Trends in the Evaluation of Biotech Development Candidates

The method of choice

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Abstract

Drug development inarguably is a risky business, especially for biotech companies pursuing novel approaches, and having only a small portfolio further aggravates overall risk of failure at a corporate level. Being able to carry out a standardised, fact-based evaluation of development candidates becomes a crucial factor for decision-making in many contexts e.g. internal portfolio investments, fund-raising, deciding on a project strategy or preparing for out-licensing.

The external environment for performing project- or portfolio level evaluations is also changing. Factors such as clinical or economical differentiation have become critical requirements in the age of hyper-competition in the most lucrative areas such as Oncology; and because of the increasing use of health technology assessments by payors.

Several trends in project evaluation have emerged, some of them directly related to the changing environment: (1) more emphasis on the originality and quality of science in early-stage decision-making, where NPV often stands for "No Predictive Value", (2) degree of product differentiation as a core evaluation criterion, (3) scenario techniques to capture the significant uncertainty both in markets and development paths, (4) tools and benchmarks for risk measurement and mitigation, and (5) understanding the organisational dynamics of decision-making.

An objective evaluation and decision-making process at the individual asset- and portfolio levels represents a critical source of competitive advantage for any biotech- or pharma company.

Zusammenfassung

Trends bei der Bewertung von Biotech Entwicklungskandidaten – „Qual der Wahl“

Die Arzneimittelentwicklung ist unbestritten ein riskantes Unterfangen, vor allem für Biotech-Unternehmen die neuartige wissenschaftliche Ansätze verfolgen. Das zusätzlich kleine Produktportfolio erhöht das Risiko auch auf Firmenebene zu scheitern beträchtlich. Das Durchführen standardisierter, fundierter Bewertungen von Entwicklungskandidaten leistet einen maßgeblichen Beitrag zur Entscheidungsfindung zahlreicher Prozesse, z. B. Verteilung interner Portfolio-Investitionen, Kapitalbeschaffung, Festlegung von Projektstrategien oder Vorbereitung für Auslizensierungen.

Auch das äußere Umfeld, das Bewertungen auf Projekt- und Portfolioebene beeinflusst, ändert sich. Im Zeitalter von Hyper-Wettbewerb in lukrativen Bereichen wie der Onkologie sind Merkmale wie klinische oder wirtschaftliche Differenzierung zu wesentlichen Anforderungen geworden. Auch die zunehmenden Technologie Bewertungen (HTA) von Erstattungssystemen verstärken diesen Trend.

Teilweise als direkte Antwort auf die externen Einflüsse sind eine Anzahl neuer Trends bezüglich Projektbewertungen entstanden: (1) ein zunehmender Fokus auf Originalität und Qualität der Wissenschaft bei Entscheidungsprozessen in frühen Entwicklungsphasen in denen der NPV / Kapitalwert oft keinen Vorhersagewert darstellt, (2) Produktdifferenzierungsgrad als ein Kernbewertungspunkt, (3) Szenarienbetrachtung um sowohl die Unsicherheit bezüglich Marktpotential als auch Entwicklungsstrategien abzubilden, (4) Verwendung von Instrumenten und Referenzmarken zur Risikoabschätzung und -minderung und (5) Verständnis der unternehmensinternen Abläufe von Entscheidungsprozessen.

Demnach stellen objektive Bewertungen und Entscheidungsfindungsprozesse sowohl auf Einzelprojekt- als auch Portfolioebene einen entscheidenden Wettbewerbsvorteil für jedes Biotech- oder Pharma-Unternehmen dar.

Abbreviations

7MM	Seven Major Markets (US, Japan, Germany, France, UK, Spain, Italy)
COGs	Costs of Goods
FDA	Food and Drug Administration (US)
HTA	Health Technology Assessment
ICER	Incremental cost-effectiveness ratio
LOA	Likelihood of Approval
NICE	National Institute for Health and Care Excellence (UK)
NME	New Molecular Entity
NPV	Net Present Value
OS	Overall Survival
OSM	Option Space Mapping
PoC	Proof of Concept
SoC	Standard of Care
TPP	Target Product Profile
VC	Venture Capital

Introduction

When one talks to investors active in the biotech sector, it is widely acknowledged that drug development is a risky business with high reward potential but also large sums to be lost.

While many pharma companies can mitigate risk by building a sufficiently large portfolio, the typical biotech company with a small number of often very novel assets is fully exposed to the large volatility that goes along with clinical success or failure.

An illustration of this theme is provided by the recent run up in Intermune's share price, more than doubling at the end of February 2014 on the back of positive data of its lung disease drug pirfenidone [1]. The same Intermune also serves as an example for the impact of negative late-stage clinical data, as it occurred in 2010 when the FDA's rejection of pirfenidone led to an immediate decrease of – 78.8 % of the company's shares [2].

On a more global level, data shows that ~44 % of US VC investments into biotech companies over a twenty year period from 1986 to 2008 resulted in partial or complete losses [3].

Technical and Commercial Risks

So what are the key drivers for this large failure risk on a compound but also company level?

Inarguably, technical/scientific risk is a predominant driver and cause of investment failures. In a very recent analysis by Hay et al. on clinical success rates of > 4,400 investigational drugs in development between 2003 – 2011, average likelihood of approval (LOA) from Phase I was only 10.4 % [4]. Even for late stage projects, risk of attrition remains high, with an average Phase III LOA of 50 %. In addition, success probabilities differ by indication. In Hay's data set, PhI-LOA for Oncology drugs

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was the lowest with 7 %, compared to e.g. 17 % of corresponding Infectious Disease assets. Next to the indication type, other identified influencing factors were type of modality (e.g. NME or biologic), and lead or follow-on indication.

However, attrition is not the only factor impacting commercial outlook of biotech development candidates and companies.

Some R&D areas are characterised by hyper-competition. Again taking Oncology as an example, developing companies in that area face substantial commercial and also clinical study enrolment challenges, as the number of drug treated patients per expected launch based on pipeline size is ~8,451 compared to e.g. > 100,000 patients in the Immunology field [5]. In addition, a substantial number of Oncology drugs that do make it to the market will not generate sufficient revenues to adequately recuperate development investments. According to analyst expectations, about 50 % of currently marketed drugs in Oncology will remain below 150mn EUR in peak sales [6]. Getting a positive Internal Rate of Return (above the sometimes significant cost of capital of biotech companies) is a challenge for Oncology drugs in that range, given the significant costs and risks of clinical development (with costs per patient having gone up to > 100,000 EUR in some areas).

Finally, long development timelines often lead to a situation where the standard of care is changing and then render results of a Phase III study commercially obsolete.

Summarising, the state of hyper-competition requires new drugs to not only be safe and efficacious, but also clearly differentiated otherwise approval and significant revenue will be challenging to achieve.

Differentiation is also a key topic for achieving reimbursement. Payors require value for money in times of scarce resources. While this has historically been a topic in Europe it is now also coming to the US as exemplified by Sanofi's ziv-aflibercept (Zaltrap), launched in August 2012 for the treatment of colorectal cancer.

Competing against bevacizumab (Avastin), Zaltrap initially was priced at double the cost, while only showing comparable efficacy and safety outcomes (Avastin: 1.4 months median OS vs. Zaltrap: 1.44 months median OS). The U.S. "buy and bill" system for drug reimbursement charges ~2,200 USD co-payment for Zaltrap – a sum greater than the monthly income of half of Medicare patients.

As a consequence, the Memorial Sloan-Kettering Cancer Center (SKCC) – the world's oldest and largest private cancer center – refused to prescribe Zaltrap [7]. Sanofi subsequently reduced the acquisition price by ~50 %. However, patient co-payments remain unchanged as they are based on the list price. SKCC still refused approval and future prescriptions are expected to be influenced by its decision [8].

This case example indicates a changing public attitude towards healthcare costs in the US and underlines the necessity of demonstrating differentiation across a wide range of healthcare stakeholders including regulatory authorities, payors, physicians and patients.

Selecting Investment Areas as a Source of Competitive Advantage

In the context of technical risks, hyper-competition and the need to demonstrate economic value to payors, choosing your investment opportunities carefully becomes a source of competitive advantage. Some investors may be able to spread the bets across large enough portfolios to mitigate some of that risk but most biotech executive teams do not have that luxury and ensuring a long enough "cash runway" is a matter of survival.

A critical assessment of development candidates in a portfolio context is a crucial strategic task for investors but also for any Biotech

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executive team. In the latter case, this can be motivated for a number of reasons:

- *For internal portfolio decision-making* – to decide which assets to fund and to advance when resources are scarce;
- *For fund-raising* – to have an objective argument for investors and shareholders;
- *For deciding on a project strategy* – there is only one chance to get it right and increasingly projects in e. g. Oncology or Immunology resemble mini-portfolios with a broad option space in terms of indications, patient populations, lines of therapy or combination partners where decisions on lead and follow-on indications have to be taken;
- *Getting ready for out-licensing to a pharma partner* – preparing for due diligence and deal negotiations. A critical review of the own project is an ideal preparation for a partnering discussion in which both sides will have to agree on deal terms. Knowing the value of the own asset is prerequisite for a successful negotiation.

The benefits of fact-based project-level and portfolio decision-making are tremendous; those companies that bet on the right targets or approaches and can differentiate their projects in highly competitive markets can reap huge rewards in terms of market appreciation or partnering success.

The cost of getting it wrong is also substantial – when individual studies can easily cost 20 mn EUR (Phase II) or even 100 mn EUR (Phase III), there is no tolerance for choosing a wrong population for a PoC study.

Typically small Biotech companies do not have a full-blown portfolio capability. Very often the argument goes "we don't have a large enough portfolio to justify such a group". However, Biotechs often have scientific advisory boards to discuss the clinical strategy of lead assets and it is only an extra step to use those inputs for a systematic decision analysis. For many Biotechs, a flexible model in which experienced decision-support consultants come in at the right time to support project teams or senior executives fits much better than building a full-blown group or nominating one person to do it "on the side" (often on top of a business development or commercial role).

Recent Trends in Portfolio Decision-Making

As an answer to the challenges discussed above, a number of trends affecting portfolio decision-making across the biopharmaceutical industry in the last years can be observed (most affect both Biotech and larger companies):

- *More emphasis on the science in early-stage decision-making* – realising that it is sometimes impossible to forecast commercial potential of highly innovative approaches, companies have put renewed emphasis on the evaluation of the quality of the underlying science (sometimes called "scientific confidence");
- *Product differentiation as a key value driver* – in the past, a number of incrementally modified drugs reaped enormous commercial rewards (cf. omeprazole vs. esomeprazole, citalopram vs. escitalopram). However in the age of value-for-money and HTAs this strategy no longer works (illustrated by the venlafaxine vs. desvenlafaxine case study, and the relative lack of commercial success of the latter). In any case, biotech companies have to be prepared to demonstrate how their drugs are differentiated clinically and economically – and good project evaluation processes should capture this essential value driver at latest after PoC;
- *Scenario techniques to capture significant uncertainty* – uncertainty should be made explicit – instead of arguing "this is what I think will happen", the focus should be on "this is what I think *could* happen". In contrast to simulations in which numerous drivers are changed at the same time, a scenario forces people to think through a realistic combination of different drivers that can then be combined and weighted;
- *Tools and benchmarks that allow measuring and mitigating risk* – typically, risk is discussed only on a qualitative level or captured in risk registers. Two problems often occur – one is the agency conflict when a project team or leader is asked to review their own project, the other is that often a transparent and comparable translation into metrics relevant for decision-making is missing. Having an objective process in place to assess and mitigate risk is a prerequisite for an effective project evaluation;
- *Understanding the soft factors and organisational dynamics of decision-making* – at its simplest it means that hidden biases or conflicts can greatly undermine the benefits of even a best practice project- or portfolio-level evaluation process. Nothing is more frustrating than spending months on developing a fact-based review of projects or the portfolio only to be swept away by senior executives who never believed in the value of doing such a process in the first place. Sometimes it is lacking courage to take "tough" decisions, sometimes it is a deeply held belief that any evaluation or early stage assets is a futile effort. Whatever the reason, taking these concerns and beliefs into account from the start is a crucial element of effective project- and portfolio-level evaluation and decision-making.

Early Stage Project Evaluation in Action – Option Space Mapping

The challenge in the evaluation of early stage candidates that are pre-

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PoC is the high degree of uncertainty with respect to a candidate's real potential. This is especially relevant in areas with a broad option space in terms of target indications, populations, combination partners or lines of therapy. Especially in Oncology and Inflammation early stage assets tend to have a plethora of possible target labels and any attempt to pin down the value of such an asset will have to appropriately deal with that complexity.

Option Space Mapping (OSM) is a process that helps project teams to identify the most suitable development strategies for early stage assets. In essence, OSM is a structured dialogue with the key project team stakeholders around the scientific confidence, the competitive landscape and the overall commercial potential at a high level. In a second step alternative development paths are defined, each with an accompanying product vision (key claims and development path). In difference to the more formal requirements of a target product profile (TPP), a product vision can still be fairly broad. The key objective of that first step in the process is to define and select 2-3 options by the team for further evaluation.

OSM can also help to identify "generic" strategy alternatives that can be used to start off discussions within project teams. In Oncology for example, an organisation can either engage in a "signal search" across selected indications or it can follow the strategy of achieving a fast PoC in the indication with the highest scientific confidence (and then go broad). An OSM-session is ideal to work out the pros and cons of both and to define alternatives that are then evaluated in a project review. As a result of the discussion, the team then selects a few alternative options and describes them in more detail along a number of dimensions such as the "lead indication", "follow-on indications", "go/no go criteria", "timelines", "resource requirements", etc. It is more important at this stage to capture the strategic intent driving an option than to aim for absolute preciseness.

Still, despite its early stage and the high uncertainty attached to it, assessment of the commercial potential of early stage assets represents an important factor for guiding decision-making in portfolio management.

At this stage, the value of creating peak sales or lifecycle sales forecasts can be debated. Often the option space is so vast that one can come up with a niche profile or a potential blockbuster for any given candidate drug. This is why many approaches focus on capturing the qualitative aspect of market attractiveness, either through a criteria-based scoring or other approaches. The most important criteria for assessing this potential are novelty, degree of differentiation, the size of the target market segment, the competitive pressure, the ability of a company to exploit the potential of an asset and the potential for a positive business case. While in the past, degree of differentiation referred mainly to clinical differentiation it should now include economical differentiation from a payor's perspective as well. Together we call these factors the "Innovativeness" of an asset. The term stresses the importance of innovation and provides a clear definition for what has become an overused buzzword with little meaning in many companies. The result of this assessment can then be converted into a peak sales range, by using pre-defined patient share ranges for given scores (Fig. 1).

Any thorough project evaluation process should include a detailed assessment of technical risk, not only to estimate likelihood of success but also to help project teams develop mitigation strategies, to inform the selection of clinical strategies or to prepare for a due diligence when the intent is to out-license an asset. It is beyond the scope of this paper to discuss the pros and cons of the various approaches (cf. [9] for a thorough description of how to deal with risk at a project and portfolio level).

Late-stage Project Evaluation – From Net Present Value to Economic Value

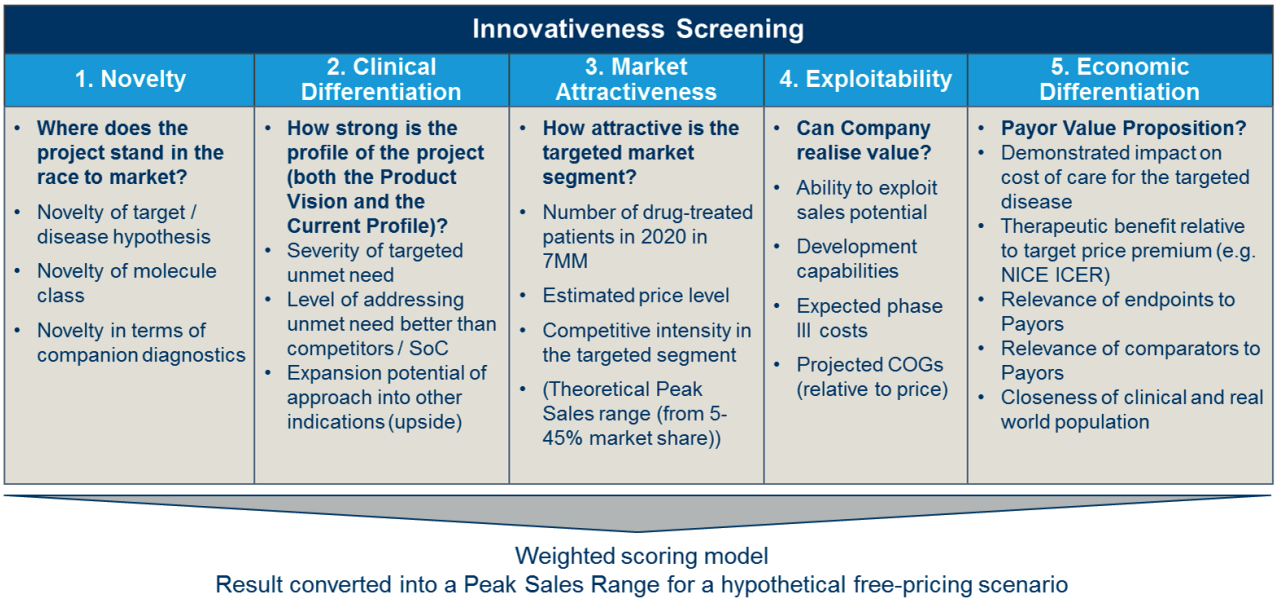
After reaching PoC, the level of uncertainty related to technical risk and eligible target patient population has decreased significantly. Evaluation of assets at this stage is usually performed using standardised, well-established tools for value prediction (most commonly NPV calculation).

While many companies routinely perform late stage asset evaluations, integration of the payor's perspective regarding list price estimates and resulting revenue potential is not yet widely done. However, the negative impact of Health Technology Assessments (HTA) on product sales can be substantial if the cost-benefit ratio vs. standard therapy is not differentiating enough (for more detail, see [10–11]). Mitigation approaches in this case include limiting the label to a stratified, more homogeneous patient population maximising efficacy, thereby improving the cost-benefit ratio (= economic value) and lowering reimbursement risk. A thorough valuation can then assist to ascertain whether a positive NPV is still to be achieved, despite the limitation in patient numbers.

Conclusion

In summary, portfolio management consists of a number of key processes and tools that need to be fine-tuned to the needs of stakeholders both at the level of project teams and senior management. These tools and processes can make a huge difference in creating buy-in and accountability for portfolio decisions. For many R&D people, NPV still stands for NO Predictive Value and convincing them usually takes more than overly simplified metrics and frameworks. Going beneath the

Figure 1



Factors for the "Innovativeness" assessment of an asset (source: figure made by the authors).

numbers to make the strengths and weaknesses of a project or portfolio come alive is a key skill in effective portfolio management. Also tools and processes need to reflect the different characteristics of early stage versus late stage projects. The latter are amenable to a full quantitative valuation whereas in an early stage setup a more qualitative or semi-quantitative method is required.

Altogether, an effective project- and portfolio-level evaluation can make a huge difference for a biotech company that has a limited number of 'shots at goal', and the effort of a thorough process is far outweighed by the benefits of developing more competitive project strategies.

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