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Pharma and Biotech Valuations:
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Pharma and Biotech Valuations: Divergent Perspectives

Over at least the past decade, risk-adjusted net present value (rNPV) has emerged as the de facto standard for valuing pharmaceutical R&D projects.^{1,2} These valuations are used for several purposes including prioritising projects within a portfolio, making investment decisions, valuing a licensing transaction and valuing intellectual property in a sale setting. Controversies remain, not least the choice of discount rate to apply, but the methodology remains very widely used, at least in big pharma and those biotech companies that have not lost faith in rNPV. This paper briefly documents an alternative risk-profiled MC rNPV valuation (rpNPV), and highlights a material divergence between the perspective of a biotech company (with a single or small number of projects) and big pharma (with a broad portfolio).

By Anthony Walker, Simon Turner and Rob Johnson, Alacrita LLP

About the Authors

Anthony Walker leverages 13 years of building and managing a biotechnology company together with over 16 years as a management consultant to the chemical, pharmaceutical and biotechnology industries. His experience includes due diligence, technology/market appraisal, business planning, licensing and raising venture capital finance.

E: awalker@alacrita.com

Simon Turner has over two decades of experience managing and advising on strategic and product development issues, and over the past decade, has focused on commercialisation of life science technologies in early-stage companies, as entrepreneur, executive, venture capital investor and advisor.

E: sturner@alacrita.com

Rob Johnson is a co-founder of Alacrita. His areas of expertise include business development and licensing, market assessments and commercial due diligence. Prior to forming Alacrita, Rob was Head of Business Development at Onyx Ltd, a biotechnology company specialising in the development of immunotherapies to treat cancer.

E: rjohnson@alacrita.com

The authors are all partners at Alacrita, a transatlantic life sciences consultancy firm.

Risk-adjusted NPV is Notoriously Fallible

In the context of high – and often unquantifiable – uncertainties inherent on pharmaceutical R&D and market forecasting,³ it is known that even rNPV techniques provide “misplaced concreteness” whereby “the tendency to overlook uncertainties, margins of error and ranges of probability can lead to damaging misjudgements”.⁴ The approach is based on standard discounted cash flow (DCF) techniques with future cash flows weighted by the probability of a drug progressing from one development stage to the next. Superimposing Monte Carlo (MC) simulations on to rNPV calculations provides explicit recognition of this and results in an rNPV expressed as a range associated with a specific probability distribution.

Conventional rNPV Valuation with Monte Carlo Simulations (Standard MC Model)

As a practical illustration, consider a novel therapeutic for non-small cell lung cancer (NSCLC) starting phase 1 clinical trials with the basic assumptions as set out in Table 1; uncertainties, especially commercial ones, are very high and reflected by wide input ranges. The probability of progressing from one development stage to the next, using

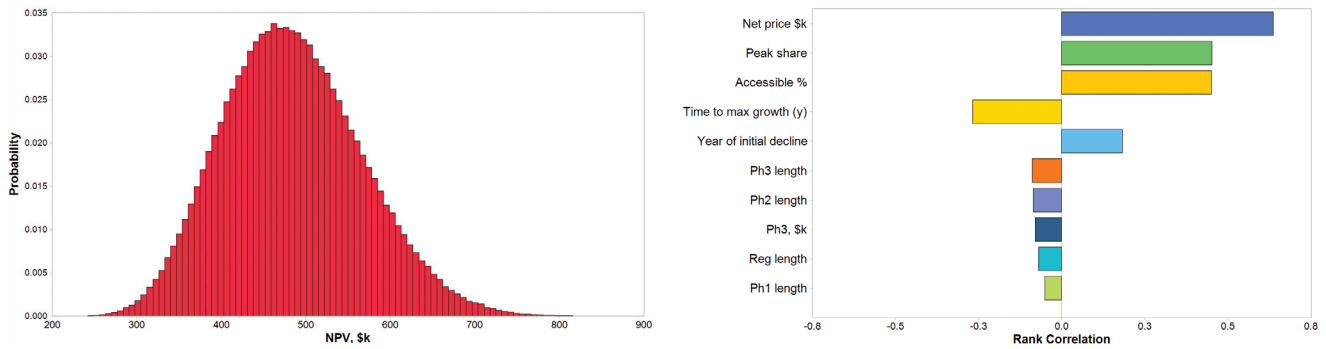
benchmarks that have been widely used in the industry,⁵ are assumed to be:

- Phase 1 to phase 2 trials: 71%
- Phase 2 to phase 3 trials: 45%
- Phase 3 trials to pre-registration: 64%
- Pre-registration to product approval: 93%

Cumulatively, the probability of technical success, from preclinical development through to product approval, is 19%; many would argue this is overoptimistic relative to contemporary experience, especially in a challenging indication such as NSCLC, but the analysis presented below holds with more stringent benchmarks based on success rates in specific indications and with different technologies (small molecules, biologics, etc.) (data not shown).⁶

In the standard rNPV model, the net cash flow is multiplied by the cumulative probabilities at each stage; i.e. all cash flows from phase 1 to phase 2 are multiplied by 0.71, from phase 2 to phase 3 by $0.71 \times 0.45 = 0.32$, etc. The formal calculation of rNPV uses a familiar standard algorithm.⁷ Using the midpoint values for all the ranges specified in Table 1, at a discount rate of 8% the rNPV = US\$485 million. Using the MC method, this calculation is repeated many times (in this example, 50,000 times) using a Microsoft Excel spreadsheet plug-in (Model Risk 5, Vose Software BVBA), each run using a different value in each of

Figure 1: Output of a Standard MC Model



a) The x axis shows rNPV in US\$ million and the y axis shows the probability for each rNPV value. This distribution is slightly right-skewed, accounting for the small difference between the mean value in this distribution (\$484 million) being marginally lower than the non-MC rNPV (\$485 million).

b) a Tornado plot showing the top ten input assumption ranges in terms of their impact on the rNPV. This is expressed as a rank correlation between the set of values generated for the output and each input in turn. It is a commonly used form of sensitivity analysis, mostly useful for identifying key variables that should be analysed in more detail. The scale runs from -1 (completely negatively linearly correlated) through 0 (no linear correlation), to 1 (completely positively linearly correlated).

the assumption ranges in Table 1. These 50,000 simulations effectively sample the range of possible outcomes based on an appropriate probability distribution for each input variable. (For most variables, this model used a Project Evaluation and Review Techniques (PERT) distribution.⁹)

The mean rNPV from these simulations is \$484 million, effectively identical to the non-MC value. More importantly, the range of rNPV values is shown in a histogram plot (Figure 1a), with the 5th and 95th percentiles for rNPV, respectively, being \$357 million and \$627 million. This probability distribution provides a far richer insight into the rNPV associated with this early-stage R&D project. In this example, all values in the range are positive, but for projects where the commercial target is smaller or the uncertainties higher (data not shown), the first quartile or even more of the rNPV range can be negative despite a positive mean rNPV, clearly providing a more accurate view of the risks involved in pharmaceutical R&D. More importantly still, the relative impact of each range of input assumptions on the outcome of the rNPV calculation is shown in a Tornado plot (see Figure 1b).

Consistent with conventional wisdom, the assumptions with the greatest impact on valuation are:

- Price
- Peak market share
- Accessible market (available market taking into account clinical, payer and other restrictions on treatment eligibility).

Assumptions such as the cost of clinical trials, even Phase 3, have a significantly lower impact on rNPV. It is precisely this sort of analysis that led many in the industry, certainly up to circa 2005, to focus very strongly on commercial parameters and to invest heavily in clinical

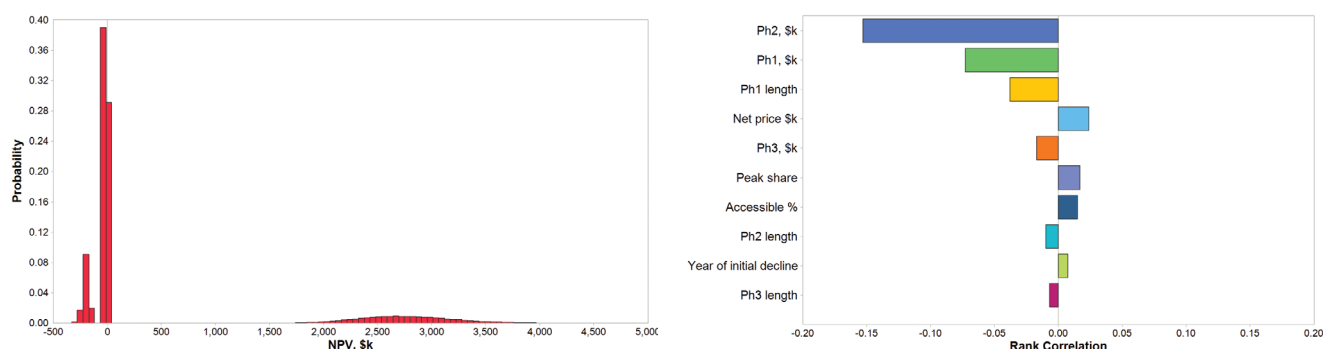
development with relatively scant regard for R&D budgets.

While it provides an illustration of the potential spread of project NPVs and the assumptions that the greatest impact on the range, the MC rNPV method still masks the reality of the situation where

Table 1: Basic Project Assumptions

	Parameter	Assumptions
Development phase	Duration of phase 1 trials	3 – 5 quarters
	Cost of phase 1 trials	\$4.0 – 5.0 million
	Phase 2, 3 cost per patient	\$100,000 – \$120,000
	Duration of phase 2 trials	7 – 9 quarters
	Number of patients in phase 2 trials	275 – 375
	Duration of phase 3 trials	11 – 13 quarters
	Number of patients in phase 3 trials	1,200 – 2,400
	Duration of pre-registration period	3 – 5 quarters
Commercial phase	Launch costs	\$75 – 125 million
	Phase 4	\$4 million
	Net annual price to manufacturer	\$70,000 – 110,000/patient
	Total theoretical patient population	135,000
	Accessible/reimbursed population	50 – 70%
	Peak market share	25 – 35%
	Time from launch to peak sales	3 – 5 years
	Year of initial sales decline	7.5 – 8.5 years post launch
	Time to maximum sales decline	1 – 3 quarters
	Dedicated marketing and sales staff	120 (50% upon sales decline)
Fully loaded sales/marketing staff cost	\$325,000/ FTE/year	
Tax rate	35%	

Figure 2: Output of a Stringent MC Model.



a) shows an rNPV probability distribution as shown in Figure 1a. In this case, the distribution is trimodal with the median value being negative (commensurate with the majority of R&D projects failing to reach the market).

b) shows a Tornado plot in the same manner as Figure 1b.

projects more often fail than succeed. As a result it has less utility in decision-making than stringent use of MC methods can provide.

Overcoming the Limitations of the Conventional Approach Using a Stringent MC Model

The fundamental problem with the standard rNPV method is that it applies a probability weighting to cash flows according to transitions through key development hurdles, e.g. it calculates 71% of cash flows from phase 1 to phase 2. In reality, however, there is no such thing as 71% of a cash flow; instead, 29% of the scenarios result in no cash flow beyond phase I (as the trial yielded a negative result), and 71% of the scenarios resulted in a full, not partial, cash flow between phase 1 and phase 2.

To reflect real-life scenarios better, we use a stringent MC model: simulations are run in which 71% proceed beyond phase 1, of which 45% proceed beyond phase 2, of which 64% proceed beyond phase 3, etc. Only 19% of the scenarios have cash flows beyond the pre-registration phase, consistent with the overall probability of the product reaching the market; 81% of the scenarios have negative rNPV.

Using the same project assumptions, the mean rNPV is still \$484 million, but the shape of the histogram is radically different (see Figure 2a). In this case, the probability distribution is trimodal; at the fifth percentile with an rNPV of -\$202

million, at the 15th percentile with an rNPV of -\$34 million and at the 90th percentile with an rNPV of \$2.7 billion.

The first peak corresponds to a late-stage development failure. By far the highest peak (the most probable outcome) is the middle one, corresponding to an outcome of a modest loss on a project cancelled at a relatively early stage. The third peak, with a very high valuation is clearly the least probable and reflects a successfully launched new product.

This model is materially more representative of the economics of drug development than the conventional method outlined first, and can therefore arguably claim higher validity. It is not in common use possibly due to the lack of MC simulation expertise and culture within the pharmaceutical and biotech industries.

The Tornado plot for the stringent MC method (Figure 2b) provides a fascinating dichotomy. In contrast to the standard method, commercial assumptions such as price, market share and market access pale in relation to development parameters, namely:

- Cost of phase 2 trials
- Cost of phase 1 trials
- Length of phase 1 trials.

Given that early development is where most projects fail, it is not surprising that these parameters have the highest impact on valuation. Interestingly, biotechs tend to be much better at minimising costs and time of early phase clinical trials than big pharma.

“In contrast to the standard method, commercial assumptions such as price, market share and market access pale in relation to development parameters.”

“ The standard rNPV approach does not serve portfolio management well as it always favours short-term and incremental projects at the expense of early stage and strategic projects. Instead, an rpNPV approach should be used to make trade-offs between projects within a portfolio. ”

Risk-profiled NPV

Using the stringent MC method, the shape of the rNPV histogram, together with the parameters of the Tornado plot, constitute a risk-profiled NPV model (rpNPV) which is more representative of the reality of life sciences R&D than standard rNPV values.

The standard method may be germane to a biotech company focusing on a single product or perhaps a small portfolio. It is particularly useful in situations addressing a single asset, such as a partnering transaction, where the Monte Carlo analysis constitutes a systematic, multi-parameter sensitivity analysis. In these situations, the histogram plot output makes explicit the range of value encompassed by the uncertainty in the input assumptions, and the Tornado plot identifies which assumptions contribute most to this uncertainty. This can be useful to focus negotiations onto key parameters rather than those which have little or no effect on the ultimate rNPV number used as the basis for the transaction. It can also be important to guide further analysis and/or market research onto parameters where a narrowing of the input assumption ranges would significantly reduce the uncertainty in the valuation.

However, the probability distribution of the rNPV range using the standard approach does not reflect reality and is materially and consistently overoptimistic. The rpNPV (stringent method), in contrast, reflects the dynamics of a large portfolio of the type present in major integrated

pharmaceutical firms or venture capital investors.

The standard rNPV approach does not serve portfolio management well as it always favours short-term and incremental projects at the expense of early stage and strategic projects. Instead, an rpNPV approach should be used to make trade-offs between projects within a portfolio.

Beyond this, a possible message from the rpNPV model is that big pharma should pay maximum attention to containing the costs and duration of early development phases as these have a higher economic impact in the context of a broad portfolio than optimising post-launch commercial parameters for individual products although, obviously, these are not unimportant. A corollary is that it may be economically most efficient for Big Pharma not to conduct early development at all, rather it would maximise shareholder value to acquire products that have already successfully navigated phase 2 proof-of-concept clinical trials. Indeed, many are already some way down this path as they increasingly outsource R&D.

The rpNPV model provides much greater insight/transparency into the dynamics driving project returns, enabling more effective comparison between alternative development paths for a project and between different projects competing for resources where they may have similar standard rNPVs but radically different risk profiles. As such it is a valuable decision-making tool for modern portfolio management.

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