Value-driven project and portfolio management in the pharmaceutical industry: Drug discovery versus drug development – Commonalities and differences in portfolio management practice

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Abstract

The concept of portfolio management has been widely used in the pharmaceutical industry. It is used to evaluate the commercial value and the risk structure of development projects. The final goal is to select a portfolio of projects that addresses the strategic objectives of the organisation optimally and that leads to the highest overall portfolio value. Companies now start to apply the portfolio management concept on their research portfolios. Although the basic principle remains the same, the methodology applied has to be adapted to the greater uncertainty that early research projects carry. Commonalities and differences of the portfolio management process in research and development are described and recommendations are given how to harmonise the two different approaches.

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INTRODUCTION

The increasing discussion about rising healthcare cost is fuelled by reports that General Motors paid more for healthcare than

for steel per vehicle in 2004,[1] and Starbucks paid more for health insurance than for coffee in 2005.[2] The continuing rise in development costs for drugs has increased pressure on R&D organisations to contribute to higher efficiency in the overall process of coming up with new drugs.

In the last few years the industry has made significant efforts to address these challenges[3] and to increase the productivity of the drug development process. Some of the initiatives have without doubt led to considerable improvements. Examples are the earlier determination of a drug's toxicology profile and early tests to investigate the suitability of a new drug candidate for oral administration or once a day dosing. The question is no longer how good we are in what we are doing but whether we are doing the right things. Further improvements of the overall process should shift from attempts of enhancing effectiveness to a greater emphasis on the efficiency of the processes applied.

In this context a lot of emphasis is put on portfolio management. In the broadest definition, portfolio management describes the process of maximising the value of R&D portfolios through proper resource allocation. This requires an alignment of portfolio management with strategic business objectives. Such objectives should not only be general (e.g., innovation) and quantitative (eg ROI or sales targets). They should also define disease areas of interest, clearly outline the remaining medical needs, and specify the indications that are considered worth pursuing. This will enable decision makers and functional R&D managers to identify projects with both strategic fit and a high value proposition. Depending on the size of the organisation, either a corporate or therapeutic area strategies need to be developed, approved, and endorsed by the entire organisation.

Value-driven project and portfolio management implies quantitative financial and risk analysis of individual projects and overall portfolios. Such analyses elucidate options for improving the value and risk structure of individual projects on the one hand and therapeutic areas or overall corporate portfolios on the other hand. They are applicable and relevant to companies of any size. Value-driven project and portfolio management is a methodology enabling the alignment of project decisions with corporate strategy and defined business objectives.

Although portfolio management has been applied in the financial industry for many years and Harry Markowitz was honoured with the Nobel Prize for outlining this concept it was only around the end of the last century that the application of value-driven portfolio management in the pharmaceutical industry was published.[4] Around the same time, an investigation across various industries provided evidence that portfolio management based on quantitative financial analyses using the net present value (NPV) algorithm correlates well with value creation. Value destruction, however, was observed more frequently in companies that built their portfolio decisions only on simplified scoring methods or semi-quantitative portfolio matrices such as those introduced in the 1980s.[5]

Most pharmaceutical companies have implemented portfolio management in drug development.[6–9] An increasing number of companies is now making efforts to apply it to discovery research and early development. Not surprisingly, given the relatively short period of use, the inherent complexity of the issue has prevented the establishment of a broadly accepted best practice in R&D portfolio management.

This review focuses on the entire portfolio management process with special emphasis on commonalities and differences in the research and development environment. For aspects where, based on the authors' experience, a best practice emerges this is clearly stated. Otherwise, different approaches are described and compared. We begin with the description of portfolio management in development because there it has a longer history than in

research. This has led to a significant body of experience on which portfolio management in early R&D can build.

CURRENT BEST PRACTICE OF PORTFOLIO MANAGEMENT IN DEVELOPMENT (BEYOND PROOF OF CONCEPT)

There are two major tasks for implementation of value-driven portfolio management: evaluation *methodology and metrics* on the one hand, and the corporate evaluation and prioritisation *process* on the other hand. There is a general agreement in the pharmaceutical industry that the evaluation of projects entering 'full' development after successful proof of concept (PoC) should include quantitative financial parameters. Furthermore, there appears to be a generally accepted set of portfolio management metrics.[6–9] The portfolio management process, however, differs, as well as the degree of implementation, reflecting individual companies' corporate structure and culture. There are some prerequisites for successful portfolio management that apply to all systems: the evaluation of projects must be sufficiently detailed, interdisciplinary, consistent, and embedded in a practicable corporate process.

Value-driven project management in development

The first step towards value-driven portfolio management is the establishment of effective project management. Project management is the predominant operative instrument for the execution of portfolio decisions. Four common tools are applied to align project management with portfolio decisions:

- Target product profile (TPP)
- A stage-gate decision process
- Timeline and budget management
- Sales forecast aligned with TPP and development plan

The four tools mentioned above provide information required to evaluate and prioritise projects, and to analyse whether the portfolio is aligned with corporate objectives. TPPs are generally applied, but not always in an effective way. The stage-gate decision process is related to the major preclinical and clinical development milestones and is also a well-established principle in the pharmaceutical industry. At each stage-gate, it is decided whether the achieved results support continuation of development, and the project may be reprioritised depending on other projects competing for resources. Time line and budget management has been the responsibility of project management for a long time. Sales forecasting and financial project evaluation is undertaken to a variable extent and level of detail, depending on companies' policies at which development stage quantitative analyses should commence.

In addition to the four tools mentioned above, risk analysis has become a particular point of concern for about five years, both in project and in portfolio management.[10] In the context of the pharmaceutical and biotechnology industry, it is helpful to differentiate two different categories of risk as they are managed by different stakeholders: strategic and operative risk.[11] In brief, strategic risks typically affect go/no-go decisions and may have a significant impact on value; therefore, they are matters of concern predominantly for project and portfolio management. Operative risks represent issues that may lead to deviations from the development plan and budget. They require particular attention by line functions and coordination by project management, as they are often cross-functional. Operative problems may eventually gain strategic relevance. Strategic risk analysis has been applied for some time in R&D portfolio management and is usually represented as estimates of the probability of achieving milestones. The systematic management of operative risk has been initiated more recently; here, risk is often not represented as probability but rather

as semi-quantitative categorisation and plotted against categories of impact.

In the following, ways towards effective application of TPPs and strategic risk analysis (in the format of decision trees) are described. In addition, sales forecasting procedures and financial analyses adapted to the needs of portfolio management are outlined.

Target product profile (TPP)

A TPP serves as a blueprint of the desired future product. It defines the disease category and targeted patient population, the requested efficacy, safety and tolerability characteristics, and technical details such as, for example, formulation and mode of application of the product to be developed. The TPP describes features of the future marketed product that can realistically be expected based on the properties of the compound and the pathophysiology of the disease to be treated. It takes into account both regulatory and market requirements, as the profile should reflect both a registrable and a commercially viable product. Ideally, TPPs for individual projects and their respective targeted disease categories are well aligned across discovery research, development, and marketing functions. The FDA has recently defined a template for TPPs to facilitate communication with the agency.[12] This is an extensive document of several pages not only requesting target criteria but also a description of trial designs and obtained development results. As internal tool for value-driven management, focused TPPs are more suitable, summarising the features that drive development and marketing plans. Such TPPs do usually comprise not more than 1–2 pages.

TPPs define the desired label in the packet insert and therefore serve as outline for R&D with respect to the required clinical trials and development activities, that is, TPPs define the scope of investment. In order to fulfil this task, efficacy and safety/tolerability parameters are defined in a commonly agreed and, as far as possible, quantitative way, as they will drive trial design and cost.

The TPP outlines the development targets, but it does not always indicate to what extent results would be allowed to deviate from the target until further development is not worth while any more. Therefore, companies often define a minimum product profile (MPP) alongside the TPP to establish a common understanding of the minimum study results required for continuation of development. All of the MPP criteria must be achieved, and they must respect regulatory requirements. While the TPP outlines the scope of investment, the MPP represents stop/go criteria.

TPPs can play a beneficial role in aligning project activities between the development functions and marketing and sales. This is best achieved if they are established through an interactive cross-functional process. TPPs also facilitate the communication of project issues and the alignment of senior management's expectations. As such, they are an important element of value-driven management.

Decision tree analysis

Decision tree analysis is an effective tool to illustrate R&D decision points, the probabilities of uncertain outcomes at each milestone, and potentially resulting decision options (Figure 1). It is well established in pharmaceutical development.[4,12] As investment decisions are made with respect to milestones, it is useful to examine the risk and cost of individual milestones and the value gained assuming successful completion. Decision trees serve as communication tool for portfolio management and for project management and line functions. They are also used for risk adjusted net present value analysis ('augmented NPV').

Decision tree analysis focuses on those activities that are essential for successful development and for achievement of the TPP. If milestones are composed of several independent uncertain activities undertaken in parallel, individual probabilities are multiplied to provide the overall probability of success

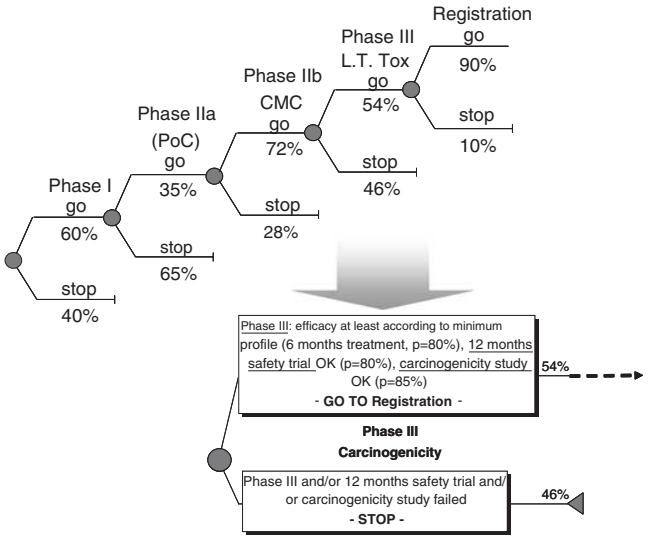

Figure 1: Example of a decision tree. Decision trees are tools to illustrate the potential outcomes at development milestones and the risk structure of projects. Outcomes are differentiated according to available decision options. For use in portfolio management and for valuation purposes, the layout is usually simplified as it assumes that development will be continued and the project will find an investor if milestones are achieved. The Phase III milestone in the present example is comprised of three uncertain studies whose outcomes are considered independent, while all studies must be successful in order to proceed. Probability estimates can then be multiplied to achieve the overall probability of success of the milestone. If several studies are undertaken at a milestone, care must be taken to identify potential interdependencies between studies in order to avoid an overestimation of risk.[11] Decision trees may sometimes reflect more than two decision options at a milestone. For example, a Phase II milestone may lead to more than one way forward: if efficacy is as outlined in the TPP, it may be decided to go directly to Phase III; alternatively, Phase II results may suggest to investigate another treatment schedule before going to Phase III in order to maximise the chance of success of the latter.

for the respective milestone. Decision trees usually extend up to approval. Market scenarios and commercialisation uncertainties are often reflected in probabilistic sales forecasts (see below).

Best practice decision tree analysis is conducted with the project teams and additional experts when appropriate. The analysis benefits from a neutral moderator, often a representative of the portfolio management function. The development plan is evaluated along the TPP/MPP and its milestone structure. For those uncertain elements that affect go/no-go decisions, the probability of success is estimated. Benchmarks can be used as orientation to outline a plausible range to the team. Probabilities are assessed based on available knowledge and the circumstances of the individual case. An interactive and systematic discussion process has proven to be most effective as participants reflect their opinions against others. This leads to a fruitful knowledge exchange among experts and in most cases to a common agreement. It is sometimes believed that the interactive process consumes too much time, there may not be access to professional moderation capabilities, or expert teams are considered overly optimistic. Therefore, some companies prefer simplified procedures, for example, the distribution of templates that have to be filled, or they use published average success rates. However, this may result in overlooking critical project issues that arise from the interaction of functions and that would not be recognised by individuals

alone. Furthermore, published benchmarks are averages across a sample of companies, and the method applied to generate them differs among sources. In addition, there is evidence that individual companies deviate significantly from average success rates, indicating differences in R&D productivity within the industry. Finally, success rates differ across therapeutic fields, and the available statistics do not provide reliable data for individual disease entities.

Very often, alternative options exist for the development of projects. These may comprise a broader or restricted target patient group, a fast and risky development to achieve earlier launch versus a step-wise, risk reduced development strategy, the cheapest possible way towards registration, or a more or less ambitious TPP with respect to efficacy or safety. Such alternatives differ with respect to cost, risk and risk structure, timelines, and commercial value. Decision tree analysis is an ideal tool to facilitate the analysis of alternative options.

The relevance of project risk structure. A project's risk structure is defined as the resolution of risk per milestone. Risk structure may be front-loaded (low probability of success in early development), balanced, or back-loaded (high risk in late development). Alternative development plans usually differ in risk structure. Mostly, but not always, this is also associated with a difference in overall probability of development success. Risk structure affects the financial value of projects because the relative weighting of outcomes is different.

This applies even if overall probability of success is not different, in cases where the relative weighting of expensive versus cheap failure scenarios is changed. In essence, it would always be advisable to reduce risk as early and quickly as possible in order to put the significant investments in the later stages at the lowest necessary risk.

R&D projects can be classified in different categories, such as, for example, first-in-class highly innovative new products, 'fast followers' with validated mechanism of action, or added-value generics, that differ in risk structure. Highly uncertain innovative drugs undergo significant risk resolution only after Phase II (PoC) or even Phase III, depending on the therapeutic category and clinical trial endpoints. Fast followers are projects of moderate risk in Phases II and III; risk will mostly be driven by the incremental benefits the sponsor wishes to establish to make the product competitive *vis-à-vis* the market leader. Added-value generics are copies of products with a commonly known benefit/risk ratio, while efficacy, safety, or convenience is enhanced, for example, through an innovative formulation. Such projects have a comparatively low development risk and often a shorter development time. The analysis of project risk and the proactive selection of projects with complementary risk structure offer opportunities to balance portfolio risk. A risk-balanced portfolio is more likely to meet productivity goals. Furthermore, projects with favourable risk structure may have a comparatively high financial value in early development (with less pronounced incremental value increase upon completion of development milestones), thus balancing not only productivity but also portfolio value.

The analysis of project risk structure facilitates the understanding of the impact of the chosen clinical trial plan and trial endpoints on risk (Figure 2). Development risk is influenced by the reliability and validity of individual studies, and by the quality of development execution. Examples are the potentially low reliability of encouraging but small pilot studies that may carry forward risk into later stages of development, leading to unexpected late stage failures. If trial results remain unclear, development may be terminated because additional investments and further trials would delay launch to an extent that the value proposition is lost. If the expected knowledge gain of particular trials and its impact on the level of confidence in

a

discount rate: 10% *tax rate: 40%*	Peak sales (EUR mill.)	Years to peak	*COST (EUR mill.)* ; probability of success*								% sales reduction in year of patent expiry
			Preclin	Ph I	Ph II	Phase III	Reg	Phase IV	CMC/ Product devel.	Marketing (year of launch)	
						Phase II/III					
Added value generic	250	5	3	6		44	39	-	5	38	-
			90%	*85%*		*85%*	*90%*				
Standard product	500	5	7	9	22	98	66	5% of peak sales (years 1-5 after launch)	13	125	75%
			70%	*75%*	*60%*	*80%*	*95%*				
Blockbuster product	3,000	7	7	10	32	258	452	5% of peak sales (years 1-5 after launch)	13	450	90%
			45%	*60%*	*35%*	*65%*	*90%*				

b

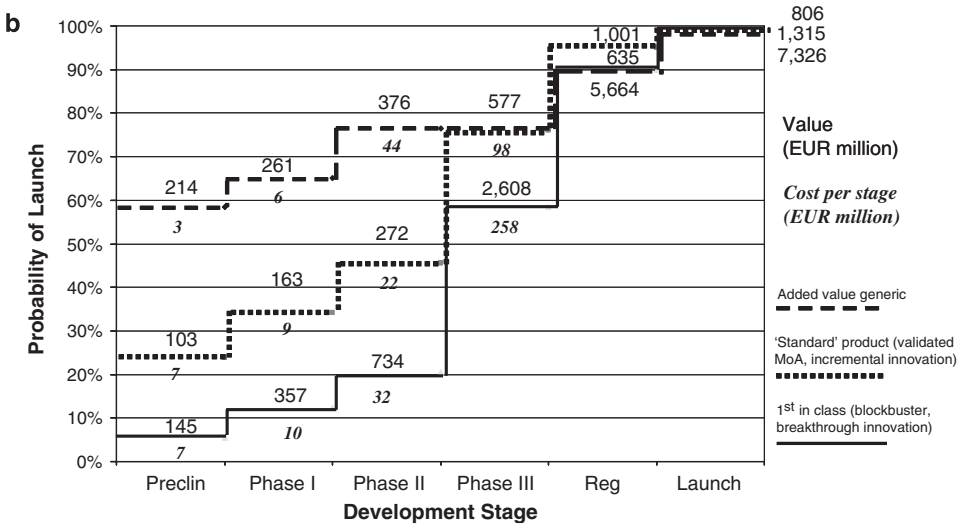

Figure 2: Portfolio risk structure. R&D projects can be classified according to risk/cost/value characteristics. For the three examples shown, both overall probability of success and risk structure is different. (a) shows three examples of development projects with different risk structures: (1) Innovative NCE ('breakthrough innovation'): high risk, high cost, blockbuster potential; (2) 'Standard' product ('incremental innovation'): for example, a product of a class with clinical PoC; moderate development risk, moderate development cost, moderate sales potential; (3) Added value generic (generic with added benefits through, eg, innovative formulation): low risk and cost, low to moderate sales, faster development. (b) illustrates the expected financial value, the probability of launch, and the cost per stage of the projects at particular development milestones. For example, a project with low risk and fast development may have a higher financial value in early development than a highly innovative project, emphasising the impact of risk structure on value. The expected value uptake of the latter is, however, much more pronounced when risk is resolved through the completion of milestones. Innovative projects usually experience their highest relative value uptake after successful PoC, whereas the value uptake of clinically validated development candidates or value-added generics is less pronounced at PoC. Value uptake profiles may also vary depending on the chosen clinical development strategy and the unique selling proposition to be established. Taking into account the effects of projects with different risk structures, R&D portfolios may be designed to achieve optimum productivity and diversification. Analysis of the risk/cost/value structure of individual projects facilitates proactive portfolio planning with respect to overall portfolio value, efficient resource allocation, and sustained growth.

forthcoming development stages is analysed, the understanding of risk along the sequence of clinical trials will be enhanced.

Commercial analysis and sales forecast

In fully integrated corporations, commercial analyses and sales forecasts are usually provided by (strategic) marketing. Representatives of the portfolio management function sometimes generate sales forecasts for projects that have not yet passed PoC or that are of low priority. In such cases, it is advisable to seek alignment of the key assumptions with marketing to ensure their buy-in.

Assuming contemporary forecasting capabilities (see below), the major issue of value-driven management is the proper alignment of commercial expectations with the planned R&D activities and clinical trials. Furthermore, project managers and decision makers benefit from investigations how product sales may change if uncertain trial outcomes move to the optimistic or pessimistic direction, related to the likelihood of the respective scenarios. As outlined above, the TPP/MPP is a valuable tool to facilitate the establishment of trustworthy forecasts and expected sales scenarios.

As a consequence of the translational medicine approach, more and more companies choose an organisational model that separates research and early development until POC from full development. As a consequence this leads also to a split of the portfolio management function. In such cases there is a tendency of initiating quantitative financial project evaluation only after PoC. This is different from portfolio management practice in the 1990s, when a development project was nominated with the start of preclinical development and its financial value analysed. Significant decisions with respect to the therapeutic indication and the development strategy are sometimes already made before the definition of the PoC programme, as they influence its objectives and design. If TPPs and quantitative analyses are established only thereafter as prerequisite for the 'full' development decision, it may turn out that data generated earlier do not support a competitive value proposition. However, with a longstanding business experience of the company in the targeted disease areas, marketing input to early R&D, and a broader set of clinical options tested, it may be adequate to initiate market analyses and financial evaluation only after PoC.

Productivity analyses of the biopharmaceutical industry indicate that approximately 20% of project terminations in Phases II, III, and registration are based on commercial and strategic considerations.[13,14] A significant fraction of these late terminations could potentially be avoided by conducting quantitative evaluation and market research earlier. The value of sales forecasting before PoC is sometimes questioned, as it is entirely based on assumptions. If, however, TPPs and MPPs are sufficiently detailed and respected in development, they represent blueprints of the future product, because R&D will be directed towards proving the claims. In essence, uncertainty would only materialise as more positive product and market scenarios, as outcomes below MPP level should lead to a termination of development. The uncertainty of assumptions and their impact on overall results can be quantified and illustrated by various techniques. Companies who apply forecasting to early projects also appreciate its educational effect, because the relation between criteria defined in TPPs and their expected impact on sales becomes transparent.

The following three approaches to the evaluation of the market potential can be applied in early R&D at a moderate cost:

i. *Sales forecasts based on desk research*: Commercially available reports on disease prevalence and incidence and market segmentation enable an estimate of patients available for treatment. Databases provide information about pipeline products and facilitate a judgment of

their competitiveness. Information of the pricing environment and dynamics enable an assessment of a potential price range for the new drug. The uncertainty of assumptions can be analysed using Monte Carlo simulation which, however, is not regularly applied in pharmaceutical companies at present. Tornado diagrams illustrating the results of one-way sensitivity analysis are often preferred over simulations as they are more illustrative.

ii. *Focused market research*: Interviews with key opinion leaders, experts, and health-care providers yield valuable information in early development, as physicians and insurances may adopt a much more pragmatic perspective towards drugs that scientists consider highly innovative. In addition, opinions may significantly differ across the countries. Such information is used to refine the desk research-based forecast.

iii. *TPP conjoint analysis*: In early R&D, conjoint analysis is an ideal tool to investigate physicians' attitudes towards (potential alternative) TPPs. Conjoint analyses are statistically relevant trade-off analyses in which physicians weight the relative importance of particular product attributes including price (if information on a feasible price range is particularly relevant, the conjoint analysis could include further customers, such as, eg insurers, formulary committees, or HMOs). In early R&D, this analysis allows investigating whether a TPP or MPP is competitive and focuses on attributes that drive the choice of products. The analysis provides preference shares for alternative TPPs or products. Thus, TPP conjoint analyses facilitate the definition of robust TPPs.

In summary, building a desk research-based sales forecast reveals the relevant issues that may lead a product to market success or failure. Further enhancing the reliability of the forecast by market research reduces the risk of pursuing development strategies that prove to be commercially unattractive in late development.

Financial project evaluation

The NPV algorithm is a generally accepted approach to the financial evaluation of investments in the pharmaceutical industry, and it is also used in R&D portfolio management.[6–8,15] Originally, the NPV algorithm has been developed for 'static' investments where managerial actions have virtually no impact on value. As described above, the situation is different for the development of new drugs. Investment decisions are made stepwise along development milestones, while assumptions are made about the cost, duration, and probability of success of individual milestones. NPV calculations that reflect the milestone and risk structure of projects are therefore more useful. Many companies report to apply 'risk-adjusted' or 'expected' NPV models, while it is not always disclosed whether such models include the probabilities per individual milestone or only the overall probability of launch. The 'augmented NPV' model[15] incorporates the probability of success at individual milestones and the option to minimise losses by terminating development if unfavourable results occur. While being built on the decision tree, the evaluation does not only include the overall probability of success but also adequately reflects the risk structure of projects. Therefore, the augmented NPV is sensitive to changes in the development plan if they affect the project's risk structure.

Augmented NPV reflects the present value of the project. In addition, this financial algorithm can be used to determine the potential future value of projects and portfolios assuming that subsequent milestones would be completed successfully. Project prioritisation decisions could refer to the relative and absolute value gain that the completion of a milestone of a particular

project would yield, in relation to its respective cost and probability of success. Furthermore, such analyses provide an optimum basis for license contracts with option elements, and for investors' decisions regarding exit strategies.

Option pricing algorithms based on risk-neutral valuation are also investigated for their applicability to R&D projects.[16,17] The major argument is that it can be concluded from financial theory that discounting in option pricing models would better reflect the optionality of such projects. So far, there is no final consensus among scientists and practitioners about the validity and advantages of option pricing methods compared to augmented NPV, and there is evidence that the results of both approaches converge and lead to similar conclusions if private risk is reflected adequately.[17,18] This and the absence of experience with this abstract valuation algorithm have prevented its widespread implementation.

Development portfolio management

Most pharmaceutical companies apply a regular and systematic approach to review their portfolio of development projects. This is undertaken once or twice per year. The portfolio review usually comprises both qualitative and quantitative evaluations of individual projects (Figure 3). Common qualitative parameters are strategic fit and degree of innovation, while quantitative parameters include NPV and expected value uptake, project productivity (ie augmented NPV divided by risk-adjusted costs), (risk-adjusted) sales, probability of launch, time to launch, and (risk-adjusted) cost.

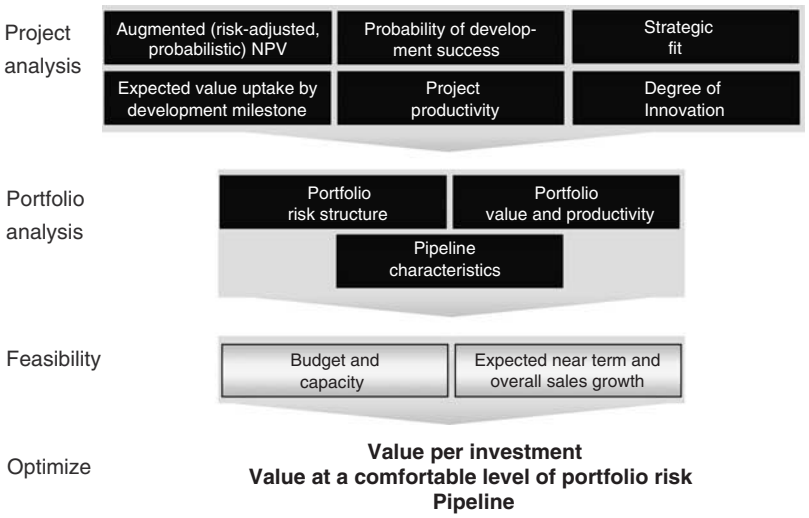

Figure 3: Commonly applied portfolio management metrics and criteria. Portfolio decisions in pharmaceutical R&D are usually built on both quantitative and qualitative criteria such as those shown above. From a purely financial perspective, one would rank projects according to expected NPV and optimum productivity. This, however, ignores that future corporate growth requires a balanced pipeline which also includes early stage projects with lower expected NPVs. Furthermore, capacities need to be available and can usually not be allocated freely. Another issue is balancing portfolio risk to ensure that productivity goals are met. A proper strategic framework outlining growth and productivity goals and the therapeutic area focus serves as guidance for portfolio decisions. Effective data analysis tools facilitate the evaluation which combinations of projects would maximise value, sales growth, or the number of new launches. In addition, companies are currently establishing tools for capacity management to investigate more thoroughly which portfolio scenarios would be practically feasible.

While there is common agreement on portfolio management metrics in development, there are differences in the portfolio management process and in the preferences for particular project value indicators. For example, some companies establish quantitative project analyses only after PoC, while others start earlier. Furthermore, some perform a project-per-project review with little emphasis on cross-project comparisons, while many use templates displaying two or three value dimensions across projects in order to facilitate project prioritisation decisions.

Data validation and buy-in of senior management

If experts and project teams evaluate their own projects they may be subjective and sometimes overly optimistic. Subjectivity can be balanced effectively when the project evaluation meetings are moderated by an experienced individual, for example, a representative of the portfolio management function who has no stake in particular projects (Figure 4).

Data quality can be further enhanced by a comparative look across projects at the assumptions made in the evaluation. In larger companies, this may be most practical for projects within therapeutic areas. The major focus should be on validity and consistency among the probability estimates in development and on the assumptions underlying the sales forecasts. Ideally, the review process would involve senior function managers. This has two advantages:

1. input of senior expertise may improve the quality of the data and cross-project consistency and
2. the involvement of senior management in the portfolio evaluation process builds the basis for acceptance of valuation results in the prioritisation discussion.

Interactive decision making as prerequisite for proper prioritisation decisions

There is no single optimal portfolio, alternative solutions are usually feasible. Project scoring methods leading to

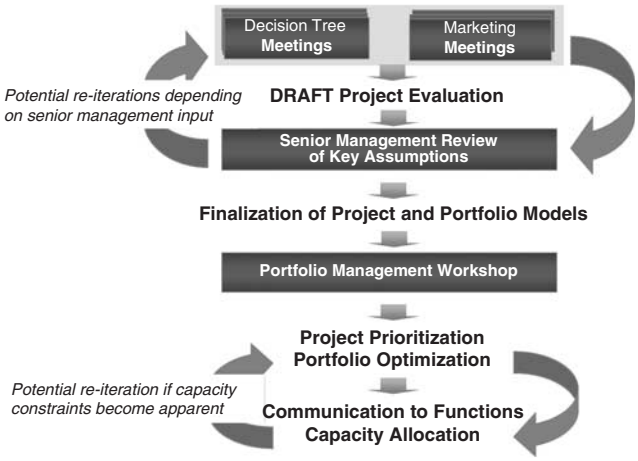

Figure 4: Portfolio management process in fully integrated companies. The evaluation of development milestones and probabilities ('decision tree meetings') and the commercial analysis ('marketing meetings') of individual projects is usually performed on the project team level. A senior management review of the key assumptions across projects facilitates the establishment of valid and consistent assumptions. As capacity constraints may limit the operational execution of portfolio decisions, effective communication and interaction with functions facilitates the translation of project prioritisation decisions into feasible actions.

computated project ranking lists have therefore not found general acceptance. Instead, portfolio review meetings benefit from thorough interactive discussion and the consideration of alternative prioritisation solutions. Corporate strategy leaves room for interpretation, decision makers' risk preferences may differ, and keeping the balance between short- versus long-term value propositions or new project versus lifecycle management investments is often a matter of diverging opinions. Therefore, robust portfolio decisions are best achieved in an interactive way. Individual opinions and attitudes of the participants become transparent. This paves the way for consensus and compromise that increases the chance that decisions are respected and translated into action on the operational level.

Understanding evaluation results that comprise a set of parameters related to a set of projects is a complex pattern recognition task. The discussion strongly benefits from moderation by a representative of portfolio management who supports the participants to achieve a balanced view.

Analysing an existing portfolio is a bottom-up approach that usually comprises the elements described below:

i. Evaluation of the overall pipeline with respect to the distribution of projects across development stages and the frequency of expected future launches; identification of gaps.
ii. Prioritisation of projects based on multiple criteria: In a first step, participants may agree on the ranking of projects with respect to individual criteria. Projects may rank high or low for different reasons, such as, for example, value, risk profile, time to market, or sales volume. In a subsequent step, overall project priorities are defined. In addition to the criteria representing value, strategic and operative aspects may be relevant for the prioritisation of projects. Care is taken that not only late stage/high value projects are assigned high priority, because a systematic under-resourcing of early stage projects would result in late stage projects with short patent life and unfavourable profile. Efficient software tools can facilitate the investigation of alternative project prioritisation options that may, for example, differ with respect to maximising productivity, maximising near or mid-term sales growth, or minimising portfolio risk.
iii. Identification of projects with firmly assigned resources, identification of remaining budget and capacities that will potentially be subject to reallocation.

Depending on the size of the corporation, prioritisation decisions are either made across the whole portfolio or within business units or therapeutic areas. The latter model would require a corporate body that assigns resources to individual business units according to their relevance for the entire corporation. Preference for a 'fractionated' approach to project prioritisation usually depends on the overall number of projects and the corporate culture.

An effective portfolio management process also requires reporting procedures to follow up actions taken upon decisions at the operational level. This facilitates establishing a culture of value-driven management.

Capacity management

An often underestimated prerequisite of successful portfolio management is appropriate capacity management.[19] The best portfolio management system cannot prevail if there is a significant gap between available and needed capacities.

The consequence of a lack of a capacity management system is not only that more or less all projects get delayed but also that the priority decisions are made on the working level, based on individual judgment and personal relationships.

In prioritisation decisions in portfolio review meetings, the ranking should not just

depend on the potential economic benefit but also on the needed capacities to reach the goal (R&D efficiency).

Portfolio management in different organisational systems

As with all new management concepts the organisational introduction of a portfolio management function has to be seen in the context of the overall organisational model that the respective company applies.

The portfolio management process involves the entire R&D organisation and all commercial functions. In most organisations, R&D and Marketing & Sales are represented on the Board level by different individuals. Therefore, the first question companies need to address is to which corporate body the portfolio management function should report.

In principle, three organisational models are possible and as a matter of fact are found in certain companies.

Either the portfolio management function reports to:

- Head of R&D
- Head of Commercial
- CEO/Head of Strategy, etc

All models could be feasible, but they face different challenges in practice.

As R&D and commercial functions are equally involved in the portfolio management process, the first two organisational models are complicated by the requirement that one stakeholder reports into the other. This could raise bias concerns given that very often R&D and commercial are different in their perspectives. This issue is avoided by a model where the portfolio management function reports either directly to the CEO or to another Board member responsible for, for example, corporate strategy or business development.

Another aspect that needs consideration is with which other functions portfolio management needs to collaborate. Given the very nature of the portfolio management process as an iterative business process, the links to corporate strategy for getting strategic directions and with project management for appropriate execution appear to be most important. Furthermore, an effective organisational link to business development would also be relevant as portfolio analysis indicates which in-licensing candidates and R&D partnerships would ideally complement the internal assets.

In larger multinational organisations composed of strong and relatively autonomous business units covering particular therapeutic areas, the portfolio management process might be broken down in an inner business unit and a corporate portfolio management process.

Observational evidence suggests that the most effective organisational model is one in which the portfolio management function is closely linked to the strategy and project management function, jointly reporting to either the CEO or another Board member that is neither responsible for R&D nor for commercial. Merck Serono is currently implementing such a model in order to enhance the cross-functional management of R&D and to improve alignment of portfolio decisions with strategic goals: all functions, along with portfolio management and business development, are represented in the new Executive Management Board reporting to the CEO.[20]

PORTFOLIO MANAGEMENT IN RESEARCH AND EARLY DEVELOPMENT

Not so long ago there was the general belief in the industry that research was hardly manageable and that portfolio management techniques were just not suitable for the discovery process. Arguments given were that changes in research direction would create a slowdown in productivity because the skill set is not readily transferable, the financial value of projects could not properly be determined so early and that serendipity would play a major role anyway.[21]

Whereas past efforts focused mainly on decreasing the time to reach the next milestone and finally the time of launch it can be questioned whether further reductions in development time are still feasible with reasonable efforts. The emphasis is shifting towards influencing attrition rates favourably, either by improving the quality of R&D execution or at least by terminating projects as early as possible by optimised decision making.[13] Doing things right is no longer enough, doing the right things becomes the rule of the game.

This paradigm shift is currently increasing the awareness that portfolio management techniques could contribute significantly by ensuring that:

- Portfolio value increases – by killing low value and unproductive projects early
- Portfolio risk is well balanced – by working on an appropriate ratio of validated and non-validated targets
- Research targets support the franchise strategy – by defining a franchise strategy

Prerequisites for portfolio management in research and early development

As for development, there is one very important prerequisite for the successful introduction of portfolio management in research – a proper strategic framework.

Furthermore, tools applied in development portfolio management, such as, for example, the stage gate decision process, TPPs, and time line, budget, and risk analysis are increasingly used in early R&D.

TPPs in early R&D

TPPs in discovery research outline the pharmacological, safety, and technical profile required for compounds to enter clinical development. Fulfilling such predefined criteria would create reasonable confidence that the optimal drug has been selected and that clinical trials can succeed. TPPs in research and development that are well aligned with each other and with strategic objectives in a cross-functional process serve as ideal tool to manage the interfaces between discovery research, development, and marketing.

Evaluation of individual projects along a stage-gate decision process

For the drug research process the following phases can be defined: target selection, assay design, lead discovery, lead optimisation, and candidate profiling (also called preclinical development, required for entry into man), see Figure 5.

Every project needs to be evaluated at the end of each phase based on the achieved data. A set of milestone criteria is defined according to the TPP that must be fulfilled to let the project move into the next phase. Some of the go/no-go criteria may be quantitative like affinity and selectivity of a compound for particular receptors, others may be more qualitative, like competitive edge versus competitors or attributes for which no validated animal models might be available. As in advanced development, a stage-gate process only for individual project decisions would, however, fail. With the decision to move a project into the next phase a certain amount of resources, either internal or external, is to be allocated. It has to be made sure that these resources are not already utilised by other projects the organisation is working on. In case bottlenecks are determined, debottlenecking strategies need to be developed or clear prioritisation decisions have to be made for the entire portfolio.

Regardless of the capacity issue, what appears to emerge as best practice in early R&D is that individual compounds are considered from the perspective of the selected pathway in comparison to other targets under investigation for the respective disease area. Trade-off decisions are made to optimise the entire franchise portfolio.

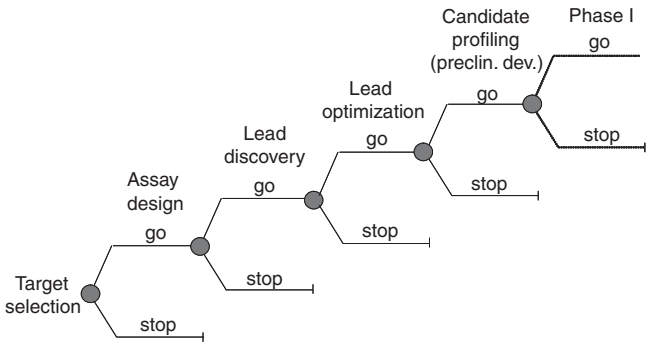

Figure 5: Stage-gate decision process in discovery research. Many companies have implemented a stage-gate decision process in drug discovery and manage their research along milestones such as those indicated above. Some companies have recently implemented an organisational model in which the responsibility of discovery research extends up to PoC. As in clinical development, go/no-go criteria are defined for each milestone according to the TPP that must be fulfilled to continue research. Companies usually set time lines for the achievement of milestones. Discovery research is nowadays also covered by benchmark initiatives which provide average success rates, time lines, and resources used per milestone.

Project risk analysis

While there is a lot of experience with project risk analysis in drug development, systematic risk and probability analysis is less established in drug discovery. It has been particularly difficult for project teams in discovery research when they worked on innovative targets in the absence of any reference data. Since recently, industry benchmarks are also available for the drug discovery stage, referring to the stage-gate decision model. These benchmarks have become particularly useful as many companies adopted the stage-gate research process. In some disease areas, commonly accepted animal models are available that are to a certain extent validated for their predictivity of efficacy in man.

To characterise the risk profile of individual projects, the following risk dimensions are evaluated:

- *Compound risk*: Risk that the compound will fail due to deficiencies of the specific molecule.
- *Mechanism risk*: Risk that the biochemical mechanism does not work in pharmacological models and in man as expected.
- *TPP risk*: Risk that the compound will not meet the specified efficacy and safety targets of the TPP.
- *Competitive risk*: Risk that the predefined TPP will not create a differentiated product with a unique selling proposition.

Companies may apply a scoring model that provides an overall judgment of project risk. Recently, some discovery organisations made favourable experience with decision tree analysis, allocating probabilities of success to each milestone of the stage gate model based on the criteria used for go/no-go decisions.[23] Probability assessments also enable the establishment of a pipeline model for discovery research, indicating the expected number of compounds entering Phase I or completing PoC per unit of time, related to a defined budget and capacity. Pipeline models in research have proven to be extremely useful in managing and monitoring productivity and performance in early R&D.

Financial evaluation

At present, there appears to be a general agreement in the pharmaceutical industry that it does not make sense to do detailed financial

analyses in the research stage. The main argument is that at this point efficacy and differentiability might not have been established and that the effective dose in man and the COGS are not known. What is used instead is a kind of ranking based on epidemiology and market data, leading to an estimate of the sales potential:

- High economic value >1bn US$
- Moderate economic potential >500m <1,000m US $
- Low economic potential <500m US $

The resulting conclusions will depend on the company's commercial situation, with larger organisations defining cut off numbers under which a further development does not appear to be appropriate, and projects may be terminated only for commercial reasons.

There are circumstances in which full NPV analyses are performed in early R&D. For example, companies establish detailed financial models in licensing situations. Biotechnology companies benefit significantly from quantitative financial evaluation for early stage projects, as these create a rational basis for fund rising and licensing purposes, especially if risk is explicitly addressed and quantified. Thus, biotechnology companies often establish more detailed and precise quantitative modelling for early projects than pharmaceutical companies, which sometimes even comprises primary market research. NPV analyses are also applied during the discovery to PoC stage in fully integrated pharmaceutical companies. In research portfolio management, such analyses allow to quantify the contribution of early research to the overall R&D value chain. In addition to using the number of drugs entering clinical development or completing PoC as productivity measure, the value added by completing individual preclinical milestones can be quantified based on the augmented NPV model.[15] It is used to demonstrate the financial benefit of investing in particular projects and to identify the value drivers in early R&D.

Research portfolio evaluation

Besides the gating decisions for individual projects that should be done as soon as the required data are available, it is common practice to review all projects every 6–12 months.[19] In such reviews projects compete with each other. The primary focus of review meetings is to have a holistic view of the whole portfolio. The number of projects in the different phases of research is evaluated in order to make sure that the overall productivity targets are met. In addition, these meetings serve to analyse whether the overall portfolio risk profile, for example, the ratio of validated to unvalidated targets, is as intended and whether the research projects are properly aligned with the agreed company or business unit or franchise strategy. It is very important that if in such meetings the projects from different research sites are compared, a common understanding is established on how to measure progress, how to set standards and how to define milestones.

Beyond evaluating individual projects, an assessment of the status of the different franchises can be done. Issues of competitiveness, ways to improve strategically and operationally need to be addressed regularly.

Scoring methods

At present, most research organisations have established scoring systems for portfolio evaluation. Although it appears that every company has developed a specific set of criteria along which their projects are rated there appears to be common sense that at the following items should be covered:

- *Value*: Scoring around market size, attractiveness, and competitiveness; if NPV models are established, parameters such as NPV and the realised or future expected value uptake upon successful

completion of milestones are included as value indicators.
- *Cost*: High, medium, low, either for research cost alone, or including development cost.
- *Timing*: Time to entry into clinical development/PoC/launch, expected time per milestone.
- *Strategic fit*: Score against therapeutic area strategy.
- *Risk/probability of success*: Scoring against TPP and milestone criteria.

Some other organisations apply a larger range of criteria and rate every item with high, medium and low. Potential meaningful criteria are:

- Innovation potential
- Specificity
- Efficacy
- Tolerability
- Appropriate early clinical PoC/availability of biomarkers
- Preclinical feasibility
- Clinical feasibility
- Degree of unmet medical need
- Competitiveness
- Number and categories of competitors
- Patent status
- Peak sale potential
- Potential follow-on indications

Although good arguments can probably be given for any of these criteria, the experience speaks for using as little as possible items because the likelihood that the scoring system does not provide enough differentiation between the projects increases with the number of criteria used. This is particularly true for the middle of the ranking.[19]

If the scoring system were used for prioritisation decisions, the so-called 'forced ranking approach' should be applied. All potential pairs of projects are compared against each other and the higher prioritised project is determined, respectively. At the end the project portfolio is ranked according to the highest number of priority ratings per project. One inherent problem of scoring systems but also of predefined milestone decisions is that projects are compared against a minimal acceptable standard to move forward. These tools do not take into account the overall capacity available.

Portfolio risk evaluation

One of the primary goals of portfolio management is to ensure that the portfolio is well balanced with respect to the potential risks and rewards. Experience has shown that focusing exclusively on 'me toos' is as dangerous as only concentrating on very exciting but unvalidated targets. There is no single optimal portfolio throughout the industry. Every organisation has to define the level of risk that optimally supports the strategy. As the strategy gets reviewed from time to time so has the risk profile of the research portfolio to be adapted from time to time.

In order to characterise the overall portfolio risk structure, research projects could be classified along the following groups:

- *Pioneer*: No known competition.
- *Novel*: Other companies work on the same target but target is not validated in man.
- *Back up*: In-house programme exists in development for same target.
- *Fast follower*: Target has been validated in the clinic by another company.
- *Me Better*: Pursuing a target that other companies have already successfully launched.

It is quiet obvious that the more pioneer projects a company pursues the more risky the portfolio becomes. If probabilities of success are determined for project milestones, pipeline models as described above can serve as highly educational tools to monitor project and portfolio risk and past and expected future productivity.

SUMMARY

Modern portfolio management techniques can play an instrumental role in enhancing the overall productivity of pharmaceutical R&D. The fact that portfolio management has been applied for some time by the major pharmaceutical companies while productivity did not increase is no disproof for the statement because the productivity crisis has many facettes, and productivity might have been even worse without portfolio management. In addition, portfolio analysis does not automatically result in objective and rational management decisions.

The portfolio management process needs to be cross-functional, involving the entire organisation. It requires the discipline to develop and constantly apply a set of tools in order to allocate the scarce resources to the most promising projects. Keeping portfolio management alive and effective *vis-à-vis* corporate reorganisations and scientific paradigm shifts is a continuous organisational effort.

Emphasis should be given to the following items:

- Define the business strategy and align the entire organisation behind it.
- Develop and constantly update a TPP for every project.
- Define clear go/no-go criteria for every milestone.
- Set up a tool to evaluate the potential value of all projects either through in-depth financial analyses for later stage projects or based on a semi-quantitative scoring system for earlier projects; do quantitative financial modelling for early-stage projects to investigate the expected value uptake upon successful completion of milestones and to facilitate licensing negotiations.
- Install a capacity management system in order to avoid a disparity between available resources and the number of projects. In case there is a lack in capacity, be ready to make tough choices and terminate the projects with the lowest value as early as possible.

The organisational embedment of the portfolio management function needs special consideration. An organisational model in which the portfolio management function could closely collaborate with the corporate/business unit strategy function and the project management function appears to be most appropriate in the authors' experience to help increasing effectiveness and efficiency in the overall drug development process.

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