The Value of Risk Reduction in CNS Drug Development: Use of Expected Net Present Value (eNPV) as a Model

Greenblatt, W., Gilbert, P., Mallinckrodt, C.H., Williams, J.B.R., Popp, D., Kane, J., Derke, M.J.

The economic impact of applying risk reduction methods to CNS trials is estimated using expected Net Present Value (eNPV). eNPV evaluates all cash-flow expected, adjusted time and the probability of success.

- For example, a product that costs $20 to produce with a 50% chance of generating $10 will have an eNPV of $(20*0.5)-$10=-$12.50.
- If there is any delay in the revenue, the annual discount rate must be applied to cover the cost of capital.
- Cost of Phase IV Commitment in Years 2-3 (per year) ($): $2,000,000
- Discount Rate (%): 12

At the time of launch, the eNPV of a drug that will deliver $1 billion peak sales is estimated to be under $1 billion, under the conditions to the right:

<table>
<thead>
<tr>
<th>Phase</th>
<th>Cost (in millions)</th>
<th>Probability of Success</th>
<th>Cost of Goods Sold (COGS; %)</th>
<th>Marginal Tax Rate (MTR; %)</th>
<th>Peak Sales ($)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phase</td>
<td>40,000,000</td>
<td>97%</td>
<td>15</td>
<td>25</td>
<td>1,000,000,000</td>
</tr>
<tr>
<td>Phase IIa</td>
<td>30,000,000</td>
<td>50%</td>
<td>20</td>
<td>25</td>
<td>500,000,000</td>
</tr>
<tr>
<td>Phase</td>
<td>30,000,000</td>
<td>91%</td>
<td>20</td>
<td>25</td>
<td>200,000,000</td>
</tr>
<tr>
<td>Final Data</td>
<td>10,000,000</td>
<td>99%</td>
<td>15</td>
<td>25</td>
<td>10,000,000</td>
</tr>
</tbody>
</table>

INTRODUCTION

Recent data suggests that the probability of success in a phase II clinical trial has the largest influence on C&D productivity of any of the features explored across all phases of discovery and clinical development. However, failure rates in phase 2 are quite high, particularly in CNS. For example, 93% of CNS clinical trials (a major depressive disorder) when a drug ultimately demonstrated to be effective is compared vs. placebo’s probability of statistically significant differences is approximately 30%, much lower than the 60% to 90% success rate expected from the statistical powering of clinical studies. Several methods have been proposed to reduce the risk of CNS drug failure. These methods include review of recorded assessments, novel clinical endpoints and extreme innovation, statistical methodologies, to name a few. However, to our knowledge, quantitative modeling has not been used to assess how much value risk reduction methods may add to the R&D process.

METHODS

The risk-adjusted value of the drug at the start of phase III is estimated using the following formula:

\[ \text{eNPV at Start of Phase III} = \frac{\text{NPV of Drug at Launch} - \text{Risk-adjusted cost of clinical trials}}{1 + \text{Discount Rate}} \]

Next, the risk-adjusted value of the drug at the start of phase IIa is calculated:

\[ \text{eNPV at Start of Phase IIa} = \frac{\text{NPV of Drug at Launch} - \text{Risk-adjusted cost of clinical trials} + \text{Cost of Clinical Trials in Phase IIa}}{1 + \text{Discount Rate}} \]

Finally, eNPV at the start of phase IIa substracts the risk-adjusted value of the drug, the time-discounted cost of bringing the drug from phase IIa to launch using the phase durations and time-adjusted costs above:

\[ \text{eNPV at Start of Phase IIa} = \frac{\text{NPV of Drug at Launch} - \text{Risk-adjusted cost of clinical trials} + \text{Cost of Clinical Trials in Phase IIa}}{1 + \text{Discount Rate}} - \text{Cost of Clinical Trials in Phase IIa} \]

Lastly, to assess the impact of applying risk reduction, eNPV is calculated under the following 6 conditions:

1. Probability of Success in Standard Risk
2. Probability of Success in Risk Reduced by 1%
3. Probability of Success in Risk Reduced by 20%
4. Probability of Failure in Standard Risk
5. Probability of Failure in Risk Reduced by 1%
6. Probability of Failure in Risk Reduced by 20%

USING THE RESULTS

Using standard risk, probability of failure in Phase IIb is 50%, probability of failure in Phase III is 30%. Total risk-adjusted cost of drug development in Standard Risk is $7,950,686. Using the Standard Risk approach, the $1.663 billion value of the drug at the time of launch is diminished to $1.379 billion. The difference in the value of the drug at launch increases to $1.379 billion by adjusting for a 12% annual discount rate. Therefore, the eNPV is increased by $394.6 million.

Increasing the probability of success in phase IIb by just one percentage point increases eNPV by $18.2 million after adjusting for the discount rate.

DISCUSSION

Quantifying the dollar value of reducing the risk of failure in phases II and III underscores the significant return on investment afforded by methods that can reduce clinical trial failure rates even slightly, not to mention their potential to advance medical science by averting false negatives that keep important new drugs from patients who need them. Serious consideration should be given, both from a medical and financial perspective, to methods for reducing attrition, especially in disease states with known high rates of failed trials, such as MDD, CNS, AD and many other CNS disorders.

There are many limitations to this analysis. All of the assumptions about costs, patient life, success rates of trials and phases, and development times and the assumption that - assumptions. They may be very inappropriate for a specific drug development plan. However, all are within the range of published literature, and the general approach taken here can be easily modified, for example, to fit a drug with 5 years of marketed product life instead of 10, etc. The quantitative estimates (1% 20% of potential impact of employing risk reduction methods are also illustrative assumptions that are easy modified but are as rigorous and as decision-making tools. Further, these estimates do not include the incremental costs of employing risk reduction methods in clinical trials. Lastly, the simulations of phase II and III failure rates assumes the development of a drug which is, for safety and efficiency and ultimately approved for commercialization. However, additional simulations can be brought to bear across portfolios of successful and unsuccessful drugs, and there is also incremental value to improved signal detection in the case of unsuccessful drugs (i.e., faster)

Word worth considering is that many aspects of improved signal detection are not assessed here, and in these cases we attempted to rely consistently on the conservative side. For example, more successful trials earlier could have several other positive impacts on NPV, such as potential first-to-market advantages in regulatory time, first mover advantage in marketing and sales, etc.