PEER REVIEWED

Data Inputs for Medical Intervention Valuations

Abstract
Positive net present value (NPV) calculation on any product in development is a good indication that upon market release, the financial return will exceed the cumulative life cycle costs of research, development, market validation, market access, market release, manufacture and sales and therefore potentially justify the initial outlay; this is summarised as return on investment (ROI).

Despite this market reality, rNPVs on projects and portfolios at the startup stage for healthcare-focused endeavours are communicated either publicly or privately that greatly exceed what is actually happening in the marketplace, which suggests that the data being used in rNPV calculations may be incorrect.

We previously reported the development of a novel valuation model for medical intervention development in this journal (Dando and Lebmeier 2019).

This article expands on our previous article, providing more detail on data inputs and their use in our previously published model. Here we describe inputs derived from published literature, especially probabilities, market size, costs and risk – and success rates including reimbursement by payers and their use to model rNPVs.

Our work highlights the necessity to identify the true value of the innovation and the influencing factors that should be taken during the whole development cycle from discovery to market release, and the risks associated with not doing this.

This article should be read in conjunction with our previous article.

Key words: Innovation management, valuation modelling, inverse modelling, risk rates, reimbursement, return on investment

Introduction

We previously reported the development of a novel valuation model for medical intervention development in this journal (Dando and Lebmeier 2019). This article expands on our previous article, providing more detail on data inputs and their use in the published model. This article should be read in conjunction with our previous article.

It is well known that a positive net present value (NPV) calculation on any product in development is a good indication that upon market release, the financial return will exceed the cumulative life cycle costs of research, development, market validation, market access, market release, manufacture and sales and therefore potentially justify the initial outlay; this is summarised as return on investment (ROI). In healthcare and particularly therapeutic intervention, development takes a long time of typically over 14 years (FDA 2016; Stewart *et al*. 2018), and is costly (up to $2.6bn, (DiMasi *et al*. 2016)) which means that significant risk has to be carried for a long duration before knowing if the product was worth the investment.

Despite this market reality, rNPVs on projects and portfolios at the startup stage for healthcare-focused endeavours are communicated either publicly or privately that greatly exceed what is actually happening in the marketplace, which suggests that the data being used in rNPV calculations may be incorrect, and there is a disconnect between stakeholders, that has serious ramifications for when an early-stage company attempts to out-license its innovation to a larger organisation.

Methods

The understood fallibilities of rNPV calculations have led to the development of new valuation models, such as the headroom method that determines the maximum reimbursable price (Cosh 2007; Girling 2015; Markiewicz 2016), early-stage health economic models (Retel 2013; Brandes 2015; Miguel-Cases 2015) which only study interventions ready for clinical trials or market launch, or multi-criteria decision analysis (Thokala 2016; Middelkamp 2016) which is based on collecting feedback from stakeholders based on hypothetical products and then using this to estimate the value of the product. The maximum reimbursable price and early-stage health economic models seem best suited when a product is already on the market for one disease, and drug repositioning is being considered as a way to increase revenues, without high development cost and risk. For earlier-stage considerations, however, and accounting for the perspective of either startup companies or early-stage R&D in larger companies, the calculation does not include previous risks and costs.

Regarding costing, there have been many studies performed since 1979 on the costs of bringing a drug to market (these studies have been neatly summarised in Mestre-Ferrandiz *et al*. 2012), however the costing indicated in each referenced study did not include current clinical data requirements of review and reimbursement agencies, post-market release costs such as manufacturing, sales and general expenses, and continued clinical trials, all of which need to be paid for from the drug revenues.

In recent years, several teams have reassessed the NPV estimation models: Svennebring and Wikberg (2013) proposed extensions to the existing model that included constant probability rates of finding a drug candidate, a dynamic probability tree for cumulative identification of new candidates and that more than one compound can be selected for clinical development. Real option-based valuations have also been proposed which are founded more in managerial flexibility and strategic value, while an effectuation model which integrates means, loss, partnerships and expecting the unexpected can be used to identify value differences between pipelines.

However, there are still several underlying issues pertinent to generating an effective valuation: Zizlavsky (2014) highlighted that one of the fundamental problems in NPV approaches is that average probabilities of success or occurrence occur, when in reality indication-specific probabilities should be used.

While many authors (Rottgen 2018; Stewart *et al*. 2018) have indicated that failure to include the total costs in their calculations can result in incorrect estimates. Fundamentally, the issue is that full economic costing of development is not used in early-stage value calculations. A risk-profiled NPV model (rpNPV) did attempt to integrate in more market-related variables (Walker *et al*. 2015); this was the closest model that attempted to integrate full economic costs. However, the model was using generic rather than indication-specific variables, such as very long clinical trial phases, and did not consider SAM and SOM (serviceable accessible market [SAM] geography differentiated market value) and serviceable obtainable market (SOM (percent of market penetrance that can be achieved within a serviceable accessible market)), as a function of terminal market value related to existing standards of care upon which decisions to reimburse are made.

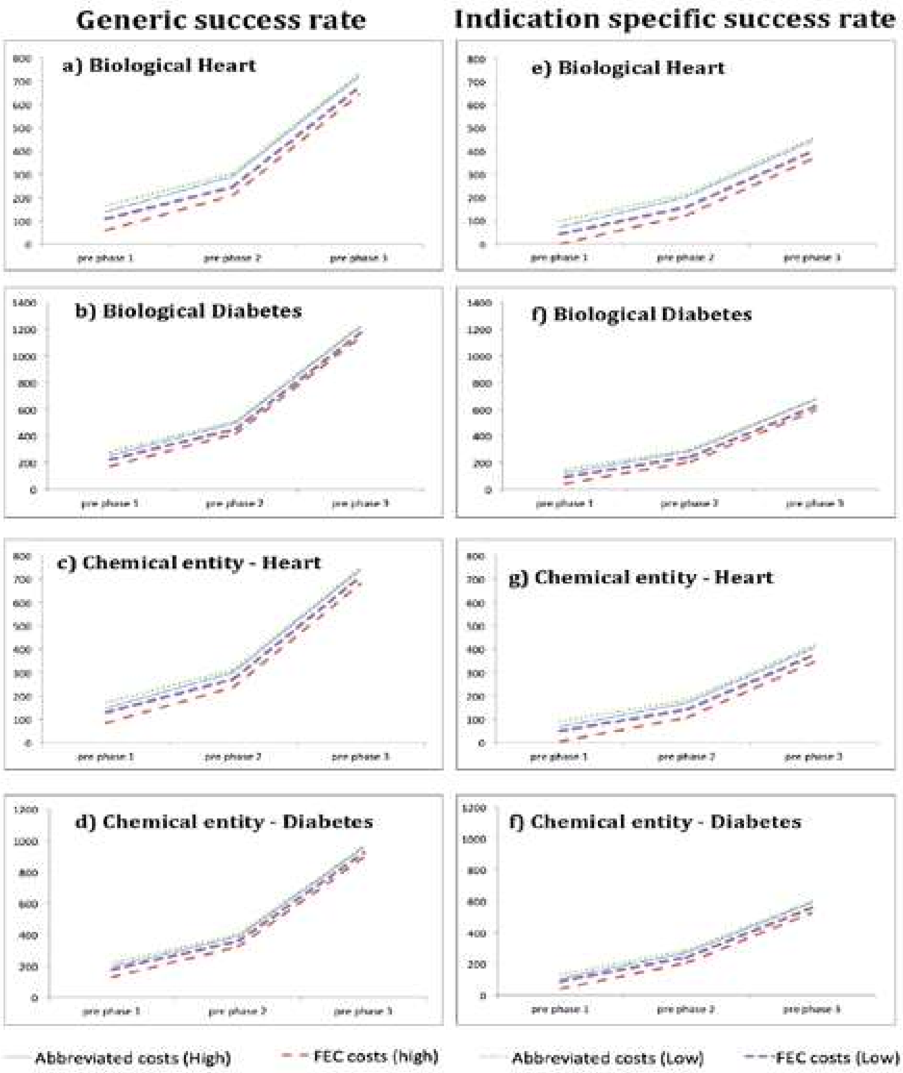
From our experience, many small to medium companies in the field still have incomplete perspectives of the full market chain and pharma marketplace, especially in the link between regulatory approval and reimbursement and what the priorities of larger entities are. The general understanding is that the two are synonymous, when in reality they are not. Petersdorf and Kanavos (2015) succinctly summarised this as follows: “HTA agencies operate within a network of other healthcare actors that, together, determine whether a medicine is allowed to enter a market, who receives the medicine, and who pays for therapies. Regulator bodies such as the European Medicines Agency’s (EMA) Committee for Medicinal Products for Human Use are responsible for assessing drugs on their efficacy and safety. Approval is required from these agencies to receive market authorisation. National or regional bodies then negotiate with the manufacturer (or the drug wholesaler) on drug price, reimbursement status (as in specifically for what based on evidence-based medicine) and allocated funding. HTA bodies inform these three latter considerations.”

There is also a lack of robust peer-reviewed publications linking pricing and reimbursement (P&R) procedures outcomes such as health technology assessments (HTAs) with the development stage values of medical interventions using relative negative predictive value (rNPV) financial model valuation-based methods: yet the outcomes of the P&R and HTAs define the terminal market value of the intervention, which by definition directly informs the rNPV of the intervention in development at any given stage. There is an emerging use of early health technology assessment (Ijzerman *et al*. 2017), which defines ‘early HTA’ as assessment “of medical products just before and also at the early stages of clinical use” and that the outcomes can be used to manage risk in technology portfolios and their market application.

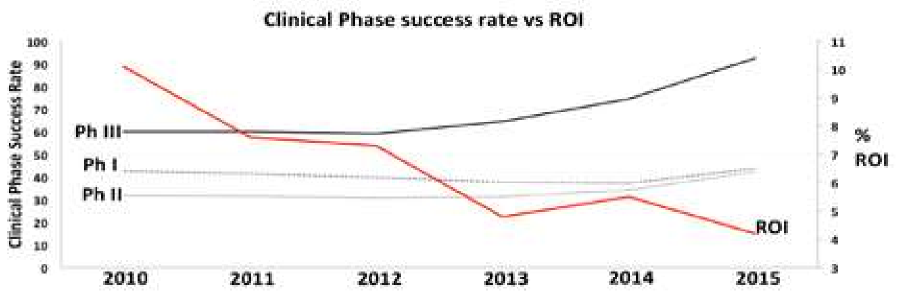
Research Question

There is a certain level of ‘value over-optimism’ of early-stage innovations, specifically those performed in startup companies, based on the incorrect perception that later-stage stakeholders, such as larger pharmaceutical and biopharmaceutical companies, are innovation stale, a perspective also indicated in the rpNPV model (Walker *et al*. 2015). However, this is contradicted by reviewing pharma and biopharmaceutical company pipelines that perform valuations that typically include all the pertinent market dynamics.

We wanted to know how and why this happens and also chose to reverse-model how up-to-date and complete market realities based on publicly available sales revenues, when integrated into the rNPV calculation, influence early valuation calculations



Stage specific rNPV calculations for the four modelled interventions, using generic success rates comparing abbreviated or full high and low costs, and indication specific success rates comparing abbreviated or full high and low costs



Clinical trial rates for CVD vs generic ROI: Phase III clinical trial success rates have increased, but this has not been reflected in the ROI

accounting for the various different data inputs.

This was enabled by two recent studies published in 2018 (Thomas *et al*. n.d.; Wong, Siah and Lo 2018), that has included indication-specific statistics and clinical success transition probabilities, based on the analysis of large sets of historical data, permitting us to use as detailed and up-to-date data as possible. Success rates are used for the probability adjustments in rNPV valuations (Villiger n.d.; Booth 2011; Booth 2014; Dillon 2015; Drummond 2013), and based on our experiences from working throughout the value chain (Salas M. *et al*. 2009; Larkin J. *et al*. 2015; Dando 2017; Dando & Weiss 2013) with the whole spectrum of stakeholders, we identified several key factors that needed to be integrated into the calculation, which would possibly provide more realistic indicators of value.

One key aspect was the link of HTA-indicated benefits and perceived terminal market values, which at present seem to be based on total accessible market, i.e. the global market, yet HTA decisions are geographically constrained. The importance, therefore, is what the values that are reported in market analyses correspond to, which are: The total sales in the precise geographic market where those sales will occur based on clinical outputs on a defined population.

Market values are typically reported by indication or specific disease application, which falls within the group of diseases linked to the indication, while total global market values are reported with percentage by geographic area. Geographic areas typically are the USA, Europe and Asia-Pacific (APAC), however for an HTA evaluation, and a medical intervention development regulatory perspective, clinical data generated in one geographic block or free trade area is not necessarily accepted in another, necessitating further development costs (Van Norman 2016). Each geographic area has its own specific health technology assessment requirement, with different constraints. This means that the intervention evaluation procedures during later-stage clinical validations are regulatorily different.

Given that the ROI on drug development is below the WACC, the implication is that the market-related outcomes of P&R procedures and HTAs play a critical role in defining if a health technology has any market viability. Indeed, as Villiger and Bogdan (2006) reported, “People want a drug to be valued to predict whether it will make money. However, valuation only calculates the odds. The value tells you whether it is worthwhile to risk the bet and how much you should bet, but it does not tell you whether you are going to win.”

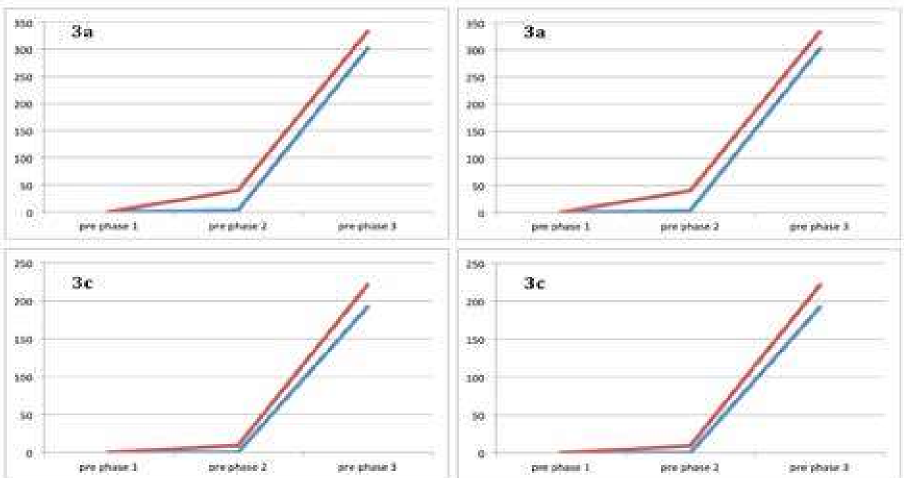
Market Size

To perform this study, we chose to focus on cardiovascular and endocrinological indications, modelling both biologics and chemical entities. For cardiovascular we modelled chemical entities for hypertension and biologics for anti-coagulants, while for endocrinology we modelled chemical entities for non-insulin drugs and biologics for insulin-related drugs. Information on market sizes was obtained from the following sources. For each modelling we elected to compare the lowest and highest markets to provide the limits of valuation calculations.

To model SOM values, we obtained information on the top ten antihypertensive drugs being sold in the United Kingdom from Statista (Statista, 2018) and converted these figures into market penetrance values, which were then used to calculate the various terminal values that should be inserted into the rNPV calculations. Values ranged from 0.62% to 40% of the market share, and we modelled terminal market values ranging from 1% to 100%. The same hypothetical per cent market shares were used for modelling in all other indications and interventions described.

Full Development Costs vs. Abbreviated Costs (High and Low Versions)

For development costs we used three different sources of information from DiMasi (DiMasi *et al*. 2016), Booth (Booth 2011; Booth 2014) or Sertkaya (Sertkaya *et al*. 2014). DiMasi’s estimates include the costs of failure (out of pocket costs) therefore representing the high cost threshold, although we did not include capitalisation-related costs as there is still debate on this point, and capitalisation costs are entity-specific,



rNPV calculations for the four interventions using indication specific FEC high and low costs and phase specific cumulative progressive success rate.

while Sertkaya's costs represent a more critical path costing, and therefore represent the lowest cost threshold. Neither team provided information on discovery or preclinical work, therefore we combined these peer-reviewed assessments with Booth's professional experience of discovery and preclinical costs to generate two costing models: low and high cost estimates in either an abbreviated (historically used values) or a full economic cost (FEC) value including all costs. Additionally, the preclinical development of biologics has been reported to be 1.45 times higher than for chemical entities, while clinical translation costs are similar (Mestre-Ferrandiz *et al*. 2012), which have also been included in the input values.

For an effective assessment of the HTA dossier, entities responsible for reimbursement perform meta-analyses and systematic reviews, in which, providing the clinical trial has been implemented correctly, the new intervention is compared to the existing standard of care. To be able to prove that the new intervention is comparable or better than the existing standard of care, for major diseases, large and well-designed Phase III trials generating robust and meaningful data for reimbursement decision-makers are required to obtain reimbursement and market access enabling sales.

To submit a reimbursement dossier without sufficient, robust and meaningful clinical evidence leads to a very high risk of not getting reimbursement, and two trials would be the minimum. Assessment of leading drugs on the market and their clinical validation steps, this may still be an underestimate. Successful interventions launched globally have revealed that typically more than 10 Phase III clinical trials in different geographies are typically required for sufficient clinical evidence to be obtained.

There is the registration cost and at the stage of market release, there is also the manufacturing cost of the intervention, which has two components: the facility and the actual therapeutic manufacture. Manufacturing a biologic requires a dedicated facility, costing on average $350mn, without considering running

Chemical Entity based intervention

Chemical Entity - Heart

	Market penetration		100%	40%	15%	10%	7%	3%	1%
		pre phase 1	39.21	15.684	5.8815	3.921	2.7447	1.1763	0.3921
	High cost	pre phase 2	204.49	81.796	30.6735	20.449	14.3143	6.1347	2.0449
		pre phase 3	526.12	210.448	78.918	52.612	36.8284	15.7836	5.2612
USA									
		pre phase 1	86.9	34.76	13.035	8.69	6.083	2.607	0.869
	Low cost	pre phase 2	240.91	96.364	36.1365	24.091	16.8637	7.2273	2.4091
		pre phase 3	556.84	222.736	83.526	55.684	38.9788	16.7052	5.5684
		pre phase 1	19.6	7.84	2.94	1.96	1.372	0.588	0.196
	High cost	pre phase 2	102.24	40.896	15.336	10.224	7.1568	3.0672	1.0224
		pre phase 3	263.06	105.224	39.459	26.306	18.4142	7.8918	2.6306
Europe									
		pre phase 1	43.45	17.38	6.5175	4.345	3.0415	1.3035	0.4345
	Low cost	pre phase 2	120.46	48.184	18.069	12.046	8.4322	3.6138	1.2046
		pre phase 3	278.42	111.368	41.763	27.842	19.4894	8.3526	2.7842

Chemical Entity - Diabetes

	Market penetration		100%	40%	15%	10%	7%	3%	1%
		pre phase 1	3.56	1.424	0.534	0.356	0.2492	0.1068	0.0356
	High cost	pre phase 2	106.94	42.776	16.041	10.694	7.4858	3.2082	1.0694
		pre phase 3	345.02	138.008	51.753	34.502	24.1514	10.3506	3.4502
USA									
		pre phase 1	48.87	19.548	7.3305	4.887	3.4209	1.4661	0.4887
	Low cost	pre phase 2	141.54	56.616	21.231	14.154	9.9078	4.2462	1.4154
		pre phase 3	374.21	149.684	56.1315	37.421	26.1947	11.2263	3.7421
		pre phase 1	1.87	0.748	0.2805	0.187	0.1309	0.0561	0.0187
	High cost	pre phase 2	56.28	22.512	8.442	5.628	3.9396	1.6884	0.5628
		pre phase 3	181.59	72.636	27.2385	18.159	12.7113	5.4477	1.8159
Europe									
		pre phase 1	25.72	10.288	3.858	2.572	1.8004	0.7716	0.2572
	Low cost	pre phase 2	74.5	29.8	11.175	7.45	5.215	2.235	0.745
		pre phase 3	196.95	78.78	29.5425	19.695	13.7865	5.9085	1.9695

Biological Entity based intervention

Biological - Heart

	Market penetration		100%	40%	15%	10%	7%	3%	1%
		pre phase 1	0	0	0	0	0	0	0
	High cost	pre phase 2	121	48.4	18.15	12.1	8.47	3.63	1.21
		pre phase 3	366.48	146.592	54.972	36.648	25.6536	10.9944	3.6648
USA									
		pre phase 1	40.41	16.164	6.0615	4.041	2.8287	1.2123	0.4041
	Low cost	pre phase 2	157.43	62.972	23.6145	15.743	11.0201	4.7229	1.5743
		pre phase 3	397.2	158.88	59.58	39.72	27.804	11.916	3.972
		pre phase 1	0	0	0	0	0	0	0
	High cost	pre phase 2	90.75	36.3	13.6125	9.075	6.3525	2.7225	0.9075
		pre phase 3	274.86	109.944	41.229	27.486	19.2402	8.2458	2.7486
Europe									
		pre phase 1	30.31	12.124	4.5465	3.031	2.1217	0.9093	0.3031
	Low cost	pre phase 2	118.07	47.228	17.7105	11.807	8.2649	3.5421	1.1807
		pre phase 3	297.9	119.16	44.685	29.79	20.853	8.937	2.979

Biological-Diabetes

	Market penetration		100%	40%	15%	10%	7%	3%	1%
		pre phase 1	41.21	16.484	6.1815	4.121	2.8847	1.2363	0.4121
	High cost	pre phase 2	205.99	82.396	30.8985	20.599	14.4193	6.1797	2.0599
		pre phase 3	592.19	236.876	88.8285	59.219	41.4533	17.7657	5.9219
USA									
		pre phase 1	90.96	36.384	13.644	9.096	6.3672	2.7288	0.9096
	Low cost	pre phase 2	242.41	96.964	36.3615	24.241	16.9687	7.2723	2.4241
		pre phase 3	622.91	249.164	93.4365	62.291	43.6037	18.6873	6.2291
		pre phase 1	20.61	8.244	3.0915	2.061	1.4427	0.6183	0.2061
	High cost	pre phase 2	102.99	41.196	15.4485	10.299	7.2093	3.0897	1.0299
		pre phase 3	296.09	118.436	44.4135	29.609	20.7263	8.8827	2.9609
Europe									
		pre phase 1	45.48	18.192	6.822	4.548	3.1836	1.3644	0.4548
	Low cost	pre phase 2	121.21	48.484	18.1815	12.121	8.4847	3.6363	1.2121
		pre phase 3	311.45	124.58	46.7175	31.145	21.8015	9.3435	3.1145

SOM rNPVs for each market using real world data potential market share (numbers in millions of USD)

Chemical Entity based intervention

Chemical Entity - Heart

		Market penetration	100%	40%	15%	10%	7%	3%	1%
		pre phase 1	2.77	1.108	0.4155	0.277	0.1939	0.0831	0.0277
	High cost	pre phase 2	22.39	8.956	3.3585	2.239	1.5673	0.6717	0.2239
		pre phase 3	65.94	26.376	9.891	6.594	4.6158	1.9782	0.6594
USA									
		pre phase 1	9.22	3.688	1.383	0.922	0.6454	0.2766	0.0922
	Low cost	pre phase 2	27.28	10.912	4.092	2.728	1.9096	0.8184	0.2728
		pre phase 3	70.43	28.172	10.5645	7.043	4.9301	2.1129	0.7043
		pre phase 1	1.39	0.556	0.2085	0.139	0.0973	0.0417	0.0139
	High cost	pre phase 2	11.2	4.48	1.68	1.12	0.784	0.336	0.112
		pre phase 3	32.97	13.188	4.9455	3.297	2.3079	0.9891	0.3297
Europe									
		pre phase 1	4.61	1.844	0.6915	0.461	0.3227	0.1383	0.0461
	Low cost	pre phase 2	13.64	5.456	2.046	1.364	0.9548	0.4092	0.1364
		pre phase 3	35.21	14.084	5.2815	3.521	2.4647	1.0563	0.3521

Chemical Entity - Diabetes

		Market penetration	100%	40%	15%	10%	7%	3%	1%
		pre phase 1	negative	negative	negative	negative	negative	negative	negative
	High cost	pre phase 2	10.7	4.28	1.605	1.07	0.749	0.321	0.107
		pre phase 3	42.01	16.804	6.3015	4.201	2.9407	1.2603	0.4201
USA									
		pre phase 1	5.09	2.036	0.7635	0.509	0.3563	0.1527	0.0509
	Low cost	pre phase 2	15.35	6.14	2.3025	1.535	1.0745	0.4605	0.1535
		pre phase 3	46.27	18.508	6.9405	4.627	3.2389	1.3881	0.4627
		pre phase 1	negative	negative	negative	negative	negative	negative	negative
	High cost	pre phase 2	5.63	2.252	0.8445	0.563	0.3941	0.1689	0.0563
		pre phase 3	22.11	8.844	3.3165	2.211	1.5477	0.6633	0.2211
Europe									
		pre phase 1	2.68	1.072	0.402	0.268	0.1876	0.0804	0.0268
	Low cost	pre phase 2	8.08	3.232	1.212	0.808	0.5656	0.2424	0.0808
		pre phase 3	24.35	9.74	3.6525	2.435	1.7045	0.7305	0.2435

Biological Entity based intervention

Biological - Heart

		Market penetration	100%	40%	15%	10%	7%	3%	1%
		pre phase 1	negative	negative	negative	negative	negative	negative	negative
	High cost	pre phase 2	12.46	4.984	1.869	1.246	0.8722	0.3738	0.1246
		pre phase 3	45.57	18.228	6.8355	4.557	3.1899	1.3671	0.4557
USA									
		pre phase 1	3.63	1.452	0.5445	0.363	0.2541	0.1089	0.0363
	Low cost	pre phase 2	17.35	6.94	2.6025	1.735	1.2145	0.5205	0.1735
		pre phase 3	50.05	20.02	7.5075	5.005	3.5035	1.5015	0.5005
		pre phase 1	negative	negative	negative	negative	negative	negative	negative
	High cost	pre phase 2	9.35	3.74	1.4025	0.935	0.6545	0.2805	0.0935
		pre phase 3	34.17	13.668	5.1255	3.417	2.3919	1.0251	0.3417
Europe									
		pre phase 1	2.72	1.088	0.408	0.272	0.1904	0.0816	0.0272
	Low cost	pre phase 2	13.02	5.208	1.953	1.302	0.9114	0.3906	0.1302
		pre phase 3	37.54	15.016	5.631	3.754	2.6278	1.1262	0.3754

Biological-Diabetes

		Market penetration	100%	40%	15%	10%	7%	3%	1%
		pre phase 1	3.03	1.212	0.4545	0.303	0.2121	0.0909	0.0303
	High cost	pre phase 2	21.65	8.66	3.2475	2.165	1.5155	0.6495	0.2165
		pre phase 3	72.66	29.064	10.899	7.266	5.0862	2.1798	0.7266
USA									
		pre phase 1	9.78	3.912	1.467	0.978	0.6846	0.2934	0.0978
	Low cost	pre phase 2	26.54	10.616	3.981	2.654	1.8578	0.7962	0.2654
		pre phase 3	77.15	30.86	11.5725	7.715	5.4005	2.3145	0.7715
		pre phase 1	1.51	0.604	0.2265	0.151	0.1057	0.0453	0.0151
	High cost	pre phase 2	10.82	4.328	1.623	1.082	0.7574	0.3246	0.1082
		pre phase 3	36.33	14.532	5.4495	3.633	2.5431	1.0899	0.3633
Europe									
		pre phase 1	4.89	1.956	0.7335	0.489	0.3423	0.1467	0.0489
	Low cost	pre phase 2	13.27	5.308	1.9905	1.327	0.9289	0.3981	0.1327
		pre phase 3	38.57	15.428	5.7855	3.857	2.6999	1.1571	0.3857

SOM rNPV for each market with Dynamic Risk Rate application (values indicated in $mn)

costs, while a chemical entity manufacturing facility costs on average $65mn. Actual manufacture of the pre-launch phase has been estimated to reach 30% of the costs of sales (Basu *et al*. 2008); for the purpose of generating the most optimistic possible rNPV, we elected to use the lowest possible value for manufacturing.

Higher downstream costs (scaled-up manufacturing, continued clinical studies) for the later stages were not included for rNPV calculations, which would have to be done on an intervention-by-intervention basis depending on the outcomes of the original clinical trials and recommendations of the reimbursing agencies.

Success Rates

We used information from the latest publications (Wong, Siah & Lo 2018; Thomas, n.d.) reported in the supplement to the article, which contains 11 years of data from 2005 to 2015, related to multiple indications and the success rate transitions from Phase I to Phase III of the clinical trial. We averaged all 11 years of success-rate data by phase for cardiovascular or endocrinological/metabolic indications and used this as the ‘success rate’ for the pertinent indication.

Results

Modelling the rNPVs

We first set out to determine the impact on output valuations when the full economic cost (FEC) or the abbreviated cost of development were used in the SAM. Using just the USA as the SAM market example, the high costs were compared to the low costs using generic success rates for four potential interventions; biologics treatment for cardiac-related disease, biologics treatment for diabetic-linked diseases, chemical entity-based treatment for cardiac-related disease, and chemical-entity based treatment for diabetic-linked diseases. As expected, independent of the disease indication or application, using FEC resulted in a reduced rNPV value along the value chain. On average and independent of clinical phase, rNPVs were $49 million dollars higher between abbreviated low costs and FEC low costs, and $71 million dollars higher between abbreviated high costs and FEC high costs. The implication being clear that whether your costs are critical-path or encompassing total out of pocket, reducing costs will increase the rNPV. When comparing phase by phase, rNPVs for abbreviated costs were on average $10.5 million higher for both Phases II and III compared to the FEC, while Phase 1 rNPVs for abbreviated costs were $36 million higher, implying that increasing the cost-effectiveness of the early-stage R&D will have a greater impact on longer-term value.

When we integrated into the rNPV calculations the latest indication-specific success rates, the impact was more dramatic. At a Phase II level, using indication-specific success rates, on average a $180 million decrease in rNPV was observed, while at the Phase III level, the average decrease was $507 million (averaging was performed across indication and therapeutic approach. The critical importance and ramifications of this are further explored in the real-world modelling).

As the FEC high and FEC low corresponded to the total value chain costs up to the first two years of market release, and indication-specific success rates arguably provide a more accurate analysis, all subsequent simulations were performed using these values, comparing the USA and European markets.

The next simulation was to integrate in level of local market penetrance, or SOM. In healthcare interventions, SOM is determined by the existing standard of care, the outcomes of the clinical trials, how convincing the clinical data is compared to the null hypothesis and the potential pricing. Much of this forms part of pricing and reimbursement decision-making through procedures like HTAs, which can therefore influence the pricing. HTAs are nowadays well established not only in traditional HTA markets like the United Kingdom, but also elsewhere like other European markets and in the United States, Canada and Asia, and it is gaining further global momentum. Whilst processes and methods may differ from one jurisdiction to another, the basic principles of the data used being relevant and meaningful to decision-makers and the value proposition being robust and able to be substantiated remains across jurisdictions. Therefore, we have researched these aspects and reflected them against our own experience conducting and advising on HTAs in these jurisdictions to inform our analyses presented in this article. We especially considered robustness, relevance and meaningfulness of the underlying data as the overlapping areas for HTA decision-making in our work. For this we considered published sources as well as our own experience. As the work we present in this article is a novel approach and has not been done before, we firmly believe this to be a robust approach to this decision analysis.

Taking the perspective of an early-stage company, considering moving forward one of its compounds in which alternative interventions would represent the competing products with different market shares, we modelled how the estimated 'market penetrance by percentage' would further influence the rNPV (It should be noted that the 100% value indicated in these tables corresponds to the SAM value). Taking into consideration that pre-Phase I would involve spending anything from $18 million to $250 million, it became clear that any intervention, for whatever rationale, would need to obtain greater than 15% market share to be worthwhile, with the lower market share only potentially making returns in the long term, with a potential to reposition the intervention in alternative diseases in the same indication to increase revenue. This was the same for all disease/intervention type combinations. As rNPVs are additive, for early-stage entities planning intervention development it also raises the strategic necessity of internationalising as early as possible: while it is tempting to establish foreign subsidiaries to access markets, this can be expensive, and for an early-stage company, longer-term strategies of joint development and partnering will potentially create future value when a more local-based perspective would not. It also addresses the importance of above regarding HTA's and reimbursement decisions taken in trading blocks such as Europe, in that one country may make a different decision to another, irrespective of the transferability of the HTA requirements, and market penetrance modelling needs to be performed in some detail.

Discussion

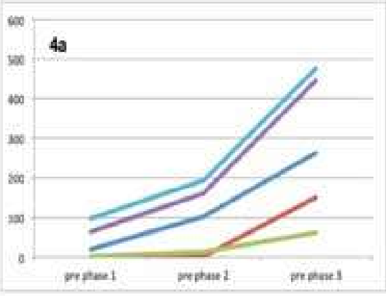
The rNPV outcomes obtained by using the full economic costs of the development that would be incurred by either one stakeholder performing everything in-house, or through multiple stakeholders transferring the technology upstream to a more relevant stakeholder versus abbreviated costs were dramatic, and if based on using accepted 'generic' values go some way to explaining why the ROI on drug development is so low. Drugs reach the market where competing products drastically diminish the value of the innovation's applicability. This was further impacted by geographic separation into SAMs and further still when the simulation included real world market penetration of interventions, in which there are multiple reimbursable interventions available. This would mean that all portfolios would need to be re-evaluated to assess true value, and then tied into the company's logistical capacities, implementation approaches and strategies, and partnering possibilities to try to maximise value.

The use of a harmonised risk value inside the calculation would go a long way to informing all stakeholders, and while the IRR is standard, because its estimation is company-specific this can change significantly. We have proposed one alternative; it is clearly more realistic than existing risk rates when put into the context of real-world data but further modelling using as many different real-world examples, including from licensing deals, would inform the utility of its application.

From the initial development of our model using the inputs and calculations described here, we are constantly updating the model and its inputs with further up-to-date data and product- and company-specific information to reflect up-to-date market realities providing true real-world valuations.

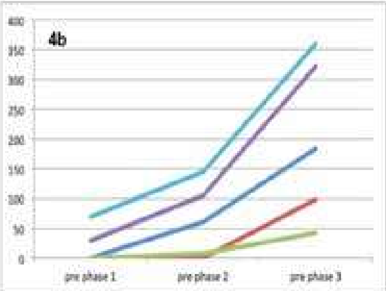
Conclusion

The resulting necessity to identify the true value of the innovation and the influencing factors indicates several approaches that should be taken during the whole development cycle. With an eye on the end goal and what is driving reimbursement, clinical development programmes, especially



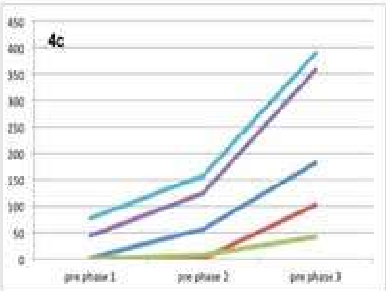
Ramipril	ind spec + IRR	prog +IRR	ind spec + pd DRR	Gen +IRR	Gen +IRR abbrev
pre phase 1	19.61	0	1.56	64.09	97.21
pre phase 2	102.31	1.67	13.75	160.39	193.35
pre phase 3	263.68	151.65	61.64	445.97	477.44

Sales	COGS/SGA	Pre dev Profit	Cost to dev.	Profit
$7bn	$4.2bn	$2.8bn	$2.72bn	$0.08bn



Reopro	ind spec + IRR	prog +IRR	ind spec + pd DRR	Gen +IRR	Gen +IRR abbrev
pre phase 1	0	0	0	29.03	69.28
pre phase 2	60.55	0	7.67	104.55	144.63
pre phase 3	183.71	98.84	42.65	321.81	360.32

Sales	COGS/SGA	Pre dev Profit	Cost to dev.	Profit
$5.44bn	$3.26bn	$2.17bn	$2bn	$0.017bn



Dapagliflozin	ind spec + IRR	prog +IRR	ind spec + pd DRR	Gen +IRR	Gen +IRR abbrev
pre phase 1	1.88	0	0	43.95	77.08
pre phase 2	56.31	0	6.94	123.82	156.78
pre phase 3	181.85	102.96	41.53	357.88	389.36

Sales	COGS/SGA	Pre dev Profit	Cost to dev.	Profit
$3bn	$1.8bn	$1.2bn	$1.1bn	$0.1bn

Comparison of rNPV models used in study when applied to real world revenue generating medical interventions.

Phase II and III trials, need to include endpoints required by and relevant to HTA organisations and payers in a way that they are considered robust by them during their assessments and appraisals. Where this is not happening, the company will face a high risk of negative reimbursement decision-making and, therefore, none to (at best) very limited uptake and sales.

There also needs to be a much closer link between the designs of the preclinical work and that during the clinical phases; performing preclinical animal work in the same way that human clinical work is now an accepted norm, but is just the starting point.

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