

# *Decision Analysis Clarifies a Difficult Go/No-Go Decision: The NK1 Antagonist Case*

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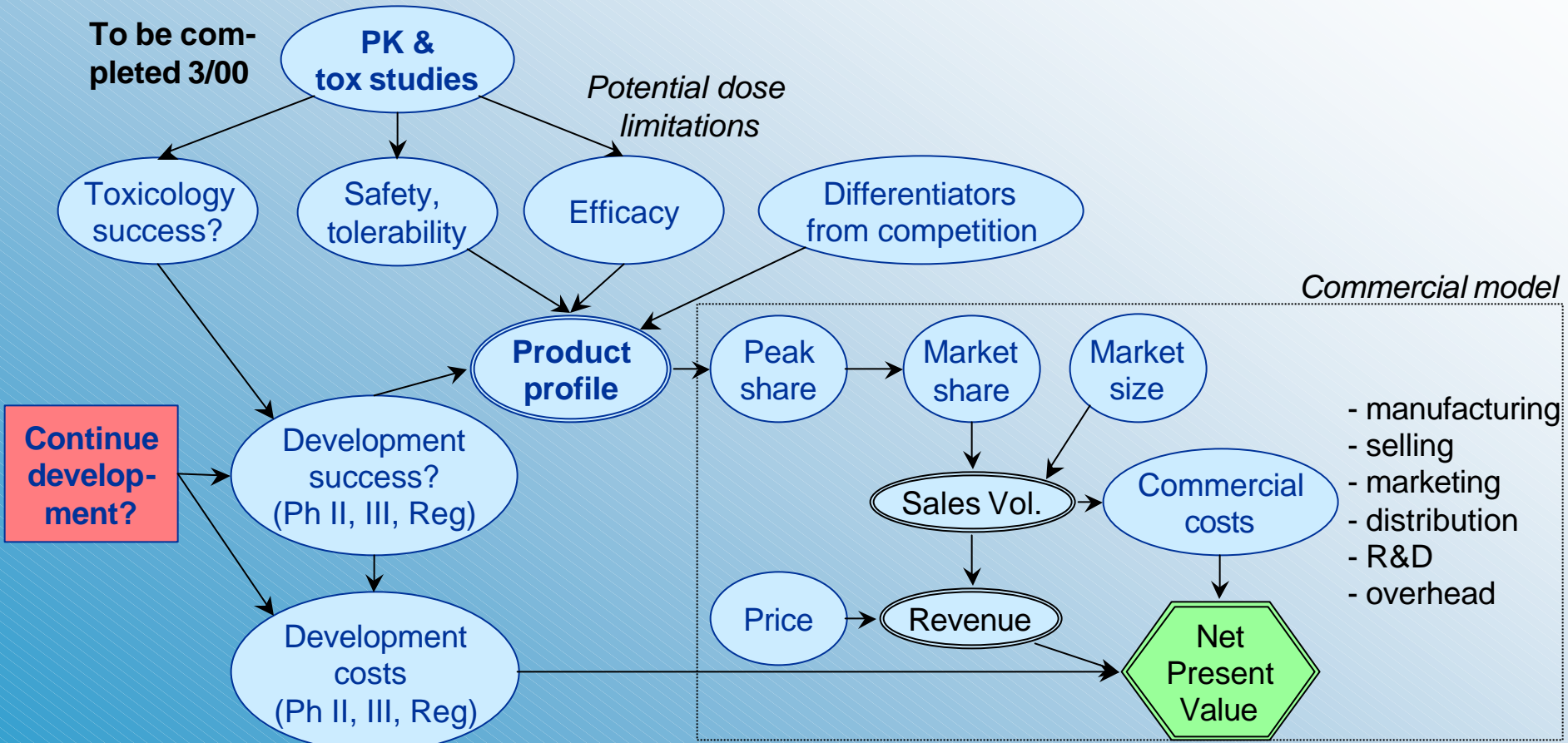
## **Abstract**

**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.**

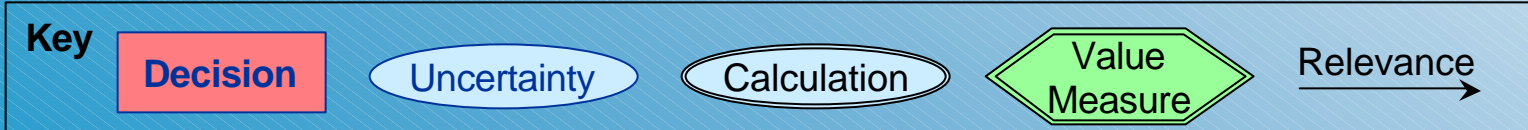
## *In early 2000 a pharma company faced a difficult go/no-go decision for its antidepressant in early clinical development.*

- The compound was completing pharmacokinetic (PK: dose-to-concentration) and animal toxicology studies. The results were to be used to decide a.s.a.p. 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.

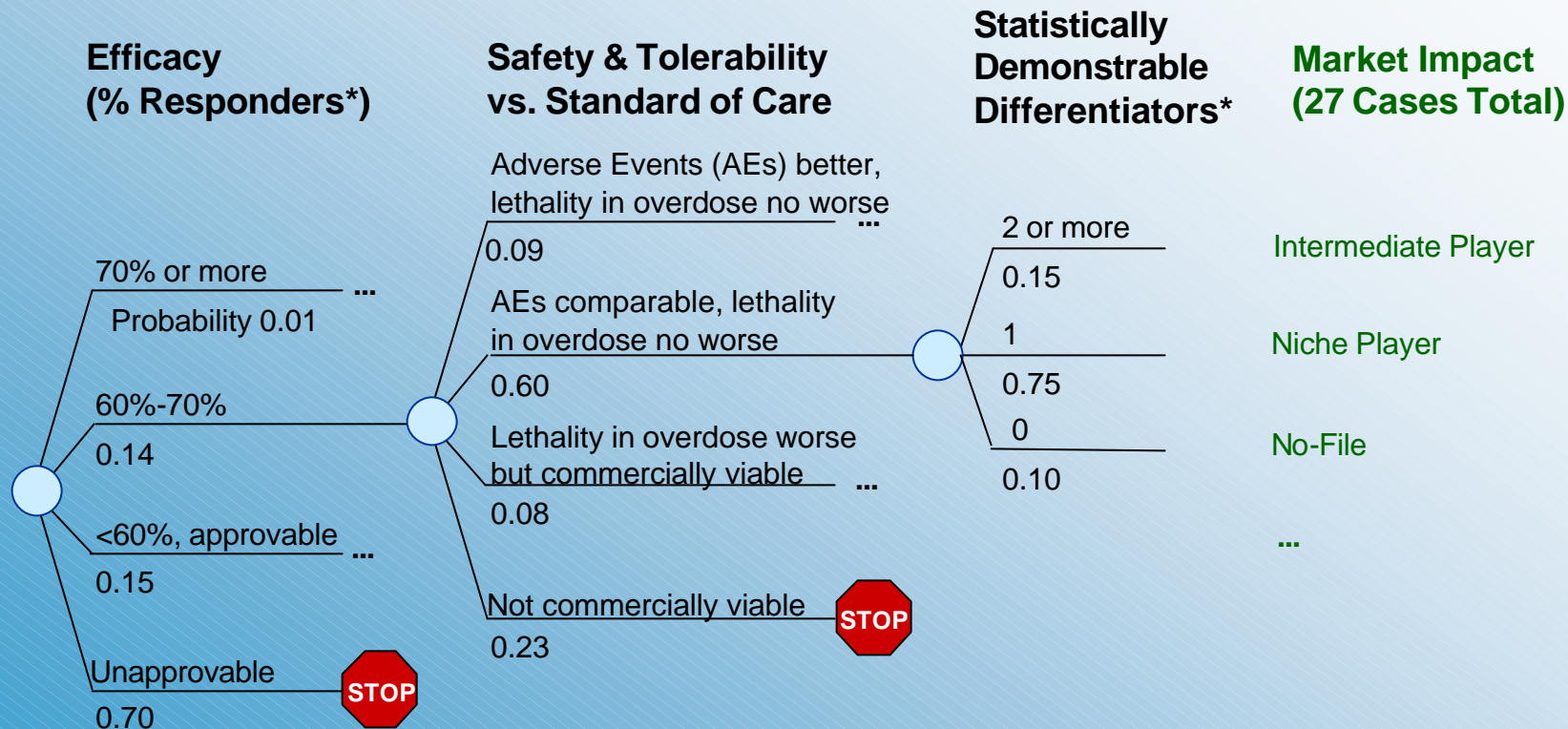


- manufacturing
- selling
- marketing
- distribution
- R&D
- overhead



# 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



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.

Clinical expert assessment 9/99 for any novel mechanism antidep.

Market expert assessment 2/00.

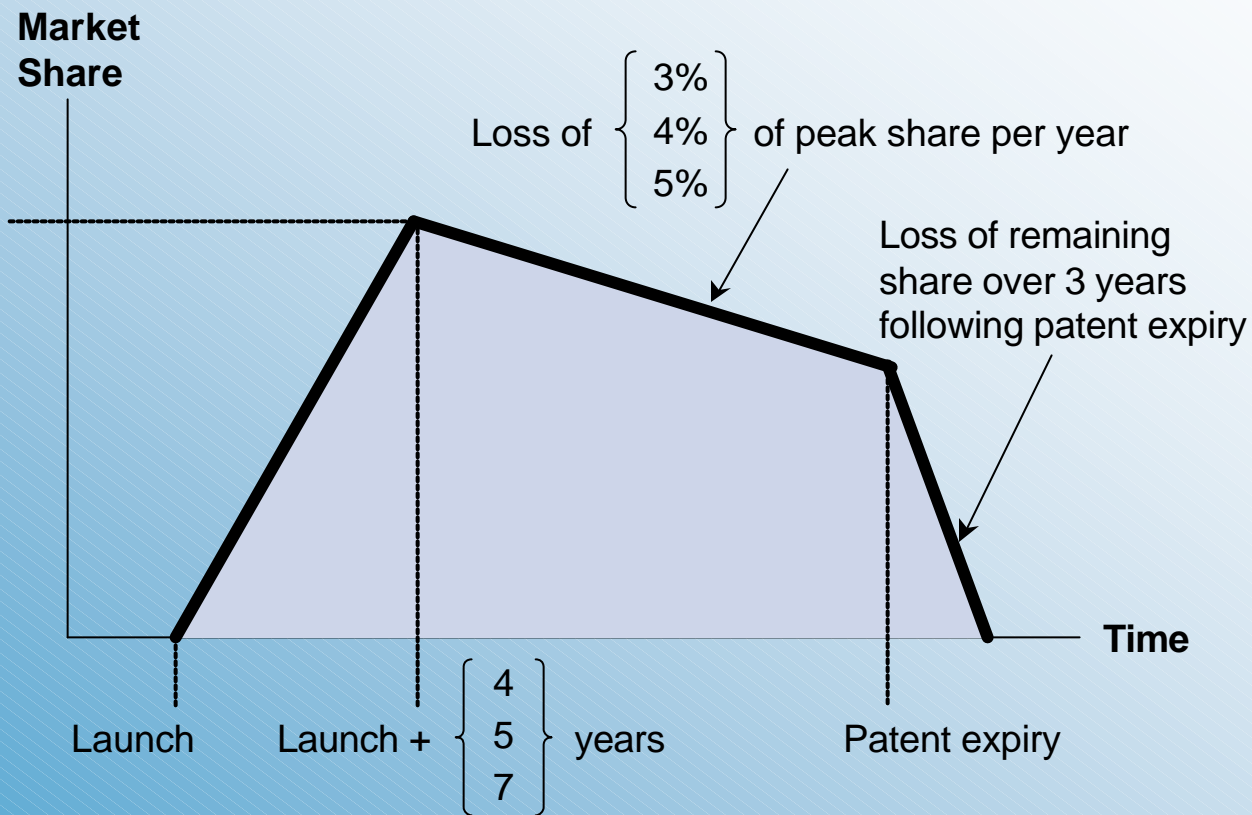
\* Response means >50% decrease in HAM-D score from baseline. Differentiators (such as lack of weight gain and rapid onset of action) must be published with 2 or more studies showing  $p > 0.05$  vs. comparator.

*The market research sub-team assigned to each market impact rating a range of possible peak shares, which were spread to shares over time.*

**Peak Share if First to Market\***

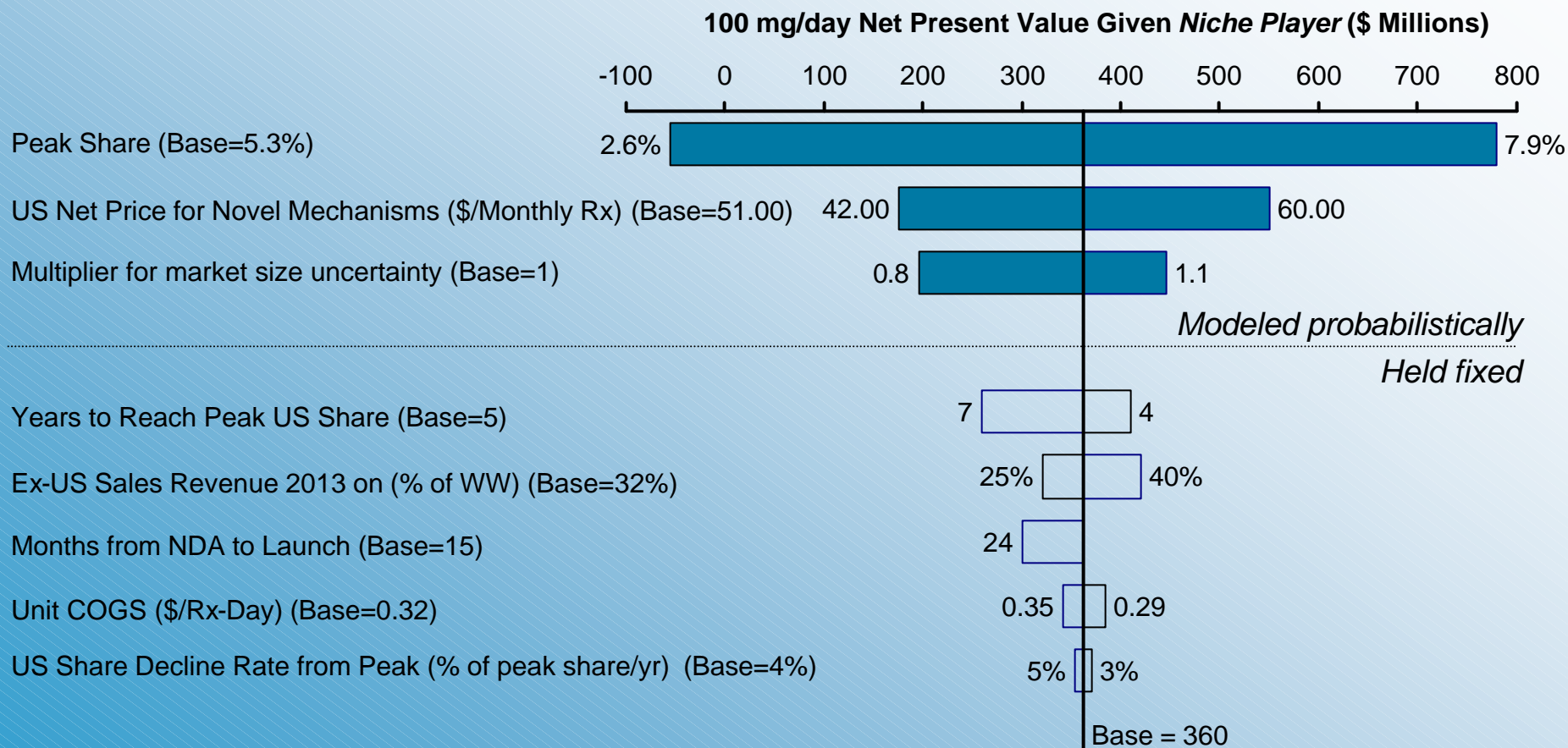
<b>Market Impact</b>	<b>Low (10%)</b>	<b>Base (50%)</b>	<b>High (90%)</b>
Major Player	19%	24%	30%
Intermed. Player	10%	14%	18%
Niche Player	3%	6%	9%

\* 2<sup>nd</sup> to market assumed 88% as high



Source: market expert assessments.

# Initial sensitivity analysis identified the commercial variables deserving probabilistic treatment in the value calculations.




**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.

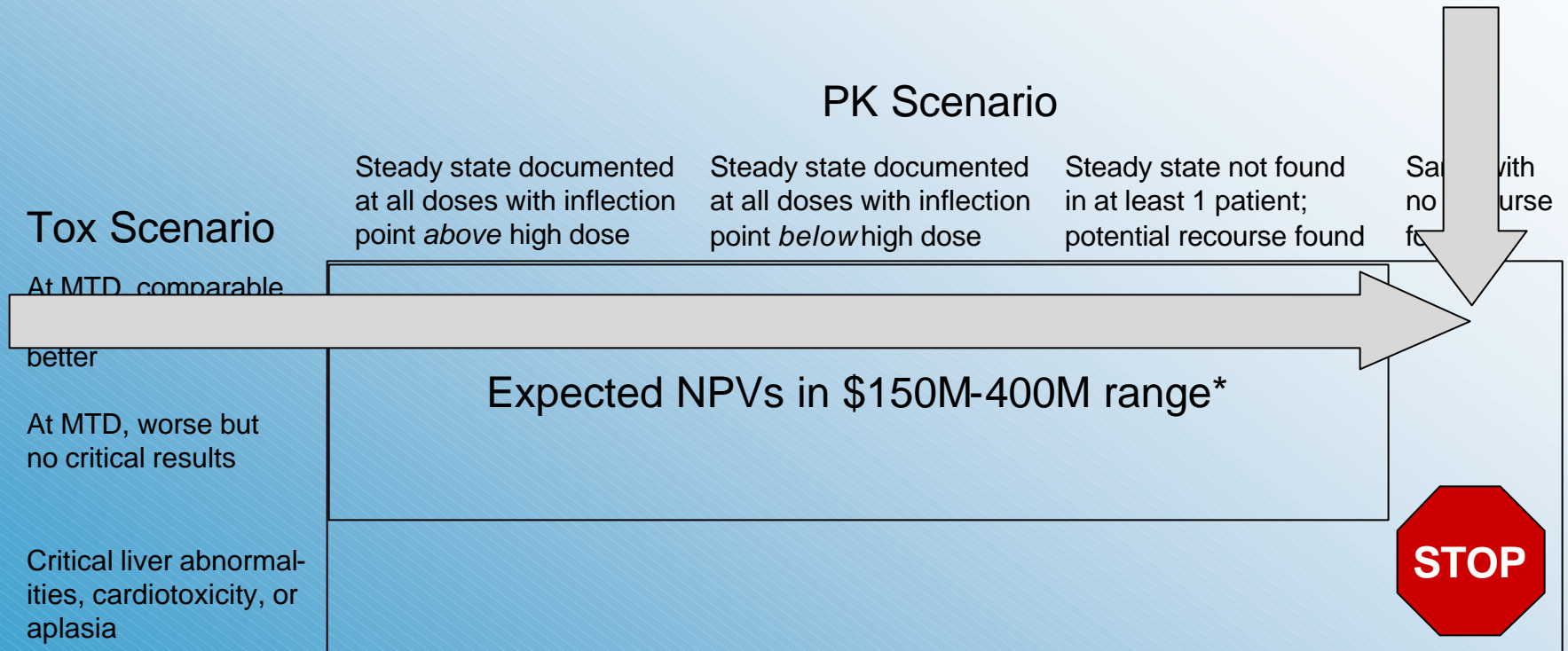
**Expected values of the compound, calculated as a function of PK and Tox scenarios, gave an advance decision policy: continue except in the worst cases.**

### Pharmacokinetic Scenario

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

\* 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.



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...**

	Dose (mg/day)		
	<u>100</u>	<u>200</u>	<u>300</u>
P(approvable safety & tolerability)	<b>20%</b>	<b>10%</b>	<b>5%</b>
P(animal toxicology success)	85%	75%	60%
P(approvable efficacy)	30%	40%	75%
P(profile worth filing given above)*	55%	53%	44%
P(reach market)	<i>Product</i> <u>2.8%</u>	<u>1.6%</u>	<u>1.0%</u>

\* Based on commercial assessments of whether to file with each product profile.

*...and suggesting that development should be halted.*

	Dose (mg/day)		
	<u>100</u>	<u>200</u>	<u>300</u>
P(approvable safety & tolerability)	20%	10%	5%
P(animal toxicology success)	85%	75%	60%
P(approvable efficacy)	30%	40%	75%
P(profile worth filing given above)	55%	53%	44%
	————	————	————
(a) P(reach market)	2.8%	1.6%	1.0%
(b) Expected NPV if reach market	\$570M	\$280M	\$3M
(c) Expected NPV if don't reach market	-\$45M	-\$41M	-\$35M
Expected NPV = (a) (b) + (1-(a)) (c)	<u>-\$28M</u>	<u>-\$36M</u>	<u>-\$35M</u>

# This changed the decision frame to finding the dose most likely to succeed, with extrapolation.

		Dose (mg/day)			
		<u>50</u>	<u>100</u>	<u>200</u>	<u>300</u>
P(approvable safety & tolerability)		??	20%	10%	5%
P(animal toxicology success)	Up	??	85%	75%	60%
P(approvable efficacy)		??	30%	40%	75% Up
P(profile worth filing given above)		??	55%	53%	44%
(a) P(reach market)			2.8%	1.6%	1.0%
(b) Expected NPV if reach market		<b>\$720M</b>	\$570M	\$280M	\$3M
(c) Expected NPV if don't reach market		<b>-\$50M</b>	-\$45M	-\$41M	-\$35M
Expected NPV = (a) (b) + (1-(a)) (c)		??	-\$28M	-\$36M	-\$35M

Need 6.5%  
to break even

# *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)

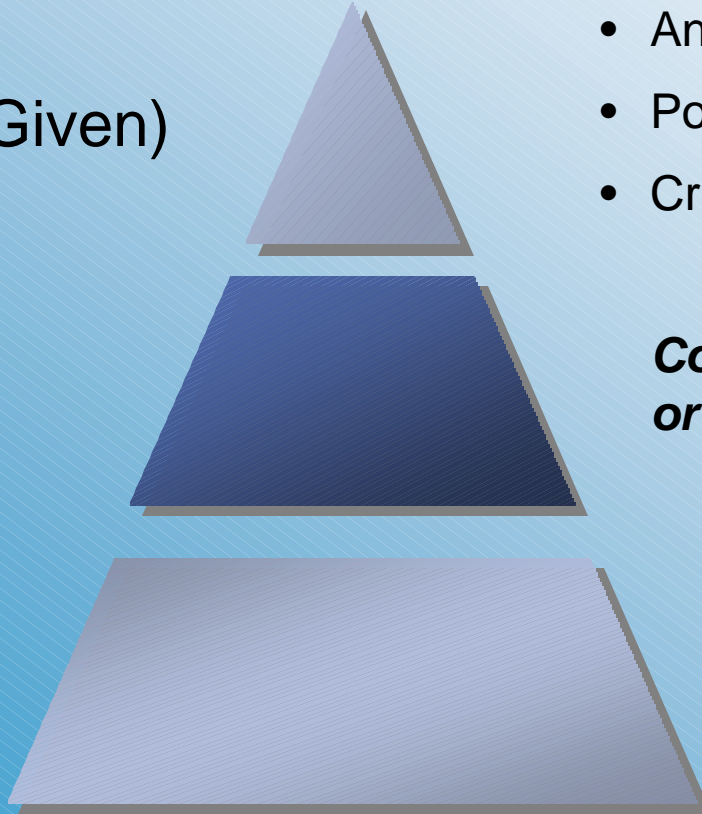
- Anxiolytic indications: ignore for now.
- Portfolio effects: ignore for now.
- Criterion for go decision: positive ENPV.

***Focus***

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

Tactics  
(Defer)

- Program & trial design details
- Manufacturing method



# BACKUP

*The model was implemented in a spreadsheet; a macro helped with probability calculations.*

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

*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

Year:	<u>2000</u>	<u>2001</u>	...	<u>2021</u>	<u>NPV@10.75%</u>
Market Size					
...					
Investment					
Cash flow					

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