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Portfolio management in early stage drug discovery – a traveler's guide through uncharted territory

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Portfolio management in drug development has become a best practice in the pharmaceutical industry. By contrast, early on in the value chain – the discovery phase – portfolio management is still in its infancy. Nevertheless, owing to the attrition of R&D projects from phase to phase and the cost of capital involved, these early phases of drug discovery play a significant part for the overall cost of bringing new, innovative drugs to the market. This paper describes various approaches to manage a portfolio of projects in early-stage drug discovery and provides crucial factors that determine the success of such an approach.

Introduction

The pharmaceutical industry is facing a productivity crisis. Although R&D spending increases from year to year, the output, measured as new drugs entering the market, is stagnant. This has led to a situation where the average costs of bringing a new molecular entity (NME) to market are now estimated to be ~US$1.8 billion [1]. This observed decreasing number of truly innovative drugs has even triggered some authors to question pharma's historical 'innovative industry' tag [2]. It is already estimated that continuing with the current business model would result in a reduction of 10% in sales and 30% in net income in the period 2012–2015 [3]. In this environment strong portfolio management is pivotal in helping to focus company resources effectively on the most attractive projects. Making the correct portfolio choices, setting priorities and making timely, well-informed decisions are all necessary components in this endeavor [4].

The identification of a clinical development candidate, through the early phases of the drug discovery value chain such as target to hit, hit-to-lead and lead optimization with early preclinical development, is at the heart of drug discovery. These are the stages when the structure of a new drug is shaped, and consequently all subsequently discovered clinical properties are pre-determined. Usually, errors resulting from this phase cannot be repaired later during development. Also, in commercial terms, the discovery phases are of critical importance, with US$824 million of the capital cost per launch almost as high as the cost for all clinical phases combined [1]. However, from a portfolio management perspective, this stage is vague and not easy to handle [5]. Questions such as: when is the right time to finish a lead optimization project? or, which projects are more promising than others? must be addressed in a situation where the level of uncertainty is particularly high. Although portfolio management in the later development phases has already become best practice in all major pharmaceutical companies, in the early part of the value chain – the discovery research phase – portfolio management is still in its infancy.

Modern portfolio management has its roots in the financial sector with tools such as mean-variance optimization to help determine the best allocation among various investment assets [6]. Key strategic frameworks have been added by Boston Consulting Group [7] and General Electric/McKinsey (e.g. business unit strength/industry attractiveness matrix), among others. The addition of decision trees, expected net present value (eNPV) calculations and, finally, real option analysis has further moved the field forward. The progress achieved has resulted in the application of portfolio management theory to pharmaceutical development as well, as exemplified in two *Harvard Business Review* articles from the 1990s [8,9]. Meanwhile, extensive literature exists describing models for valuation of pharmaceutical R&D projects [10–13], but the applicability of all these methods for early-stage drug discovery

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portfolios has, nevertheless, remained questionable, although the importance of strict portfolio management in this phase is generally acknowledged as a critical success factor [14].

It has previously been shown that the feasibility of a given R&D project can be assessed according to specific criteria, and such criteria have been amply defined and discussed in the literature [15–19]. Likewise, the application of such criteria on the problem of project portfolio management has met considerable coverage in the literature [20–23]; from the early work on scoring models [24] to more-complex mathematical programming models [25] and the analytical hierarchy process [26]. Nevertheless, the problem of discovery portfolio management still remains largely unresolved, although pharmaceutical R&D portfolio management would clearly benefit from a suitable methodology.

Owing to the special nature of this phase, portfolio management in discovery needs a tailored approach. Although every project handled by portfolio management during development usually covers only a single development candidate, portfolio management in discovery has to deal with projects covering multiple compounds, sometimes hundreds or even thousands each, that are synthesized, profiled and further optimized in the noble endeavor ultimately to identify the development candidate that fulfills the needs of efficacy, safety, convenience and commercial feasibility. Although, for example, criteria such as 'how easy is it to modify the structure of a given lead compound' or 'how long is the cycle time required to profile compounds in the screening cascade' and 'how high is the throughput' are of utmost importance in judging the probability of project success in the discovery phase, they play virtually no part in development when the optimal candidate has already been identified. Accordingly, it is not possible simply to 'copy and paste' the project evaluation and portfolio management methods established for development and apply them to the discovery phase of R&D. Instead, the development of new approaches, tailored to the specific needs of discovery, is essential.

Successful portfolio management relies on a synergistic interplay of various building blocks: a clear definition of objectives; the corresponding organizational structure and reporting lines for the portfolio management group, combined with suitable approaches, processes, as well as fitting methods and tools.

Purpose and objectives of the portfolio management group are usually defined by senior management that is sponsoring the existence of the team. In general, two principal setups can be distinguished: (i) a strong central group providing independent benefit:risk analysis and prioritization recommendations to the executive management board; or (ii) service function for therapeutic area leadership. In the first case a direct reporting line to the CEO is the fitting organizational structure, which guarantees independence of the group removing them from the reach of therapeutic area power play and politics. In the second setup therapeutic area specific portfolio groups are required; however, making a cross-therapeutic area portfolio management difficult. A third possibility is to run the portfolio assessment not with in-house resources but with an external consultancy company.

In terms of processes, again one can differentiate between a portfolio review process running across the entire portfolio in regular intervals (e.g. annually) or with an event-triggered model (e.g. when major milestone decisions have to be taken) or in times of changes in the available R&D budget, for example before or after major restructurings.

Portfolio assessment methods can be placed roughly into three groups that are briefly described here. Criteria-based scoring methods work with lists of specific questions designed to provide quantitative answers that, according to pre-defined criteria, determine the allocated score. Such methods can be time and resource consuming, but are also considered to be an objective assessment, because basically no personal preferences or biases are possible and scoring is based on clear quantitative criteria only. However, the diversity of drug discovery projects makes it difficult, if not impossible, to establish questions and scoring definitions that are general but still concrete enough to fit the special situation of each potential project.

The other group of assessments are the 'expert black box' methods, where scoring is at the discretion of an expert, representing their respective area of expertise, without pre-defined questions and/or answers and corresponding scores. This approach gives tribute to the complexity of the drug discovery process and the expert functions can lever their knowledge and experience, taking into account the specific situation of each project, which cannot be captured by general definitions.

Finally, there are the 'open surveys', which aim to capture an overall confidence level for projects in a portfolio from a target audience. Further along that line, exploiting the ''wisdom of the crowd's approach', methods based on prediction markets can be used. Research utilizing such markets for the purpose of aggregating beliefs regarding a future event originated at the University of Iowa in 1988 and the prediction record achieved is apparently superior to alternative mechanisms [27]. The method has been taken up by several pharmaceutical companies that are using internal markets to help predict which developmental drugs might have the best chance of advancing through clinical trials [28]. Prediction markets allow participants to buy or sell shares for each R&D project at a virtual stock market, according to how much they believe in its success, and reward them for betting on outcomes that turn out to be correct. Even a public prediction market has been started harnessing collective intelligence to predict the likelihood of breast cancer drugs succeeding through the three phases of clinical trials (http://pharmersmarket.crowdcast.com).

In summary, top management mandate, high organizational reporting lines of the portfolio management group, a fit-for-purpose methodology, continuous efforts to manage stakeholder expectations, limiting administrative burden for project teams, as well as getting along with silo thinking and the 'tapping on my turf' syndrome are all aspects of critical importance.

The remainder of this article will discuss a series of approaches that I have used to assess the benefit:risk profile of drug discovery portfolios at two pharmaceutical companies over the past ten years, creating a basis for prioritization, stop/go and resource allocation decisions. I also discuss key success criteria that can make or break a portfolio management exercise.

Criteria-based scoring models – 3D analysis

The 3D analysis is an example for a semi-quantitative evaluation tool to assess the benefit:risk profile of lead optimization projects and to create a basis for prioritization decisions focusing on the two dimensions of 'feasibility' and 'maturity'.

Feasibility describes how difficult it is to pursue a lead optimization project under the given conditions. The criteria applied are: (i) chemical and/or biological feasibility; (ii) screening cascade; (iii) historic performance; and (iv) IP (intellectual property) and/or FTO (freedom to operate). Feasibility is largely determined by factors that can only marginally be influenced by the project team during the course of a lead optimization program. Accordingly, additional allocation of resources will not readily improve feasibility.

Maturity describes how close the best compounds of the current project are to the desired target product profile. The criteria applied are: (i) efficacy; (ii) safety; (iii) convenience; (iv) formulation; (v) production; and (vi) biomarkers and/or companion

TABLE 1

Possible definitions to be used in the 3D analysis.

Dimension	High	Medium	Low
Feasibility			
Chemical feasibility New chemical entity (NCE)	Easy to synthesize/purify and derivatize, support through structural information available, structure activity/side-effect/ pharmacokinetic (PK) profile established	One of the detailed criteria is not fulfilled	Two of the detailed criteria are not fulfilled
Biological feasibility New biologic entity (NBE)	Easy to express/purify, non-critical isoform profile (e.g. glycosylation), structure activity/ side-effect/PK profile established	One of the detailed criteria is not fulfilled	Two of the detailed criteria are not fulfilled
Screening cascade	Complete, validated and fast screening cascade with not more than six weeks per optimization cycle including *in vivo* models (incl. availability of species compatible surrogates for NBEs)	Complete, validated but slow screening cascade with more than six weeks per optimization cycle	Incomplete screening cascade or screening cascade with unclear validity
Historic performance	So far project has moved faster than benchmark	So far project has moved comparable to benchmark	So far project has moved slower than benchmark
IP/FTO	FTO given globally, patent protection for product feasible	FTO with certain restrictions, patent protection for product feasible	FTO or patent protection for product at risk
Maturity			
Efficacy	Sufficient efficacy *in vivo* demonstrated in relevant pathophysiological models	Sufficient efficacy *in vivo* demonstrated in mechanistic models	Efficacy *in vivo* not yet shown
Safety	Acceptable tox/safety profile for the given indication	Tox/safety issues identified, but reasonable possibilities exist to overcome the problem	Critical tox/safety profile for the given indication; limited possibilities to overcome the problem, or not known
Convenience	Expected dose/dosing frequency/route optimal	Expected dose/dosing frequency/route acceptable	Expected dose/dosing frequency/route critical or not known
Formulation	Expected PK profile in human allows for standard formulation	Expected PK profile in human will require more risky advanced formulation technologies	Formulation critical or not known
Production	Non-critical cost of goods, sufficient leeway for all derivatives under consideration and non-critical scale-up feasibility	Borderline cost of goods, production only adequate for early development program	Severe issues, production for material critical even for early development program, or not known
Biomarkers/ companion diagnostics	All companion diagnostics required for development established	Candidate biomarkers identified (e.g. predictive biomarker for patient stratification, pharmacodynamic biomarker to monitor target effects, or disease progression biomarker to monitor therapeutic efficacy)	Biomarker program not defined or has not delivered yet
Potential			
Target degree of validation	Precedented target with a drug already on the market or with positive proof of concept from Phase III clinical trials	Unprecedented target with positive evidence from clinical studies (Phase I/II)	Unprecedented target or target not known
Development money at risk	Proof of concept can be obtained in Phase I or small Phase II study	PoC (proof of concept) can be obtained in Phase II study	PoC not before large Phase III study
Competitive situation	Clear potential for first in class or best in class drug	Clear differentiation potential versus current and future expected competitors	No clear unique selling proposition visible
Market size	Estimated peak sales >€1 billion	Estimated peak sales €100–1000 million	Estimated peak sales <€100 million
Portfolio fit	Filling critical gap in portfolio or combination potential with marketed own drugs	Fit into current portfolio	No strategic fit or redundant

diagnostics. Maturity should improve during the course of a lead optimization program. It can be positively influenced by allocated resources, and thereby is largely under the control of the project team. To assess maturity properly it is essential that a target–product profile is available, agreed between all relevant stakeholders, involving clinical development and marketing functions in particular. Table 1 shows how feasibility and maturity might be assessed.

The project evaluations can be done together with the respective project teams, but to avoid bias and ensure that criteria are applied uniformly across the entire portfolio the assessment should be checked for consistency across projects. Following the evaluation according to the given criteria a 'low' rating is allocated a score of 0, 'medium' is allocated a score of 10 and 'high' is allocated a score of 15. For each project a total feasibility and maturity score is calculated by summing up the individual scores for the various criteria, divided by the highest theoretically possible total score (Eq. (1)). In the example given above, the scores 0, 10 and 15 were chosen such that one low and one high rating will result together in an overall lower total score versus two medium ratings, giving credit to the assumption that a low assessment in one criterion cannot be compensated by a high assessment in another criterion. Of course, one could consider using other scoring numbers, more-complex algorithms or a different weighting of various criteria.

$$\text{M or F} = \frac{\sum_{i=1}^{n} \text{actual score criterion}_i}{\sum_{i=1}^{n} \text{maximal score criterion}_i} \quad (1)$$

where M = maturity, F = feasibility, n = number of different criteria for M or F.

The risk profile of the complete project portfolio can be visualized in a graph plotting feasibility versus maturity (Fig. 1). Relative high risk of failure in this matrix is associated with low feasibility and low maturity. However, even projects exhibiting a low maturity and medium feasibility or conversely a medium maturity and low feasibility can be categorized as high-risk projects (Fig. 2; also for medium and low risk projects).

To be able to rank projects in the portfolio according to risk, a project-specific risk score can be calculated. A corresponding algorithm can be developed by considering that risk is proportional to 1 – maturity (risk is 0 when maturity is 1, i.e. the development candidate has been found). At the same time risk is inversely proportional to the feasibility of a project (1/feasibility). The resulting equation can also be visualized by the car race analogy (Fig. 3).

The distribution of the resulting risk score, dependent on maturity and feasibility, can be seen in Fig. 4. The impact of project feasibility on the project risk score can be fine-tuned with

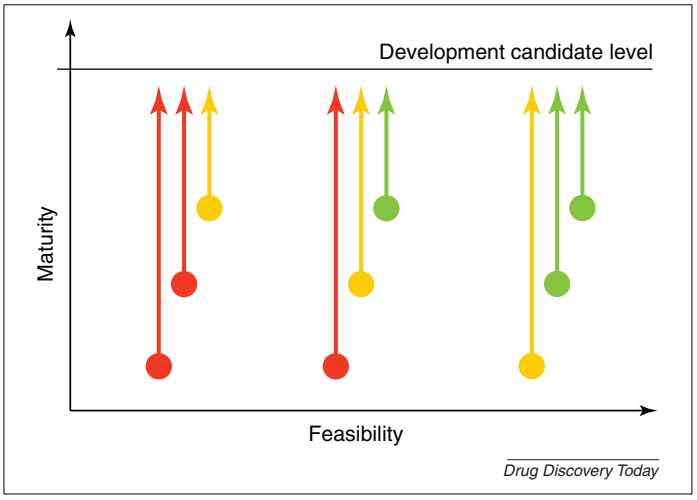

FIGURE 2

Distribution of project risk in the feasibility–maturity matrix. The overall risk of failure for a project depends on its feasibility and its maturity. High-risk projects are depicted with red arrows, medium risk projects are shown as yellow arrows and low risk projects are visualized as green arrows. The beginning of the arrow shows the situation at project start. For simplicity in this figure it is assumed that project feasibility does not change during the course of the project.

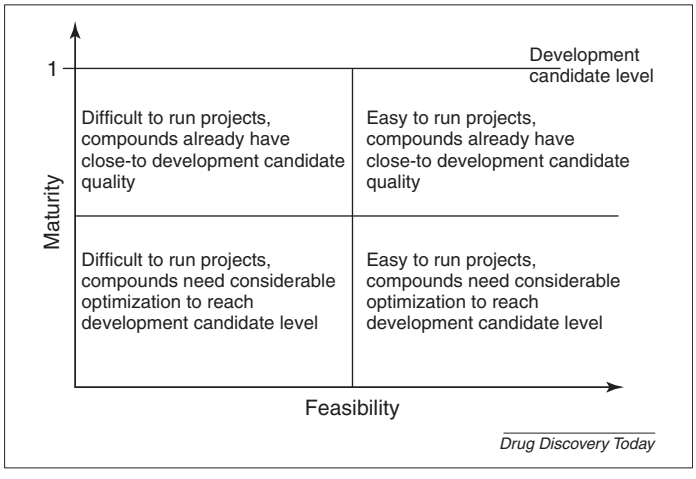

FIGURE 1

Feasibility–maturity matrix. Evaluation of discovery projects can be performed according to their feasibility and maturity. A maturity score of 1 is reached when a suitable development candidate has been identified. Projects in a portfolio can be grouped in the four quadrants of the feasibility–maturity matrix.

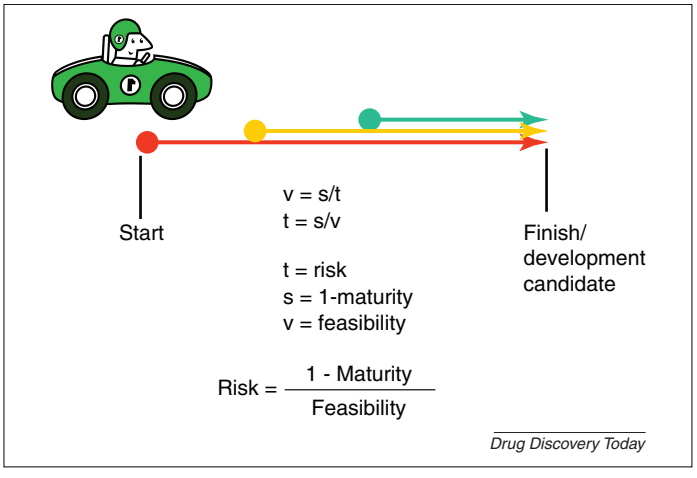

FIGURE 3

The racing car analogy. It is possible to visualize the three dimensions using the analogy of a car race. When the distance yet to go to reach the finish is an analogy for project maturity and car speed an analogy for project feasibility, the time still needed to reach the finish would correspond to project risk of failure. Accordingly, the risk score can be calculated with the velocity formula.

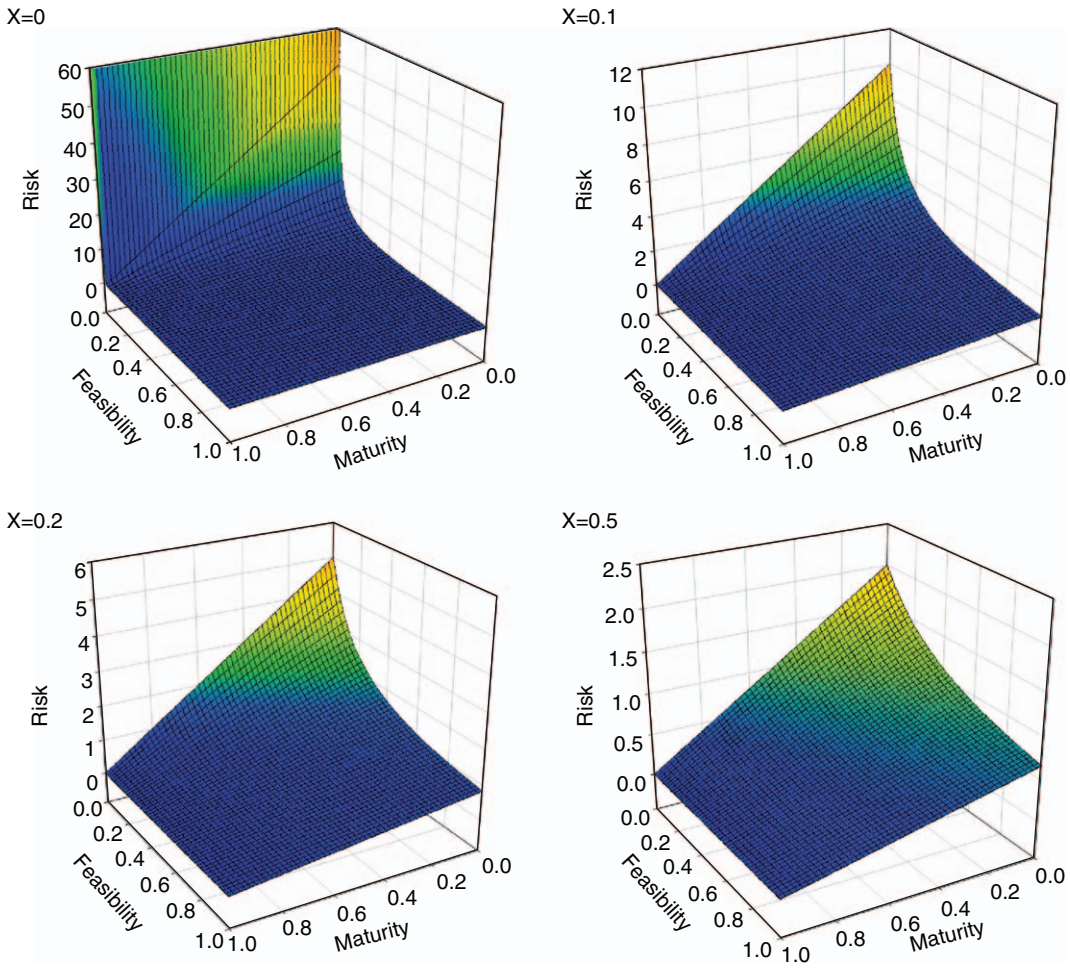

FIGURE 4

3D project risk plots. Calculated project risk plotted against underlying feasibility and maturity for various correction factors ($a = 0$, $b = 0.1$, $c = 0.2$, $d = 0.5$). Risk is decreasing with increasing feasibility and maturity. The impact of feasibility is higher for projects with a low maturity compared to projects with a high maturity. The overall impact can be fine-tuned with the chosen correction factor.

the help of a correction factor (X) (Eq. (2)). The risk distribution is visualized in Fig. 4 for correction factors ranging from 0 to 0.5. As apparent from Fig. 4, the risk factor is decreasing with increasing maturity and feasibility of the project. Likewise, the effect that feasibility has on the total risk score is decreasing with increasing maturity of the project. This also intuitively makes sense, because the feasibility gets less important the closer the project is to its desired end goal. The size of the correction factor determines the maximal impact of the feasibility on the risk score at low maturity. To address this more quantitatively, a conceptual risk ratio can be defined, which is the ratio of risk scores at feasibility and maturity approaching 0, and at feasibility approaching 1 and maturity approaching 0 (Eq. (3)). Figure 5 shows the impact of the correction factor on the conceptual risk ratio. The correction factor can be chosen according to the desired conceptual risk ratio and therefore tailored to the project characteristics in a given business as desired.

$$\text{risk} = \frac{1 - \text{maturity}}{X + \text{feasibility}} \tag{2}$$

where X = correction factor.

$$\text{conceptual risk ratio} = \frac{(1 - M_0)/(X + F_0)}{(1 - M_0)/(X + F_1)} = \frac{(1 - O)/(X + O)}{(1 - O)/(X + 1)} = \frac{1 + X}{X} \tag{3}$$

where M_0 = maturity set to zero, F_0 = feasibility set to zero, F_1 = feasibility set to one, X = correction factor.

It is a classic approach to assess portfolios via plotting risk against potential. To do this in the method described here, a third dimension 'potential' is added in addition to feasibility and maturity.

Potential in the 3D analysis describes the attractiveness of the expected development candidate and is a mixture of criteria evaluating development feasibility and marketing feasibility. The criteria used are: (i) target degree of validation; (ii) development money at risk; (iii) competitive situation; (iv) market size; and (v) portfolio fit. Potential is determined by many factors that cannot be influenced by the project team during the course of a lead optimization program. There is one exception, however, the competitive situation, which can be favorably improved by optimizing the compound to be either first in class or having a substantial unique selling proposition. Table 1 assesses the criteria

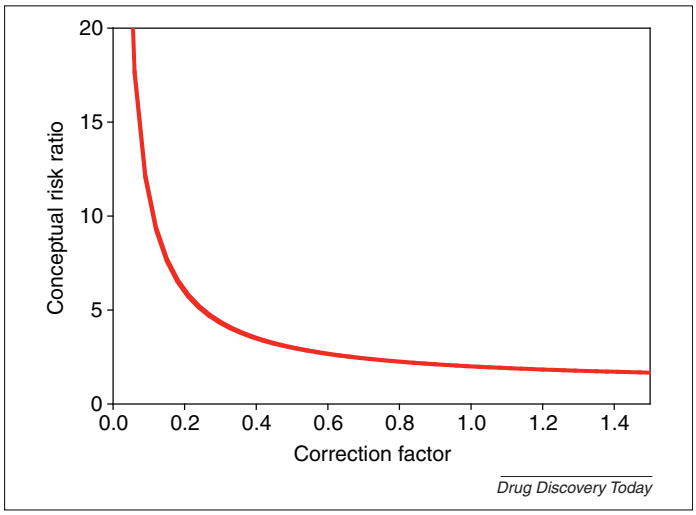

FIGURE 5

Conceptual risk ratio. The conceptual risk ratio (risk of a project at maturity 0 with feasibility 0 versus risk of a project at maturity 0 with feasibility 1) is affected by the correction factor. With increasing correction factor the conceptual risk ratio approaches 1, with decreasing correction factor the conceptual risk ratio approaches infinity.

for potential. For portfolio decisions, the risk score is then plotted against potential. Projects with a low risk and high potential should be preferentially resourced.

The method was used to prepare the portfolio discussions of the corresponding management committees. Of course, there can never be an automatism in terms of prioritization and/or resourcing based on the calculated score. Project-specific fact-based in-depth discussions are required for good decision-making – the tool is well suited to trigger such discussions.

Expert black box scoring models

TAPE analysis

Black box scoring models do not provide pre-defined criteria for scores but leave scoring completely to the discretion of the responsible expert function. In TAPE, which stands for the three graphs 'target, project, expectation', each project is scored according to five dimensions: (i) competitor situation; (ii) target validation; (iii) discovery project feasibility; (iv) clinical development feasibility; and (v) commercial feasibility. Competitor situation is best assessed by the respective project leader in collaboration with a business intelligence function. For the purpose of this analysis only competitor approaches on the same target are considered. The therapeutic area should evaluate the degree of target validation. Degree of target validation can then be plotted against competitor situation resulting in the first graph (Fig. 6a), 'target'. Projects with a high degree of target validation and low competition should be prioritized.

Because this first graph only takes into account the molecular target and leaves the available compounds out of the picture, more dimensions are required for a comprehensive evaluation. These are discovery feasibility and development feasibility. Discovery feasibility needs to be aggregated from assessments made by therapeutic area biology, medicinal chemistry, toxicology, formulation, production and DMPK units. Development feasibility is scored by the clinical development departments. Discovery feasibility is plotted against development feasibility, resulting in the Fig. 6b, 'project'. Here, preferentially, projects with a high discovery and high development feasibility should be prioritized.

The fifth dimension looks at the commercial attractiveness of the expected product. This is probably the most difficult dimension to judge, given the inherent uncertainties in predicting the final profile. Scoring can be done by the marketing unit in collaboration with therapeutic area biology. The commercial attractiveness can be plotted against technical probability of success, which can be calculated by multiplying discovery and development feasibility. This results in the Fig. 6c, 'expectation'. Projects with a high probability of success and an interesting commercial potential should be preferentially resourced.

Although the three graphs in Fig. 6 can be taken as a basis for prioritization decisions, they of course cannot replace an in-depth discussion and tailored case-by-case assessments. Nevertheless, owing to the relatively low effort required to prepare the data, this analysis can handle larger portfolios and can be performed in regular intervals without burdening the organization with too much work.

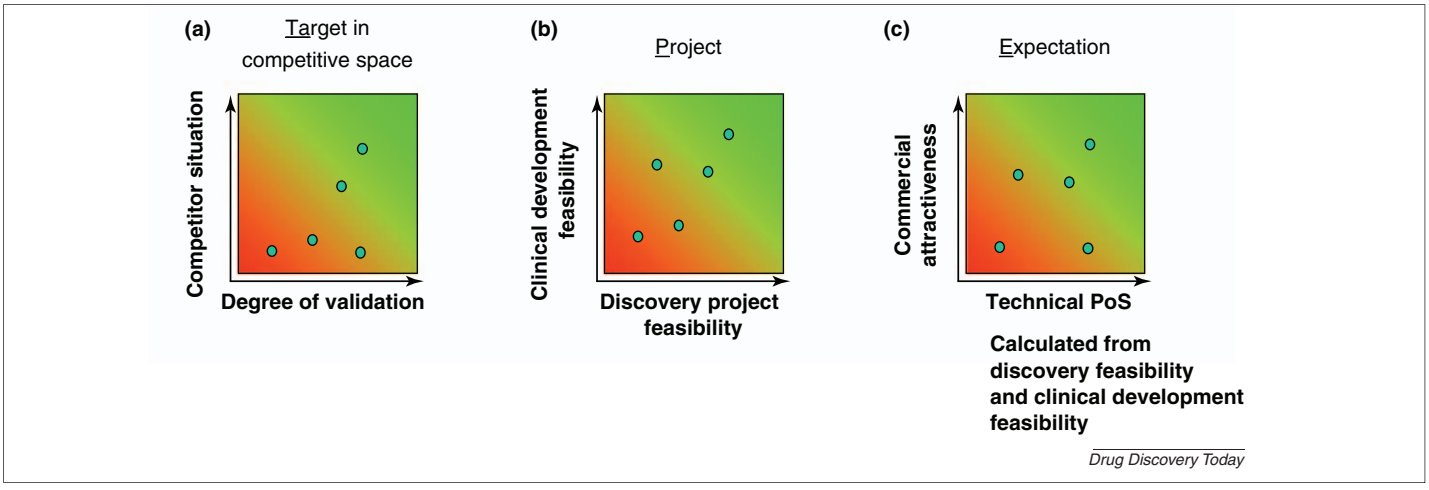

FIGURE 6

TAPE analysis. The five dimensions of the TAPE analysis plotted in three graphs for portfolio visualization and guiding of prioritization decisions of the decision committee. Projects located in the green areas should be preferentially prioritized for resourcing.

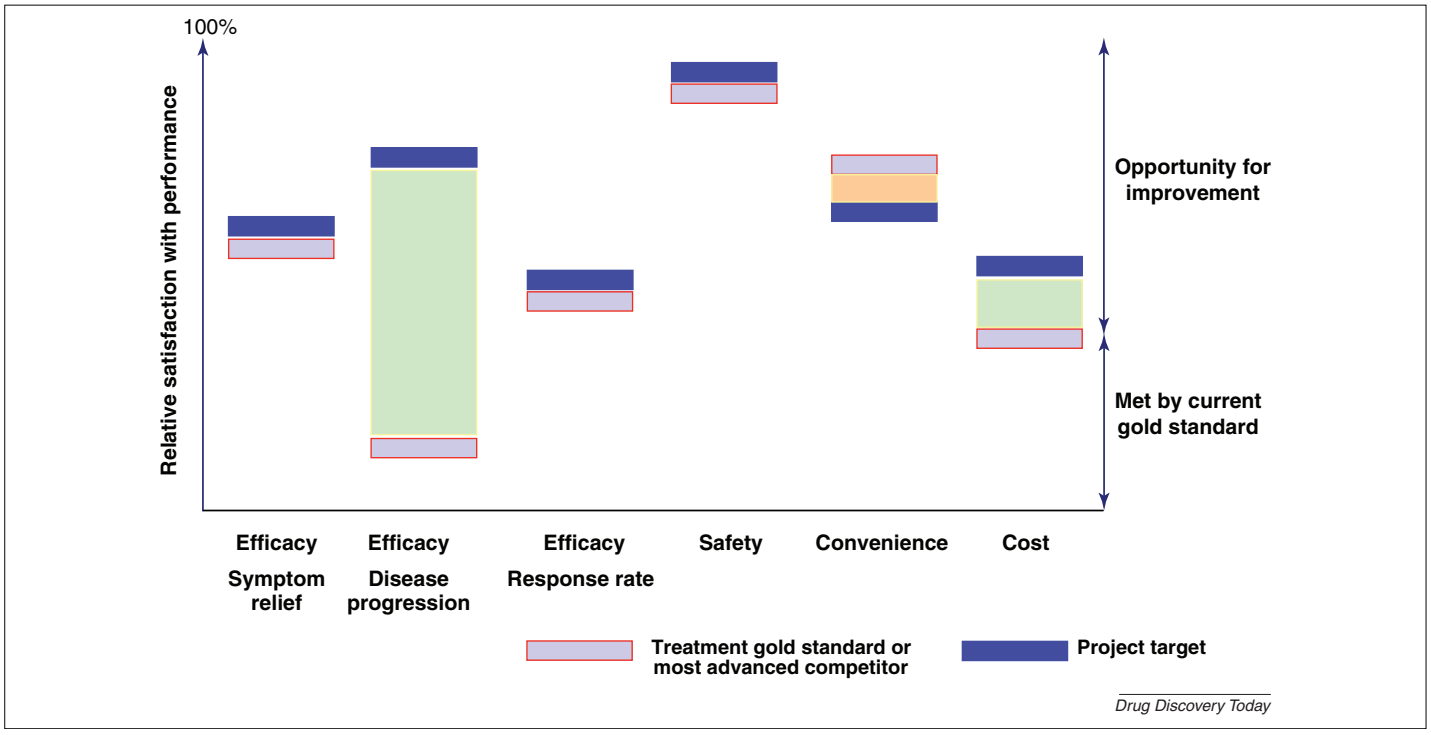

FIGURE 7

Opportunity space graph. Relative performance of the treatment gold standard for a given indication is shown across six criteria in comparison with the targeted product profile of an R&D project. In the example shown, the goal of the R&D project is to improve, versus the gold standard, strongly in terms of efficacy on disease progression and less so in the treatment costs, but allowing for a slightly reduced convenience profile.

It is important to note that TAPE analysis does not violate the 'MECE' paradigm (designing mutually exclusive, commonly exhaustive criteria) – although competitor situation is overlapping with commercial feasibility, and target validation with clinical development feasibility. Fig. 6c (technical probability of success versus commercial attractiveness) provides the classic risk versus potential matrix, whereas Fig. 6a and b focus on subaspects of it. Figure 6a (target validation versus competitive situation) is especially important for choosing the right molecular targets for starting discovery projects and Fig. 6b (discovery feasibility versus development feasibility) shows details on technical probability of success by separating discovery versus development phases.

Opportunity space

Opportunity space mapping is another example for a black-box scoring tool. This method maps the opportunity space of a given drug discovery project by comparing it to the current treatment gold standard in an intuitive graphical overview (Fig. 7). The following dimensions are assessed: (i) efficacy in symptom relief; (ii) efficacy in disease progression; (iii) efficacy in terms of response rate; (iv) safety/tolerability; (v) convenience; and (vi) treatment costs. Current performance of the treatment gold standard is estimated for these six criteria on a relative scale of 0–100%. The result is then compared to the same assessment done with the hypothetical product profile targeted by the project team. The resulting graph gives a good overview of the opportunity space and the project's strategic goals within this space. The scoring is best done by the respective project team. For each dimension summing up the deltas of scores of gold standard versus target product profile for all projects in a portfolio can give an indication on whether the portfolio is well balanced in terms of efforts spent on improving efficacy, safety, convenience and cost. Alternatively, instead of the current treatment gold standard, the most relevant competitor in development can be used. Performing the assessment in comparison to various competitor approaches can be done to map-out the competitive space and get clarity on the possible unique selling proposition. Quantitative approaches are described e.g. at http://www.equinox-group.com/disease_area_strategy.html.

Surveys

Surveys can be an easy and fast method to measure confidence levels for projects in a portfolio. A survey questionnaire can, for example, be distributed among members of the decision-making committee with the request to score each project in the portfolio according to: (i) probability of success to reach the preclinical development phase; and (ii) expected attractiveness of the development candidate. To avoid a tendency for medium assessments, it is advised to use a scale consisting of an even number of scoring possibilities. Average probability of success is then plotted against average expected attractiveness for each project in the portfolio and projects with a high probability of success and a high attractiveness of the expected development candidate should be preferentially resourced. It can also be of high value to plot for each project the standard deviations of the assessments done by various committee members. This highlights the projects about which there are apparently diverging opinions in the decision committee. These projects should be discussed in detail to explore whether the disagreement is because of information gaps of some committee members or in fact represents different judgments.

A further extension of the survey model is online voting platforms that can reach out to all employees with the rationale that the 'wisdom of the crowds' can be a valuable predictor of project fate. This approach was successfully used at Merck KGaA for a ranking of proposals that had originated from an idea competition in 2010. In this case we applied a fast and easy 'thumbs up/thumbs down' voting approach and ~1000 employees gave their votes within one week.

External advisory boards reviewing the portfolio and providing independent second opinion can be another valuable approach that can be grouped under the subheading ''surveys''. By the end of 2010 at Merck Serono we had excellent experience with such an external advisory board, comprising ten advisors from various expertise areas such as: regulatory, health economics, venture capital, research, clinical development. In addition, payers and patients can be brought in to provide a well-balanced sounding board.

Last, but not least, surveys can also be used as a way to get information about key stakeholder satisfaction with the portfolio management activities themselves. Together with Strategyn (http://www.strategyn.com) we were using a 2D assessment tool. In this tool a series of typical tasks for a portfolio management group was presented (e.g. assess individual project uncertainty, allocate resources, prioritize across portfolio, capture lessons learned, etc.) to the survey participants, with the request to score: (i) how important they think the task is; and (ii) how well they think the task is currently covered. Tasks that score high in importance, but low on how well they are currently covered, constitute key opportunities for further improvement. In a survey that we conducted in 2009 with senior management the following tasks were ranked highest in importance for discovery portfolio management: (i) prioritize projects within a portfolio; (ii) resolve project quality problems; and (iii) allocate resources. Project leaders confronted with the same questions ranked highest: (i) capture lessons learned from past projects; (ii) resolve project quality problems; and (iii) allocate resources. Feedback gathered in this way can then be used to improve the service provided by the portfolio management group.

Project prioritization and resource allocation

The result of portfolio assessment activities and corresponding prioritization discussions can be a list ranking projects in the order of priority. An alternative can be to group the projects in baskets. I have often found the latter to be the superior approach, because it avoids making preferences among high priority projects, thereby avoiding many unnecessary discussions, and is usually fully sufficient to guide resource allocation. For example a 4-basket model can be used. Basket 1 contains projects with priority 'high'. All resources required to move these projects forward as quickly as possible should be readily allocated. This means that all activities on the critical path for these projects are preferentially resourced versus activities for projects in basket 2, 3 and 4. Projects in basket 2 have 'medium' priority in terms of resource allocation. Projects in basket 3 are in 'issue resolution'. For these projects only those resources should be allocated that are required to clarify and hopefully resolve the current critical issue, all other activities are put on hold. Finally, basket 4 contains those projects that are recommended for 'termination'.

Beyond the project portfolio

Portfolio management of a discovery engine can expand beyond the portfolio of projects. It can be very rewarding, for example, to have a look at the portfolio of molecular drug targets, the portfolio of drug discovery technologies and the portfolio of external partnerships and alliances. Tailored methodologies for these applications need to be developed, of course, but this approach makes sense especially for organizations that are spending a large proportion of their R&D budgets on technology development or external alliances.

Discussion

In this paper we discuss approaches for portfolio management in early discovery. To date, this topic has not been covered well in the literature, which focuses on management of development portfolios. Adequate project prioritization, timely project terminations to achieve a 'kill or nurture' culture and dynamic resource allocation throughout the complete discovery project lifecycle and across the entire portfolio of projects can be facilitated by regular semi-quantitative project portfolio assessments.

To support a consistent and comparable benefit:risk analysis of all projects, a portfolio assessment process receiving continuous input from R&D management and project leaders is invaluable. The process should not only focus on the comprehensive and comparative assessment of all projects, especially in regards to their technical feasibility and their commercial attractiveness for the company, but also involve aspects of portfolio balance and risk management. The assessment process by itself is educational for the project teams and the results are informative for decision-making management. It is obvious that no theoretical model of benefit:risk analysis can predict the future and forecast the real outcome of projects. However, learning from the past, making assumptions about the future and modeling project risk by assessing important criteria seem part of a sensible way to approach this dilemma. In the hands of experienced research managers the portfolio management process becomes a valuable tool to monitor, discuss, understand and archive important project and portfolio aspects and prepare project priority and resource allocation decisions for the responsible decision making body. The methodology described above can help to present the risk profile of the current portfolio and present portfolio and resource allocation decisions on a more rational basis.

It is important to involve all relevant functions in the portfolio management process, for example project leaders, research, clinical and non-clinical development, production, regulatory, health economics and marketing. The portfolio management group should, at all times, also be well linked to its interface partners in strategy, finance and operations. Likewise, the business development and licensing groups should be put in the loop to ensure that: (i) in/out licensing objectives are well aligned with portfolio requirements; (ii) due diligence assessments are done with the same methods also applied for in-house project assessment; and (iii) accurate forecasts are obtained, in terms of projects expected to join the portfolio from in-licensing activities.

The methods presented in this paper range from quantitative criteria-based scoring models, black-box expert scoring approaches to online surveys with a large audience. The selection, which method among those presented to apply, needs to be

decided case by case, based on corporate culture, portfolio size, strategic situation and budget available. Criteria-based scoring models usually are more resource intensive than the black-box scoring or survey tools and the results tend to be challenged more. Owing to the fact, however, that consistent criteria and definitions are applied uniformly and transparently to all projects in a portfolio, they also tend to be the most objective ones. A sophisticated example of a criteria-based scoring model is the R&D risk assessment tool setup by Catenion Strategies (http://www.catenion.de). This risk assessment scheme differentiates phases of R&D and drug types [new chemical entity, new biologic entity (NCE, NBE)] and is based on the tacit knowledge of hundreds of R&D experts from various pharmaceutical companies and has also been used at Merck Serono [29]. Black-box scoring methods by contrast tend to trigger less discussion because the scores are left to the full discretion of the responsible expert functions. Surveys are often subjective and only work well if most of the participants are informed well about the respective projects. This needs to be ensured beforehand.

In essence, portfolio evaluation always comes down to three fundamental dimensions: probability to get the product, commercial potential and fit to the chosen strategic direction of a company. These fundamental dimensions also appear in the approaches discussed in this paper. In the 3D model feasibility and maturity are used in a sophisticated way to calculate risk, which is plotted against potential. In TAPE risk is compiled from discovery project feasibility and clinical development feasibility plotted against commercial attractiveness. In the survey methods risk and potential are often queried directly. As much as fast (time), cheap (resources) and good (quality) is the golden triangle for engineering, technical risk, commercial potential and strategic fit is the golden triangle of portfolio management.

Although assessment of individual projects is an important part of the portfolio management exercise, the holistic view on the entire portfolio has to have the highest priority. It is essential to consider interdependencies between projects. For example, several projects based on one common, but yet unproved, mechanism of action, or an application of the same non-validated formulation technology to several projects, can constitute a high risk for the portfolio. In the case of target and/or technology failure, several projects would be hit at the same time. Accordingly, it is advisable to diversify the portfolio, even with alternatives that are in individual comparison more risky but in combination lead to a reduced overall portfolio risk. It is flawed to assume that an optimal portfolio is equivalent to a collection of (individually) optimal projects [18,30].

To guide the decision-making committee in managing a portfolio it is beneficial to provide additional data, such as a forecast of development candidates originating from the discovery engine in the next five years, a correlation of number of running projects per phase versus number of projects expected from a steady state model operating with benchmark attrition rates and cycle times, and correlation to the sales growth targets of the company. The latter is usually challenging and a simple calculation can show that the current pharmaceutical R&D business model can hardly fuel intended ambitious growth scenarios. As can be seen from Eq. (4), calculating with an average of 20% of sales spent on R&D, 20% of R&D spent for generating new development candidates with an average cost of €40 million per preclinical development candidate, multiplied by a probability of success to reach the market of 10% and an expected average peak sales of €300 million produces a 3% compound annual growth rate of sales – multiple years down the road. Subtracting erosion of sales of current products essentially results in a no or negative growth scenario, even using high-end benchmark numbers.

$$\begin{aligned}&\text{expected new sales generated with products originating from discovery engine}\\&= \frac{\text{total current sales} \times \%\,\text{of sales spent on R\&D} \times \%\,\text{of R\&D spent on discovery}}{\text{benchmark R\&D costs per development candidate}} \times \%\,\text{PoS to reach market}\\&\quad \times \text{expected peak sales per product}\end{aligned} \tag{4}$$

As in our example above, productivity models are often calculated with standard attrition rates, which can vary considerably from company to company. Comparing such attrition rates between companies, however, is only of limited value, because a lower attrition rate does not necessarily mean a more efficient R&D engine. In the end, only output versus investment counts and you can achieve the same result with a discovery engine run in a high attrition or in a low attrition mode. In the high attrition mode the number of projects channeled through the pipeline is higher, but average investment per project is low and in case of major issues projects are readily terminated. By contrast, in the low attrition model fewer projects are simultaneously pursued, with higher resource allocation per project and multiple rescue approaches in case problems are encountered. There is a long unresolved debate about which model is preferable. School 1 says that attrition is a bad thing and should be avoided at all costs (do what you can to stop your project from dying), whereas school 2 says that attrition is unavoidable and allows you to sort out approaches that will not work, thereby saving unnecessary costs down the road. Of concern in terms of resource efficiency is certainly the 'strategic attrition' that stacks up on top of the technical attrition. One source can be mergers and acquisitions or simply changes in management within a given company, often leading to a corresponding shift in strategy and consequently termination of projects or entire therapeutic area research efforts that do not fit the new corporate strategy any longer.

Portfolio management tools alone cannot guarantee a favorable outcome and improvement of pipeline value. Improvements will only be realized through the application of additional research management activities. Scientifically sound, transparent and integrated project reviews that result in consistent technical and business-driven decision-making are mandatory for success. This especially involves open and integrated discussions between discovery and development functions. I have also found it helpful to interact closely with the project leaders of the drug discovery projects and to collect, for example, quarterly bottleneck surveys. In these surveys the project leader can indicate which resource is

currently rate limiting and the project leader is encouraged to propose an alternative resource scenario to speed-up his project. These proposals and bottleneck alerts can be a valuable data resource in the prioritization and resourcing sessions of the management committee. In that sense, an important output of good discovery portfolio management is full transparency. It is essential to keep comprehensive and freely accessible lists of currently active projects, such that there is full visibility across the entire organization on where the available resources are actually spent.

Of utmost importance for the success of a portfolio management exercise is full support and backing by top management – having full support from the decision committee chairman is essential. After all, it is necessary for a good portfolio manager to have the complete portfolio in mind, highlight critical issues and recommend decisions that might be against the interest of some therapeutic area heads. Therefore, it is a misconception to set up a portfolio management group as a service function for the therapeutic area heads only.

There is also no 'best tool' or approach or final golden recommendation on which approach to choose. In general, it depends very much on the individual context of the organization and also preference of the respective management team. To keep enthusiasm high it is even advisable to change methodologies from time to time. This ensures that project and portfolio issues and opportunities are seen in a new light, potential blind spots get eliminated and new stimulating discussions are triggered.

Last but not least, I want to emphasize that the most important factor for the success of R&D projects is that the project leader believes in their project, overcomes barriers and ultimately makes it successful. The saying goes that there is no blockbuster on the market that was not at least once in its R&D lifetime terminated or at least close to being terminated, only revived or saved through the efforts of scientific geniuses and visionary entrepreneurs (often in combination). Nevertheless, in large pharma companies management is often a source of frustration for the scientist and many rules and corporate policies are discouraging innovation, as intriguingly summarized by Cuatrecasas [31,32]. I firmly believe that the pharma industry has to get rid of the industrialization mindset in R&D and start to foster its innovators and entrepreneurs more. Creating an environment where scientists can flourish and entrepreneurs are encouraged to move 'their' project forward is essential [33,34]. We have had good experience at Merck with self-assembling teams of volunteers picking the project in which they believe in the frame of a cross-divisional innovation initiative and idea competition (innospire).

After all the recent bad news about drug discovery and R&D cuts throughout the industry, it is time to regain the dynamics and the optimism in drug discovery, there is no way around it, the remaining medical need is just too high.

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