

IDENTIFYING THE SWEET SPOTS IN MILESTON DECISION MAKING: MONTE CARLO SIMULATION OF NPV FOR PIPELINE PROJECTS

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<u>Simple rNPV</u> and <u>rNPV</u> are both systematically over-optimistic and steadily favor short-term, incremental projects at the cost of strategic early pipeline projects

Risk profile made fully transparent through *Detailed rNPV* method only

Early stage projects are often much more attractive than <u>*rNPV*</u> and <u>*Simple rNPV*</u> calculations show -> use <u>*Detailed rNPV*</u>

At early stages the focus to maximize a project's NPV should be on cost and length of phase I and II management and NOT on being overly right in post launch assumptions

Sensitivity analysis supports licensing and partnering negotiations to know which variables to peg milestone payments and other royalties on

How do we balance to manage risk and opportunities transparent?

We calculate the Net Present Value (NPV) of the same project buy using three different methodologies and compare the results

The mean of all three methodologies should be in the same range

- This is only true, if the assumptions for all input variables are symmetrically distributed around the mean of a variable. In practice this is seldom the case
- In our example we don't assume symmetrical variable distributions, so NPVs don't fit perfectly among the three methodologies applied

A positive NPV is not enough – further questions to be asked

- What are the most critical factors impacting the NPV
- A sensitivity analysis helps to answer this question
- Compare a companies abilities and general strength and weaknesses with sensitivity results
- Discuss NPV's sensitivities in a portfolio context to prioritize attractive risk/reward projects



Basic Assumption for CNS Development Project @ start of Phase 1

bevelopment phase		Cost p. year @ start of each stage in mill \$			Time (in months)				# of Patient in trail		Cost p.patient p. year in 1,000 \$	
		min	Most Likely	max	min	Most Likely	max	Probability of Success	min	max	min	max
	Ph1	6	10	12	12	18	30	40.7% (6.3%)				
	Ph2				23	31	46	30.2% (15.4%)	300	500	\$80	\$100
	Ph3				26	37	46	54.9% (51.1%)	1.300	2.500	\$80	\$100
	Filing	4	6	8	6	11	18	93.0% (93.0%)				

Commercial phase	Discount rate = 10%; 100% equity financed, no loan, no tax shield generated	Min		Most likely		Max	
	Launch Cost in mill. \$		120		150		170
	Cost Phase IV in mill \$		15		20		25
	Net anual price in \$	\$	5.800	\$	6.200	\$	6.800
	Patient population	1	.200.000	1.400.000		1.700.000	
	Patients accessible or Reimbursed		55%		60%		65%
	Peak share in %		18%		33%		48%
	Time to peak in years		3		4		5
	Marketing and sales stuff (FTE)		120		130		140
	Total expenditure for sales an marketing (per FTE / year) in \$	\$	310.000	\$	325.000	\$	340.000

* Source: Wong, Chi Heem; Siah, Kien Wei; Lo, Andrew W.; Biostatistics (2019) 20,2, pp. 273–286

Some background about Monte Carlo Simulation

The sample

- Sample has to be drawn randomly
- Law of large numbers: repeated independent tests, to get close to the true probability of a process
- What's the universe of our sample vs. our sample size
- Sample size should be large, for NPV calculations 10,000 simulations cover a lot

Thinking in confidence intervals is better than providing a mean

- If variance grows, we need a larger sample to get confidence
- Confidence depends on variance

The chosen probability distribution

- Assumptions about the probability distribution are critical for output interpretation
- To assume variance within a random variable should on average lead to be better results than modeling it static, with no variation

Three methodologies of risk adjusted NPV calculation in comparison





1. Calculating <u>rNPV</u> (mean: \$111 million)

	NPV of stage @ start of phase in mill \$	Length in years	Probability weight	Cash Flow @ start of phase	PV Cash Flow
Ph1	\$ 15	1,5	100,0%	\$ (15)	\$ (15)
Ph2	\$ 48	2,6	40,7%	\$ (19)	\$ (17)
Ph3	\$ 412	3,1	12,3%	\$ (51)	\$ (34)
Filing	\$6	0,9	6,7%	\$ (0)	\$ (0)
Profit	\$ 6.113	9,9	6,3%	\$ 384	\$ 178
NPV of Project	\$ 111				



Assumptions for Monte Carlo Simulation in our CNS example

Assumption about distribution of random variables to be taken

- We mostly used PERT-distribution for variables (min, most likely, max)
- In our example no assumption about correlations between random variables are taken
- One could argue, that pricing, peak share, time to peak are positively correlated since the all depend on the therapeutic advantage of a drug (to be modeled by Copulas in more sophisticated models)

We run 10,000 simulations

• This generates an effective range of possible outcomes



Jevelopment p		min	Most Likely	max	min	Likely	max	Success	min	max	min	max
	Ph1	6	10	12	>12	18	30	41%				
	Ph2				23	31	46	30%	300	500	\$80	\$100
	Ph3				26	37	46	55%	1.300	2.500	\$80	\$100
	Filing	4	6	8	6	11	18	93%				

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2. Calculating *Simple rNPV* (mean: \$129 million)



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2. Tornado diagram showing rank of correlations between input for each set of simulation inputs and NPV outputs for <u>Simple rNPV</u>



3. Calculating *Detailed rNPV* (mean: \$130 million)

in 6.3% of cases the NPV is positive, but then substantially positive





3. Tornado diagram showing rank of correlations between input for each set of simulation inputs and NPV outputs for *Detailed rNPV*



4. Distribution Comparison of NPV range between the three methods
means: <u>rNPV</u>= \$ 111 mill; <u>Simple rNPV</u>= \$ 129 mill; <u>Detailed rNPV</u>= \$ 130 mill



4. Sensitivity Comparison between <u>Simple rNPV</u> and <u>Detailed rNPV</u> red bars show the true risk – blue bars are truly misleading





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<u>Simple rNPV</u> and <u>rNPV</u> are both systematically over-optimistic and steadily favor short-term, incremental projects at the cost of strategic early pipeline projects

At early stages the focus to maximize a projects NPV should be on cost and length of phase I and II management rather than being overly right in post launch commercial phase product potential forecasting in great detail

Sensitivity analysis supports licensing and partnering negotiations to know which variables to peg milestone payments and other royalties on

The larger a companies portfolio is, the more critical it is to understand the full risk and opportunity profile of reach compound to make good prioritizing in milestone decisions