A pharmaceutical company had to decide whether to start expensive efficacy trials for a potential antidepressant with an unproven mechanism of action and toxicity risks that increased sharply with dose. Analysis incorporating probabilities of development success and ranges of commercial value as a function of dose made the decision clear.
In early 2000 a pharma company faced a difficult go/no-go decision for its antidepressant in early clinical development.

- The compound was completing pharmacokinetic (PK: dose-to-concentration) and animal toxicology studies. The results were to be used to decide asap whether to enter expensive Phase II efficacy trials in patients.

- The compound had an unproven mechanism of action: blocking the brain receptor for the neurotransmitter neurokinin-1.
  - This is believed to regulate emotional behavior and stress responses.
  - Animal and early clinical studies suggested antidepressant effects, but a competitor had given up on its NK1 antagonist when placebo response came out comparable to the compound.

- The antidepressant market is huge, with unmet needs.
To accelerate decision making, the development planning team started analysis before the PK and tox studies were done.

Continue development?

PK & tox studies

- Toxicology success?
- Safety, tolerability
- Efficacy
- Differentiators from competition

Potential dose limitations

Product profile

- Peak share
- Market share
- Market size

Development success?

(Ph II, III, Reg)

Development costs

(Ph II, III, Reg)

Sales Vol.

Price

Revenue

Commercial costs

Net Present Value

Commercial model

- manufacturing
- selling
- marketing
- distribution
- R&D
- overhead

Key

Decision
Uncertainty
Calculation
Value Measure
Relevance
The key to a practical model was a simple characterization of the product profile, with a mapping to a market impact rating.

At **200 mg/day Dose**

### Efficacy (% Responders*)
- 70% or more
  - Probability 0.01
- 60%-70%
  - 0.14
- <60%, approvable
  - 0.15
- Unapprovable
  - 0.70

### Safety & Tolerability vs. Standard of Care
- Adverse Events (AEs) better, lethality in overdose no worse
  - 0.09
- AEs comparable, lethality in overdose no worse
  - 0.60
- Lethality in overdose worse but commercially viable
  - 0.08
- Not commercially viable
  - 0.23

### Statistically Demonstrable Differentiators*
- 2 or more
  - 0.15
  - 1
  - 0.75
  - 0
  - 0.10

### Market Impact (27 Cases Total)
- Intermediate Player
- Niche Player
- No-File

**Source:**
- Clinical team 3/00, based on pre-clinical & early clinical results, analogy to competitor’s compound.
- Clinical team 3/00, based on preliminary results from PK/tolerability study.
- Market expert assessment 2/00.

* Response means >50% decrease in HAM-D score from baseline. Differentiators (such as lack of weight gain and rapid onset of action) must be published with 2 or more studies showing p > 0.05 vs. comparator.
The market research sub-team assigned to each market impact rating a range of possible peak shares, which were spread to shares over time.

<table>
<thead>
<tr>
<th>Market Impact</th>
<th>Low (10%)</th>
<th>Base (50%)</th>
<th>High (90%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major Player</td>
<td>19%</td>
<td>24%</td>
<td>30%</td>
</tr>
<tr>
<td>Intermed. Player</td>
<td>10%</td>
<td>14%</td>
<td>18%</td>
</tr>
<tr>
<td>Niche Player</td>
<td>3%</td>
<td>6%</td>
<td>9%</td>
</tr>
</tbody>
</table>

* 2nd to market assumed 88% as high

Source: market expert assessments.
Initial sensitivity analysis identified the commercial variables deserving probabilistic treatment in the value calculations.

<table>
<thead>
<tr>
<th>Sensitivity Results</th>
<th>Conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>100 mg/day Net Present Value Given Niche Player ($ Millions)</td>
<td></td>
</tr>
<tr>
<td>Peak Share (Base=5.3%)</td>
<td>2.6%</td>
</tr>
<tr>
<td>US Net Price for Novel Mechanisms ($/Monthly Rx) (Base=51.00)</td>
<td>42.00</td>
</tr>
<tr>
<td>Multiplier for market size uncertainty (Base=1)</td>
<td>0.8</td>
</tr>
<tr>
<td>Years to Reach Peak US Share (Base=5)</td>
<td>7</td>
</tr>
<tr>
<td>Ex-US Sales Revenue 2013 on (% of WW) (Base=32%)</td>
<td>25%</td>
</tr>
<tr>
<td>Months from NDA to Launch (Base=15)</td>
<td>24</td>
</tr>
<tr>
<td>Unit COGS ($/Rx-Day) (Base=0.32)</td>
<td>0.35</td>
</tr>
<tr>
<td>US Share Decline Rate from Peak (% of peak share/yr) (Base=4%)</td>
<td>5%</td>
</tr>
</tbody>
</table>

Notes:
- Each variable is varied one-at-a-time from its 50th percentile to its 10th and 90th percentiles.
- Market impact (Niche/Intermediate/Major Player) and development uncertainties were also modeled probabilistically.
**Expected values of the compound, calculated as a function of PK and Tox scenarios, gave an advance decision policy: continue except in the worst cases.**

### Pharmacokinetic Scenario

<table>
<thead>
<tr>
<th>Topx Scenario</th>
<th>Steady state documented at all doses with inflection point <strong>above</strong> high dose</th>
<th>Steady state documented at all doses with inflection point <strong>below</strong> high dose</th>
<th>Steady state not found in at least 1 patient; potential recourse found</th>
<th>Same with no recourse found</th>
</tr>
</thead>
<tbody>
<tr>
<td>At maximum tolerated dose, results at least comparable to before</td>
<td>Expected NPVs in $150M-400M range*</td>
<td><strong>STOP</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>At maximum tolerated dose, worse but no critical results</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Critical liver abnormalities, cardiotoxicity, or aplasia</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Assuming no delays in the development timeline. The expected loss of NPV from a plausible delay due to additional tox study requirements (5-12 months) was $50-$120M.
The PK and Tox results arrived in mid-March, and the results dictated a no-go decision.

**PK Scenario**
- Steady state documented at all doses with inflection point above high dose
- Steady state documented at all doses with inflection point below high dose
- Steady state not found in at least 1 patient; potential recourse found

**Tox Scenario**
- At MTD, comparable results to before or better
- At MTD, worse but no critical results
- Critical liver abnormalities, cardiotoxicity, or aplasia

Expected NPVs in $150M-400M range*

STOP

Is that the end of the story? What were the tradeoffs as the dose varies?
The PK study showed drug accumulation at all doses studied, leading to very low assessed probabilities for safety...

<table>
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<th>Dose (mg/day)</th>
<th>100</th>
<th>200</th>
<th>300</th>
</tr>
</thead>
<tbody>
<tr>
<td>P(approvable safety &amp; tolerability)</td>
<td>20%</td>
<td>10%</td>
<td>5%</td>
</tr>
<tr>
<td>P(animal toxicology success)</td>
<td>85%</td>
<td>75%</td>
<td>60%</td>
</tr>
<tr>
<td>P(approvable efficacy)</td>
<td>30%</td>
<td>40%</td>
<td>75%</td>
</tr>
<tr>
<td>P(profile worth filing given above)*</td>
<td>55%</td>
<td>53%</td>
<td>44%</td>
</tr>
<tr>
<td>P(reach market)</td>
<td>2.8%</td>
<td>1.6%</td>
<td>1.0%</td>
</tr>
</tbody>
</table>

* Based on commercial assessments of whether to file with each product profile.
...and suggesting that development should be halted.

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<td>53%</td>
<td>44%</td>
</tr>
</tbody>
</table>

- **P(reach market)**
  - 2.8%  
  - 1.6%  
  - 1.0%

- **Expected NPV if reach market**
  - $570M
  - $280M
  - $3M

- **Expected NPV if don’t reach market**
  - -$45M
  - -$41M
  - -$35M

**Expected NPV** = (a) (b) + (1-(a)) (c)

  - -$28M
  - -$36M
  - -$35M
This changed the decision frame to finding the dose most likely to succeed, with extrapolation.

<table>
<thead>
<tr>
<th>Frame</th>
<th>Model</th>
<th>Sensitivity</th>
<th>Results</th>
<th>Conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Up</td>
<td>Up</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Dose (mg/day)

<table>
<thead>
<tr>
<th></th>
<th>50</th>
<th>100</th>
<th>200</th>
<th>300</th>
</tr>
</thead>
<tbody>
<tr>
<td>P(approvable safety &amp; tolerability)</td>
<td>??</td>
<td>20%</td>
<td>10%</td>
<td>5%</td>
</tr>
<tr>
<td>P(animal toxicology success)</td>
<td>??</td>
<td>85%</td>
<td>75%</td>
<td>60%</td>
</tr>
<tr>
<td>P(approvable efficacy)</td>
<td>??</td>
<td>30%</td>
<td>40%</td>
<td>75% Up</td>
</tr>
<tr>
<td>P(profile worth filing given above)</td>
<td>??</td>
<td>55%</td>
<td>53%</td>
<td>44%</td>
</tr>
</tbody>
</table>

- **(a)** P(reach market)
  - Need 6.5% to break even
    - 2.8% 1.6% 1.0%

- **(b)** Expected NPV if reach market
  - $720M $570M $280M $3M

- **(c)** Expected NPV if don’t reach market
  - -$50M -$45M -$41M -$35M

Expected NPV = (a) (b) + (1-(a)) (c)

<table>
<thead>
<tr>
<th></th>
<th>??</th>
<th>-$28M</th>
<th>-$36M</th>
<th>-$35M</th>
</tr>
</thead>
</table>
The team could not justify further testing of the ultra-low dose, and development was halted in March—a timely, high-quality decision.

- At 50 mg, the team could not ascribe sufficient probabilities to reach a breakeven expected NPV.
  - The expected value of information on 50 mg safety and efficacy from a potential new PK study was not high enough to do this study.
  - The expected value of control of manufacturing cost would have been high, if only the chance of successful development had been higher.

- The advance analysis was essential: the go/no-go decision would have been made rapidly with or without quantitative decision support.
  - The lowered-dose question was unanticipated but quickly analyzed.
  - The decision policy “wasted” analysis of various unrealized PK and tox scenarios, but this inefficiency was worthwhile for speed.

- Considering that many drugs enter large-scale trials based largely on wishful thinking in the face of large uncertainties, this was a success story.
  - Had the company continued development, expected new losses would be at least $20M, with larger losses given the very likely event of development failure.
The analysis team limited the decision scope to Go or No-Go for the depression indication only.

**Policy (Given)**
- Anxiolytic indications: ignore for now.
- Portfolio effects: ignore for now.
- Criterion for go decision: positive ENPV.

**Focus**

*Continue to large-scale trials, or abort development?*

**Tactics (Defer)**
- Program & trial design details
- Manufacturing method
The model was implemented in a spreadsheet; a macro helped with probability calculations.

<table>
<thead>
<tr>
<th>Input</th>
<th>Low</th>
<th>Base</th>
<th>High</th>
<th>P(Low)</th>
<th>P(Base)</th>
<th>P(High)</th>
<th>Source</th>
<th>Date</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Toxicology success?</td>
<td>No</td>
<td>Yes</td>
<td></td>
<td>0.25</td>
<td>0.75</td>
<td></td>
<td>Smith</td>
<td>3/3/00</td>
<td>See Clinical Inputs sheet. Probabilities vary by dose.</td>
</tr>
<tr>
<td>US net price ($/month)</td>
<td>42</td>
<td>51</td>
<td>60</td>
<td>0.3</td>
<td>0.4</td>
<td>0.3</td>
<td>Jones</td>
<td>8/16/99</td>
<td>Base calculated from AWP=72. Upward force: novel mech. Downward force: mgd. care &amp; generics. Probabilities discretize 10-50-90 percentiles.</td>
</tr>
</tbody>
</table>

Base column used below (deterministic) Low, High, & P's used by add-in macro that changes base column to calculate NPV for all relevant combinations

Calculations for Current Scenario: Launch at 2008.08, Intermediate Player, Base Market Size

<table>
<thead>
<tr>
<th>Year:</th>
<th>2000</th>
<th>2001</th>
<th>...</th>
<th>2021</th>
<th>NPV@10.75%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Market Size</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>...</td>
<td></td>
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<td></td>
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<tr>
<td>Investment</td>
<td></td>
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<tr>
<td>Cash flow</td>
<td></td>
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</tr>
</tbody>
</table>

Note: the level of detail is kept low, as appropriate with large development & commercial uncertainties.