework that can be used to assess impacts of different incentives on private and social returns to new antibacterial drug development

ANTIBACTERIAL DRUGS FOR TREATING:
- ABOM
- ABSSSI
- CABP
- CIAI
- CUTI
- HABP/VABP
Private Expected Net Present Value (ENPV) Model
Example: CABP Decision Tree (Values in $ million)

PRECLINICAL: 5.5 years
PHASE I: 0.9 years
PHASE II: 1.3 years
PHASE III: 1.0 years
NDA/BLA: 0.8 year

Success
Success
Success
Success
Success
Failure
Failure
Failure
Failure
Abandon

Model Frame of Reference

Develop

$37

$1,724

$-97

$-62

$-34

$-22

$-16

$0
Private ENPV (in $ million) by Indication

- Private ENPV variable across indications
- CABP has the highest private ENPV & HABP/VABP the lowest
- Large variation in private ENPV for all indications
- Lower bound private ENPV < $0 for all

<table>
<thead>
<tr>
<th>Indication</th>
<th>Private ENPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABOM</td>
<td>-$3</td>
</tr>
<tr>
<td>ABSSSI</td>
<td>$27</td>
</tr>
<tr>
<td>CABP</td>
<td>$37</td>
</tr>
<tr>
<td>CIAI</td>
<td>$9</td>
</tr>
<tr>
<td>CUTI</td>
<td>$22</td>
</tr>
<tr>
<td>H/VABP</td>
<td>-$4</td>
</tr>
</tbody>
</table>

Note: Error bars represent 90% confidence bounds around the mean value.
Evaluating Incentives for Antibacterial Drug Development
Incentives Selected for Analysis

<table>
<thead>
<tr>
<th>INCENTIVE</th>
<th>IMPACT ON PRIVATE ENPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intellectual Property (IP) extensions [a]</td>
<td>Delays generic entry</td>
</tr>
<tr>
<td>Tax incentives</td>
<td>Decreases cost of capital</td>
</tr>
<tr>
<td>Modifications to the clinical trial process and approval standards aimed at shortening the drug development process</td>
<td>Reduces time to market</td>
</tr>
<tr>
<td>Private grants, awards, and prizes for antibacterial product research and development (paid out sequentially)</td>
<td>Decreases R&amp;D costs</td>
</tr>
</tbody>
</table>

[a] IP collectively refers to patents/DE/ME/PTAs/PTEs/SPCs
Threshold Analysis of Select Incentives, by Indication

E(NPV\textsubscript{R4321,0}) = $100 Million
**Difference b/w $100 Million Threshold & Private ENPV**

- Private ENPV < $100 million threshold for all
- Private ENPV <0 for ABOM and HABP/VABP

<table>
<thead>
<tr>
<th></th>
<th>ABOM</th>
<th>ABSSSI</th>
<th>CABP</th>
<th>CIAI</th>
<th>CUTI</th>
<th>H/VABP</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Private ENPV</strong></td>
<td>-$3</td>
<td>$27</td>
<td>$37</td>
<td>$9</td>
<td>$22</td>
<td>-$4</td>
</tr>
<tr>
<td><strong>Difference b/w $100 M and Private ENPV</strong></td>
<td>$103</td>
<td>$73</td>
<td>$63</td>
<td>$91</td>
<td>$78</td>
<td>$104</td>
</tr>
</tbody>
</table>
## Incentive Values Needed to Get to the $100 Million Threshold

<table>
<thead>
<tr>
<th>Incentive</th>
<th>Model Parameter</th>
<th>Baseline</th>
<th>ABOM</th>
<th>ABSSSI</th>
<th>CABP</th>
<th>CIAI</th>
<th>CUTI</th>
<th>HABP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intellectual Property (IP) extensions [a]</td>
<td>Time to Generic Entry (in years)</td>
<td>12</td>
<td>N/S</td>
<td>N/S</td>
<td>N/S</td>
<td>N/S</td>
<td>N/S</td>
<td>N/S</td>
</tr>
<tr>
<td>Tax incentives</td>
<td>Real Opportunity Cost of Capital</td>
<td>11%</td>
<td>N/S</td>
<td>2.4%</td>
<td>7.4%</td>
<td>N/S</td>
<td>2.1%</td>
<td>N/S</td>
</tr>
<tr>
<td>Modifications to the clinical trial process &amp; approval standards</td>
<td>Total Time to Market (in Years)</td>
<td>Varies</td>
<td>N/S</td>
<td>~3.5</td>
<td>~4.0</td>
<td>N/S</td>
<td>~2.0</td>
<td>N/S</td>
</tr>
</tbody>
</table>

| Grants/Awards/Prizes paid out sequentially (in $ million)                 |                                           |          |      |        |      |      |      |      |
| Pre-clinical                                                              |                                           | $0       | $98  | $59    | $46  | $79  | $53  | $103 |
| Phase 1                                                                   |                                           | $0       | $98  | $76    | $67  | $89  | $86  | $103 |
| Phase 2                                                                   |                                           | $0       | $196 | $165   | $159 | $203 | $223 | $207 |
| Phase 3                                                                   |                                           | $0       | $586 | $495   | $477 | $617 | $694 | $621 |
| NDA/BLA Approval                                                          |                                           | $0       | $147 | $124   | $119 | $154 | $173 | $155 |

[a] IP collectively refers to patents/DE/ME/PTAs/PTEs/SPCs. The example is more applicable to patent extensions, however. N/S = No solution.
Observations on Incentive Analysis Results

- IP extensions are not sufficient by themselves
- % reduction in cost of capital needed through tax incentives ranges from 33% (ABSSSI) to 81% (CUTI) from the baseline level of 11%
- Decreasing the overall time to market through modifications to clinical trial process and approval standards insufficient for ABOM, CIAI, and HABP/VABP. For ABSSSI, CABP, and CUTI, the total time to market needs to reduce significantly to 2 to 4 years
- Grant/award/prize amounts increase substantially if paid out at later stages of clinical development
- Inclusion of the pre-clinical phase and its duration has a big impact on private ENPV and hence incentive results
Observations on Incentive Analysis Results (cont.)

- Incentive results are **highly** sensitive to opportunity cost of capital value!
# Sensitivity of Incentive Values Needed to Get to the $100 Million Threshold to Opportunity Cost of Capital Assumption

<table>
<thead>
<tr>
<th>Grant/Prize/Award Paid out Sequentially (in $ million)</th>
<th>ABOM</th>
<th>ABSSSI</th>
<th>CABP</th>
<th>CIAI</th>
<th>CUTI</th>
<th>HABP</th>
</tr>
</thead>
<tbody>
<tr>
<td>R=11% R=9%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre-clinical</td>
<td>$98</td>
<td>$75</td>
<td>$59</td>
<td>$21</td>
<td>$46</td>
<td>$6</td>
</tr>
<tr>
<td>Phase 1</td>
<td>$98</td>
<td>$80</td>
<td>$76</td>
<td>$58</td>
<td>$67</td>
<td>$42</td>
</tr>
<tr>
<td>Phase 2</td>
<td>$196</td>
<td>$160</td>
<td>$165</td>
<td>$123</td>
<td>$159</td>
<td>$125</td>
</tr>
<tr>
<td>Phase 3</td>
<td>$586</td>
<td>$593</td>
<td>$495</td>
<td>$480</td>
<td>$477</td>
<td>$404</td>
</tr>
<tr>
<td>NDA/BLA Approval</td>
<td>$147</td>
<td>$132</td>
<td>$124</td>
<td>$90</td>
<td>$119</td>
<td>$101</td>
</tr>
</tbody>
</table>

R = Real opportunity cost of capital
Observations on Incentive Analysis Results (cont.)

- Incentive results are dependent on where a sponsor is on the development process when making the decision at present!
Value of 5 Years of Delay in Generic Entry for a Sponsor at Start of Pre-Clinical Phase

<table>
<thead>
<tr>
<th>Phase</th>
<th>Success</th>
<th>Failure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preclinical</td>
<td>35%</td>
<td>65%</td>
</tr>
<tr>
<td>Phase I</td>
<td>67%</td>
<td>33%</td>
</tr>
<tr>
<td>Phase II</td>
<td>50%</td>
<td>50%</td>
</tr>
<tr>
<td>Phase III</td>
<td>67%</td>
<td>33%</td>
</tr>
<tr>
<td>NDA/BLA</td>
<td>85%</td>
<td>15%</td>
</tr>
</tbody>
</table>

Δ = $9

Model Frame of Reference

5.5 years Preclinical
0.9 years Phase I
1.3 years Phase II
1.0 years Phase III
0.8 year NDA/BLA

$37 → $46

$1,724 → $1,987

$0
Value of 5 Years of Delay in Generic Entry for a Sponsor at Start of Phase 3

New Frame of Reference

PRECLINICAL | PHASE I | PHASE II | PHASE III | NDA/BLA
---|---|---|---|---
Develop | Success | Success | 85% Success | $4,035→$4,642
Abandon | $0 | $0 | $0 | $0

Develop | Success | 67% | $2,255→$2,601 Δ = $346
Abandon | $0 | $0 | $0 | $0

Develop | 33% Failure | $0 | $0 | $0

Success | 15% Failure | $0 | $0 | $0

Failure | $0 | $0 | $0 | $0

Δ = $346

Success | $0 | $0 | $0 | $0

Failure | $0 | $0 | $0 | $0

Abandon | $0 | $0 | $0 | $0
## Value of a 5-year Delay in Generic Entry, by Stage of Development & Bacterial Disease

<table>
<thead>
<tr>
<th>Bacterial Disease</th>
<th>Developer at the Start of</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pre-clinical</td>
<td>Phase 1</td>
</tr>
<tr>
<td>ABOM</td>
<td>$2.8</td>
<td>$15.1</td>
</tr>
<tr>
<td>ABSSSI</td>
<td>$7.2</td>
<td>$38.3</td>
</tr>
<tr>
<td>CABP</td>
<td>$8.7</td>
<td>$46.3</td>
</tr>
<tr>
<td>CIAI</td>
<td>$4.6</td>
<td>$24.4</td>
</tr>
<tr>
<td>CUTI</td>
<td>$6.4</td>
<td>$34.2</td>
</tr>
<tr>
<td>HABP/VABP</td>
<td>$2.8</td>
<td>$14.7</td>
</tr>
<tr>
<td>ABOM</td>
<td>$2.8</td>
<td>$15.1</td>
</tr>
</tbody>
</table>
Study Limitations

- Simplified decision tree
- High model parameter uncertainty
  - Opportunity cost of capital
  - Market size
- Sponsor-specific factors and private ENPV threshold
  - New product candidate portfolio
  - Size of company (small versus large)
  - Type of company (pharmaceutical or biopharmaceutical)
- Evaluation of incentives one at a time when combination of incentives might be preferable
- Consideration of US market rather than global market
Implications of the Study for Incentive Choices

- Indifferent among the 4 different incentive methods considered
- Optimal incentive levels
  - Dependent on
    • Type of indication the drug is designed to treat
    • Development stage the drug developer is in
  - Hard to estimate precisely given the high degree of parameter uncertainty
Acknowledgments

- HHS ASPE: Amber Jessup, Hui-Hsing Wong
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