Supporting Innovation in Early-stage Pharmaceutical Development Decisions

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Florian Methling

Decision Theory and Financial Services Group, RWTH Aachen University, Aachen
Strategic Decisions Group, Düsseldorf

Steffen A. Borden

Head of Portfolio Management, Bayer Pharmaceuticals, Berlin

Deepak Veeraraghavan

Strategic Decisions Group, Düsseldorf

Insa Sommer

Strategic Decisions Group, Düsseldorf

Johannes Siebert

MCI Management Center Innsbruck, Innsbruck

Rüdiger von Nitzsch

Decision Theory and Financial Services Group, RWTH Aachen University

Mark Seidler

Strategic Decisions Group, Düsseldorf
Corresponding author: mseidler@sdg.com

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Abstract

Pharmaceutical companies have frequent portfolio reviews to monitor development progress and prioritize development assets. The earliest assets are drug candidates whose efficacy is unknown and whose effects on the human body have yet to be fully investigated. These assets are characterized by a high degree of uncertainty in reaching the market and in being used in clinical practice. In addition, not all potential applications are foreseen and can often be very different. In the absence of satisfactory methods for making decisions on resource allocation among early-development assets, decision-makers focus almost exclusively on assessments of an asset's probability of technical success.

This study proposes a more holistic methodology to support early-stage pharmaceutical development decisions using value-focused thinking and multi-criteria decision-making. The methodology operates within the decision quality framework and provides a consistent evaluation of various early-development assets across a diverse set of disease areas. This combination of concepts and methodologies has been implemented and proven valuable at Bayer Pharmaceuticals, which needed a new, more robust decision-making process for early development. Thus, this study discusses how to enable concrete trade-offs at the level of corporate objectives to align, communicate, and translate corporate strategy to portfolio strategy. In addition, this study presents learnings for decision analysts and decision-makers in the pharmaceutical industry on how to develop a set of fundamental objectives, how to create scales to operationalize these objectives, and how to take steps to debias an organizational decision-making process.

1. Introduction

The pharmaceutical industry has been facing a decline in research and development (R&D) productivity for some time (Smietana, et al., 2015; Schuhmacher, et al., 2016). Several factors drive this trend. The hurdles for a new drug become continually higher, regulators reduce their risk tolerance, and instead of working on improving selectivity and product differentiation, companies shy away from innovation and stick to what they know (Scannell, et al., 2012). Shying away from innovation manifests itself as a consistent behavior in the judgment of decision-makers responsible for R&D to avoid uncertainty in R&D decisions. This behavior hampers their ability to create more and better alternatives, and, ultimately, leads to selecting suboptimal strategies for development (Seidler, et al., 2019). When facing the uncertainty of early-stage research decisions, this leads to an exclusive focus on a drug's probability of development success, i.e., the likelihood of technical success and regulatory approval of a product, ignoring the multi-objective aspects of the decision. Hence, lower-risk drug candidates with shorter times to market are preferred leading to fewer long-term bets and less innovation (Phillips & Bana e Costa, 2007). However, innovation is a fundamental prerequisite for an originator pharmaceutical company (Ding, et al., 2013; Owens, et al., 2015; Lakdawalla, et al., 2018). Consequently, those decisions are made in contradiction to the corporate objectives. This is an example of not acting in the company's interest and, ultimately, not in the interest of patients and society. This study presents a multi-criteria decision-making (MCDM) methodology using value-focused thinking to help decision-makers better reflect on their early-stage pharmaceutical development decisions (Keeney & Raiffa, 1993; Keeney, 1996).

In pharmaceutical R&D, drug candidates follow a well-defined stage-gate process. In research, tens of thousands of compounds are typically screened, either exploratively or driven by a hypothesis to target a particular mechanism, until a candidate is selected. This candidate is subsequently transferred to development starting with preclinical studies followed by clinical

trials. In preclinical development, an attempt is made to predict the selected candidate's effects on the human body by studying results in organ models, living animals, or ex vivo tissue. Clinical development, the testing in humans, then follows, split into three different phases. Authorization by regulators completes the stage-gate process. The whole process of drug R&D often takes 10-20 years (Seifert, 2019; Lexchin, 2020). In early-stage development, which includes the preclinical development and the early clinical development, development progress (first signals of resolution of uncertainty in the ability to achieve the desired product profile outcome) and pipeline balance are monitored frequently. Furthermore, each drug candidate is regularly assessed using both qualitative and quantitative indicators to adjust portfolio composition by prioritizing individual assets. These indicators can be estimated time to market, risk, e.g., the likelihood of not meeting specific endpoints in the next trial, and cost (Kaitin, 2010). However, at this point in the drug development process, drug candidates often have yet to prove their efficacy in the human body, and the lead indication, which describes the primary medical need that is about to be served, is often still subject to change. This leads to a high degree of uncertainty regarding potential outcomes and makes the prioritization decision particularly challenging while also setting difficult demands on decision-making methodologies.

There are satisfactory approaches to making decisions in late-stage development. However, these are not fully appropriate for early-stage decision-making. Net present value (NPV) plays a dominant role as a decision criterion in asset reviews for the later stages (Hartmann & Hassan, 2006). The NPV estimates the current value of a project by predicting and adding up discounted expected future cash flows. Due to the depth of experience in late-stage development decisions, an expert's judgment and predictions are broadly accepted as a basis for generating these cash-flow estimates. In contrast, in early-stage decisions, many unknowns undermine the credibility of detailed assessments (Stewart, et al., 2001). In addition, the earlier the asset is in its

development, the later the timing of the positive cashflows. Hence, the long time-horizon, high degrees of uncertainty about the circumstances under which a product might reach the market, and large up-front investments lead to NPVs of early-stage assets close to zero with only minor differences in absolute terms. As a result, a general belief of R&D decision-makers is that the financial value in early development cannot be properly determined (Phillips & Bana e Costa, 2007; Bode-Greuel & Nickisch, 2008). From the perspective of the decision-makers, the trade-offs to be made remain unclear and opaque. However, clear trade-offs represent a fundamental prerequisite for making high-quality decisions (Howard, 1988; Spetzler, et al., 2016). Consequently, in early-development decisions, there is little confidence in the NPV (Phillips & Bana e Costa, 2007). Hence, there is a need for methodologies for resource allocation decisions in early-stage pharmaceutical development to help decision-makers express their preferences and decide accordingly (Angelis, et al., 2017).

This study proposes an MCDM methodology based on value-focused thinking (VFT) for supporting early-stage pharmaceutical development decisions. MCDM models allow efficient decision-making in resource allocation problems, especially when objectives are included which cannot be "suitably evaluated using standard financial metrics" (Kleinmuntz, 2007). They have been increasingly employed in the context of health-related prioritization decisions (Montibeller, et al., 2020). In combination with VFT, it provides a powerful tool for structuring these decisions (Montibeller, et al., 2009). VFT approaches are designed to support complex decision problems with multiple conflicting objectives (Keeney, 1996). MCDM focuses on highlighting these conflicts and enables compromises in a transparent process (Ijzerman & Steuten, 2011). Therefore, it is well suited to elicit preferences to estimate values of new development opportunities and technologies relative to each other (Ijzerman, et al., 2017). Several examples have demonstrated that transforming the decision-making process and sharpening its underlying criteria strengthen companies and further improve their R&D

productivity (Cook, et al., 2014; Morgan, et al., 2018). In particular, MCDM applications improve decision-making by creating transparency and consistency in allocation decisions across projects (Phillips, 2007; Phillips & Bana e Costa, 2007; Thokala, et al., 2016).

The presented methodology will provide a consistent, transparent evaluation of various early-stage assets within a heterogeneous set of disease areas, thereby enabling trade-offs based on agreed-upon decision criteria. The methodology has been implemented and proven valuable at Bayer Pharmaceuticals which needed new, more robust approaches to decision-making for early-stage development assets to further increase overall performance. The remainder of the paper is structured as follows: Section 2 describes the proposed methodology. Section 3 presents the practical application at Bayer Pharmaceuticals and the learnings for applications of decision analysis in business situations. The study ends with a discussion of key conclusions.

2. Methodology

This study applies methods Keeney suggested in his value-focused thinking framework to support clear values and tradeoffs by developing a set of so-called fundamental objectives (Keeney, 1996). “Fundamental objectives concern the ends that decision-makers value in a specific decision context” (Keeney, 1994). They can be identified by interviewing decision-makers and stakeholders (Keeney & Raiffa, 1993). In addition, separate indirect efforts using publicly available material to derive fundamental objectives have proven to be a valuable enhancement (Siebert, et al., 2017; Siebert & von Winterfeldt, 2020). The set of fundamental objectives should ideally have a certain set of properties (Keeney & Raiffa, 1993). Fundamental objectives should be complete and operational to the extent that they are meaningful for everyone involved and the implications of them are fully captured and understood. Also, they need to be decomposable so that complex assessments can be broken down into smaller pieces facilitating unbiased assessments and understanding. Finally, the fundamental objectives

should be non-redundant and minimal in number. On the one hand, this ensures that all the objectives are still fundamental, and on the other hand, this helps the decision-maker keep control and maintain a clear picture of the decision and the situation. (Keeney & Raiffa, 1993) Further, it ensures the differentiability of assets to provide meaningful results (Bode-Greuel & Nickisch, 2008).

In this study, the fundamental objectives are evaluated using a value model. A value model allows comparing alternatives according to their degree of achievement of the defined objectives (Keeney & Von Winterfeldt, 2007). Hence, the alternatives must be consistently measured, and their levels of achievement must be aggregated. In the literature, these measures are varyingly called scales, attributes, criteria, or descriptors (Keeney & Raiffa, 1993; Bana e Costa, et al., 1999; Keeney & Von Winterfeldt, 2007). Further, the aggregation must define the relationship between the individual alternatives' characteristics and the overall value *v* of an alternative *a*. This makes it possible to indicate a preference for the differences among the alternatives (Dyer & Sarin, 1979). We consider here an additive value model:

$$v(a) = \sum_{i=1}^{n} w_i v_i(a_i)$$

In this notation, $v_i(a_i)$ defines the value of an alternative *a* in objective *i*, w_i denotes the objective weight/scaling parameter, and *n* shows the total number of objectives. This additive value model requires preferential independence among the objectives (Dyer & Sarin, 1979). Preferential dependence occurs when a decision-maker changes preference for one objective as a function of the valuation of another objective. More details on the methodological requirements and independence concepts can be found in the literature (Fishburn & Keeney, 1974; Von Winterfeldt & Edwards, 1986; Keeney & Raiffa, 1993; Smith & Dyer, 2021).

In the aggregation of the different values, every objective is weighted by the corresponding objective weight w_i. There are different approaches, e. g., direct ratings or trade-offs. The approach of eliciting direct ratings requests direct assessments of the objectives' relative importance. However, studies have shown that objective scale ranges, which strongly influence a decision, are only partly reflected by decision makers' objective weight choices (Von Nitzsch & Weber, 1993). Hence, direct ratings are prone to biases. For a detailed discussion on biases, see Montibeller and von Winterfeldt (2015). In contrast, the application here facilitates the definition of trade-offs by comparing alternatives with opposite characteristics in the considered objectives (Keeney & Raiffa, 1993). The idea is to find combinations of alternatives that the decision-maker finds equally valuable so that the relative preference for different objectives becomes transparent. For example, assume two assets that are rated equally in all objectives but two. If the decision-maker finds these assets equally valuable, the differences in the two objectives with unequal ratings offset each other. So, for the two objectives *i* and *j* with alternatives *a* and *b* and the statement of indifference of the decision-maker, the objective weights can be determined by (for a detailed example and graphical illustrations, see, e.g., (Keeney, 2002)):

$$w_i = \frac{v_j(b_j) - v_j(a_j)}{v_i(a_i) - v_i(b_i)} w_j,$$

defining the sum of objective weights to be 1 (Keeney & Raiffa, 1993).

3. Application at Bayer Pharmaceuticals

In 2019, Bayer Pharmaceuticals started developing and implementing the multi-criteria evaluation methodology for its early-asset portfolio management. In that year, Bayer Pharmaceuticals spent €2.8 billion in overall R&D (Bayer AG, 2020). The drug development pipeline consisted of 51 assets of which 41 were in phase I and phase II (Bayer

Pharmaceuticals, 2019). The framework was developed to consistently evaluate all early assets across the various disease areas and inform decision-making, i.e., portfolio management. A project team was nominated to support the decision-makers responsible for these R&D decisions. The project team consisted of eight members including the head of portfolio management as well as some members of the company's R&D senior management and project managers from different disease areas. The group of decision-makers was made up of seven executive committee members and functional area heads providing diverse perspectives including discovery research, development, commercial, innovation, finance, and corporate strategy. Earlier efforts to provide an MCDM evaluation focused on the unmet medical need and determining the value of an asset by its benefit to the patient (Vennemann, et al., 2019). However, this analysis did not provide a holistic portfolio overview. Doubt persisted whether the highest value portfolio and R&D productivity would be realized. Therefore, this new initiative was initiated to evaluate and differentiate the individual assets in the drug development pipeline. In the following, we describe the proposed methodology and how it has been implemented, how it affected decision-making within the company, and what lessons for the decision analysis community can be identified.

The proposed methodology is split into two workstreams separating strategic preference from scientific support (see Figure 1). Strategic preferences, i.e., objectives and their weights, are determined by the decision-makers. Scientific support information, i.e., the considered alternatives, the evaluation framework, and the assessment of the alternatives, is determined by clinical development leaders and project managers, among others.

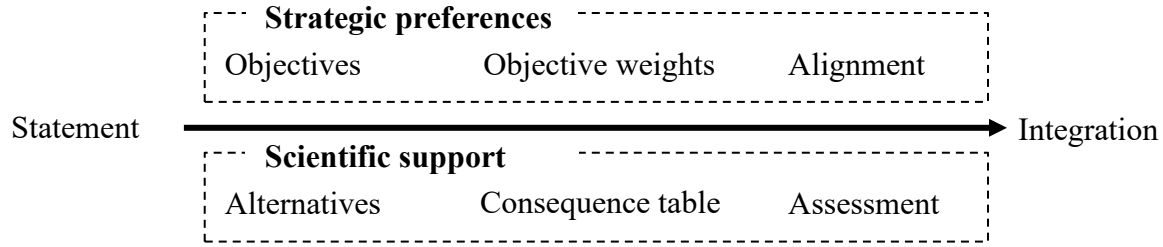

Figure 1: Outline of the methodology

The process was applied at Bayer Pharmaceuticals in a facilitated mode. In a facilitated mode, consultants work together with the client (Franco & Montibeller, 2010a). The process is described in the following order: defining a decision statement, identifying the set of fundamental objectives, defining alternatives, measuring the achievement of objectives, eliciting objective weights, aligning on objective weights, assessing the early-stage assets, and impact of integrating the decision process. In practice, however, MCDM processes can often be more iterative (Marsh, et al., 2016).

3.1. Defining the decision statement

Although there is a common understanding of what portfolio management means, it is important to have clarity on the specific types of decisions in focus when designing a process. At Bayer Pharmaceuticals, the project team was accompanied by a consulting group to jointly develop the MCDM framework. To set the right frame for the exercise, the team facilitated an issue-raising session. In a facilitated approach, there are always divergent and convergent phases of thinking (Franco & Montibeller, 2010a). In the first explorative phase, all issues were discussed that could be connected to what determines a good methodology, what determines a good early-development asset, or what types of problems arise in the current process. In the second focusing phase, the issues were discussed to identify the extent to which they needed to be addressed in the decision statement. The agreed decision statement was “to allocate resources for ongoing and newly started projects for the greatest value to the company”. These projects described drug candidates in their early development requiring decisions to either

terminate or progress the development. The following paragraph describes some observations and conclusions from the process.

A good decision statement needs to incorporate purpose, perspective, and scope (Spetzler, et al., 2016). Different perspectives were discussed, and the group clearly stated the overarching goal, i.e., to provide benefits to the company. The agreed-to scope would focus on ongoing and newly started projects, i.e., early-development assets. In contrast, defining the purpose of the decision process is more challenging. When asset development teams typically present their asset to decision-makers, they focus on describing their asset in the best possible manner. However, the decision at hand is to allocate resources across several different assets and choose among them. Consequently, the evaluation needs to focus on differentiating and describing the differences of the individual assets. The evaluation should not be understood as an end in itself but as a tool to enable making choices among these assets. Thinking about the frame and the benefit to the company led to the right purpose for the methodology and the right decision focus. It is expected that companies, in general, need help through facilitation to be clear about their decisions.

3.2. Identifying the set of fundamental objectives

The process of developing and identifying fundamental objectives for the decision utilized different methods. First, a literature review was conducted to understand what potential objectives had already been discussed in past research. In a second step, all seven decision-makers were interviewed individually. The interviewers were highly experienced decision analysis professionals. The interviewees received a questionnaire (see Appendix) and some introductory material one week in advance. The questionnaire was used as a semi-structured interview guideline during the meeting itself. The WITI test (“Why is that important”) and the learnings from the initial issue raising were used to stimulate more ideas (Keeney, 1994;

Siebert, et al., 2020). After the interviews, the transcripts were consolidated, and the summary of objectives that were discussed was sent back to the interviewees individually for confirming the understanding. In a third step, the project team members were asked to raise issues, e.g., values, uncertainties, or attributes affecting the desirability of an asset, online and anonymously using the questionnaire mentioned above. In the end, 213 objectives-related issues were raised and processed.

In general, structuring these issues can be approached either top-down, i.e., focused on exploring and understanding dimensions of fundamental objectives, or bottom-up, i.e., led by characteristics of alternatives (Buede, 1986; Von Winterfeldt & Edwards, 1986). For a detailed review of problem structuring methods applied to value trees, see Franco & Montibeller (2010), who discuss the two mentioned approaches (Buede, 1986; Von Winterfeldt & Edwards, 1986), means-end networks (Keeney, 1996) as well as cognitive mapping (Eden, 1988) and more (Franco & Montibeller, 2010b). However, there is no single best solution or method for structuring an objective hierarchy. The facilitator needs to know a number of them and how to combine them effectively (Belton, et al., 1997).

Using a combination of these methods, all aspects from the interviews and the issue raising were sorted into a structure. This structure describes an objectives hierarchy (Keeney & Raiffa, 1993), also called a value tree (Von Winterfeldt & Edwards, 1986), with the fundamental objectives on top. Subject matter experts helped to clarify links between different aspects. Following best practices for structuring multiple objectives presented by Parnell, et al. (2013), the objectives were described using terms from the client's domain and formulated with verbs and objects (Parnell, et al., 2013). Finally, the final set of objectives was discussed with the whole group of decision-makers. In the past, several of these objectives had not been discussed explicitly in making early-development decisions, even though they emerged from the interviews. The reason was a previous lack of context, forum, or structure for the discussion

and consideration of these objectives. Facilitating this discussion thus led to the decision-makers aligning on the following set of objectives:

- Increase benefit to the patient
- Increase level of innovation
- Increase market attractiveness
- Reduce economic cost to society
- Utilize operational and scientific expertise
- Increase development success

In the following description and decomposition of each of the objectives, relevant literature references are added for further information and background. The assets should contribute to increasing the benefit to patients by meeting the future unmet medical need. The objective "Increase benefit to the patient" is determined by the potential impact on mortality, the reduction of the disease-related burden, treatment-related burden, and impact from side effects. (Bunnage, 2011; Plenge, 2016; Morgan, et al., 2018; Vennemann, et al., 2019; Angelis, et al., 2020a; Angelis, et al., 2020b) Reduce mortality and disease-related burden is determined by the relative risk reduction, the physical health and impairments, the mental health and psychological burden as well as the social health, i.e., disruption of social life. Reduce treatment-related burden is determined by the frequency of administration, invasiveness of administration, and duration of administration. Reduce side effects is determined by the reduction of severity and frequency of side effects as a result of the treatment.

Increasing the level of innovation is broadly discussed in the literature and also acknowledged by the decision-makers at Bayer Pharmaceuticals as one key value driver (Steven, 2002; Bode-Greuel & Nickisch, 2008; Plenge, 2016; Lakdawalla, et al., 2018; Angelis, et al., 2020a; Angelis, et al., 2020b). Hence, the assets should have a high level of novelty. The objective

“Increase level of innovation” is determined by the absolute size of the innovation steps relative to the market regarding the modality and the mechanism of action. The level of innovation of the considered modality can be determined by comparing the modality to benchmark projects ranging from small molecule applications to cell and gene therapies. The mechanism of action is assessed with regard to competitors working on this mechanism and those who are likely to spend the most money on this mechanism in the next few years.

The objective “Increase market attractiveness” is described by the potential market size and the competitive advantage. Regulatory incentives can provide an additional boost to a project. (Tiggemann, et al., 1998; Bode-Greuel & Nickisch, 2008; Cook, et al., 2014; Morgan, et al., 2018) The market size is assessed by the target population sizes and the corresponding price levels of the indication in the market. Regulatory incentives to deal with health inequality can further increase the market attractiveness. Hence, assets improve when serving a rare or orphan disease, protecting against pandemics and epidemics, and serving as medical threat countermeasures. The competitive advantage of an asset is determined by existing commercial capabilities and the time to market required relative to the competition. Furthermore, Bayer’s strength in terms of the potential competitive barrier built is assessed, and existing competitors’ barriers need to be considered. Finally, the competitive intensity is measured in terms of the number of players.

The assets should contribute to society. The objective “Reduce economic cost to society” is determined by the potential impact on societal costs in terms of the impact on the labor pool and the expenditures for the healthcare system. (Vennemann, et al., 2019; Angelis, et al., 2020a; Angelis, et al., 2020b) The impact on the labor pool is determined by the average age of the population and comparable project impacts. Expenditures for the healthcare system are determined by the main cost drivers of the future standard of care for the healthcare system.

The assets should be pursued efficiently. The objective “Utilize operational and scientific expertise” is determined by the use of existing operational expertise and internal and external scientific expertise. (Tiggemann, et al., 1998; Stonebraker, 2002; Bunnage, 2011) Operational expertise questions whether the expertise comes from whole teams and historic projects, existing related capabilities, or only a few individuals. Internal scientific expertise is determined by expertise in terms of preclinical, translational, and clinical knowledge and whether there is an active network established. External scientific expertise is determined by the access to other sources of knowledge and how tightly they can be bound to the company.

The assets should have a high probability of development success. The objective “Increase development success” is determined for an asset by the probability of success for crossing the next decision point and the degree of uncertainty reduction for late-phase outcomes. (Tiggemann, et al., 1998; Bode-Greuel & Nickisch, 2008; Bunnage, 2011) Reduce uncertainty for late-phase outcomes [de-risk] is determined by the applicability of PD-markers and PD/PK models to reduce next phase uncertainty.

Overall, the combination of collecting objectives by facilitating both interviews with decision-makers and an issue-raising session with the project team was very valuable. The interviews with the decision-makers were indispensable to understand their strategic beliefs and preferences while the issue raising helped operationalize them. The interviewers were able to guide the discussion during the interviews to identify high-level objectives and ensure the preferential independence of the objectives. In comparison, the issue-raising, which was explorative by definition, helped identify less-abstract means-objectives. The challenge was to find the right balance between high-level strategic objectives and concrete operational objectives. However, linking the corporate fundamental objectives with these means-objectives established a clear communication and a common understanding. Understanding and filling the gaps of these links in more detail also led to more objectives. Hence, this list of fundamental

objectives can provide a starting point for other pharmaceutical companies to reflect on their own fundamental objectives. The combination of different methods, i.e., anonymous issue-raising, individual interviews, and literature review, as well as relying on people from the company with different functions delivered enormous value by providing a comprehensive perspective. This also contributed to getting buy-in to the methodology in anticipation of implementation for regular use of the approach.

3.3. Defining alternatives

The initial starting point at Bayer was a list of early-development assets. The drug candidates under consideration came from diverse disease areas and were at different phases of the development process. The assets ranged from early to mid-stage, e.g., from assets like an antibody in immuno-oncology in phase 1, to phase 2 assets in such different areas as cardiology or women's health. Considering the purpose of the process, i.e., the allocation of resources, the list of assets was presented with each of two options: to further invest in that asset or not. However, additional value could be created by providing more options for each asset, with alternative plans for how to develop the drug candidate with more or fewer resources. For example, development time can be shortened if additional resources are used to recruit patients in multiple facilities in parallel. In contrast, removing an additional experimental study from the development plan of the drug candidate could lead to a reduction of resources needed. Hence, decision-makers would be provided with more options to allocate resources across the portfolio. A shortage of alternative options is a challenge that many pharmaceutical companies face. Using objectives as prompts has proven valuable to strengthen the ability to create more and better alternatives to address this problem (Siebert & Keeney, 2015; Siebert, 2016). Providing a clear and transparent guideline on objectives to be achieved by the assets, researchers and scientific support staff can come up with more targeted asset development options, increasing the value of the portfolio. When discussing the objectives and alternatives

at Bayer Pharmaceuticals, there was spontaneous recognition from decision-makers that the fundamental objectives should also form a basis for the search for business development opportunities, i.e., looking for alternative assets to add to the portfolio. Hence, the open discussion and reflection on corporate objectives stimulated new ideas and ways to get better assets into the portfolio.

3.4. Measuring the achievement of objectives

The evaluation needs to decompose and break down the objectives into measurable criteria and requires the development of scales. The decomposition has been supported by a literature review and interviews with subject matter experts. In the following example, the scale "Degree of innovation of modalities" is described. This scale, one of the few with only three steps, differentiates assets based on their modality. The lower end describes a "Technology not differentiated from those already in the market, not indication-specific (e.g., Small Molecule, monoclonal Antibody)". The upper end describes a "Pioneering technology with obstacles to overcome (e.g., gene therapy, cell therapy)". The step in between describes a "Technology used in a highly differentiated way using new routes, potentially individually tailored (e.g., selection biomarker, dependence on companion diagnostics)". Detailed descriptions and examples enabled the assessor to evaluate the drug candidate individually. However, not all scales were that self-explanatory and easy to assess. One of the scales that provided more challenges assessed the fundamental objective "Increase benefit to the patient" (see Figure 2). This scale combined assessments of, e.g., the reduction of disease-related burden and the increase in survival benefit.

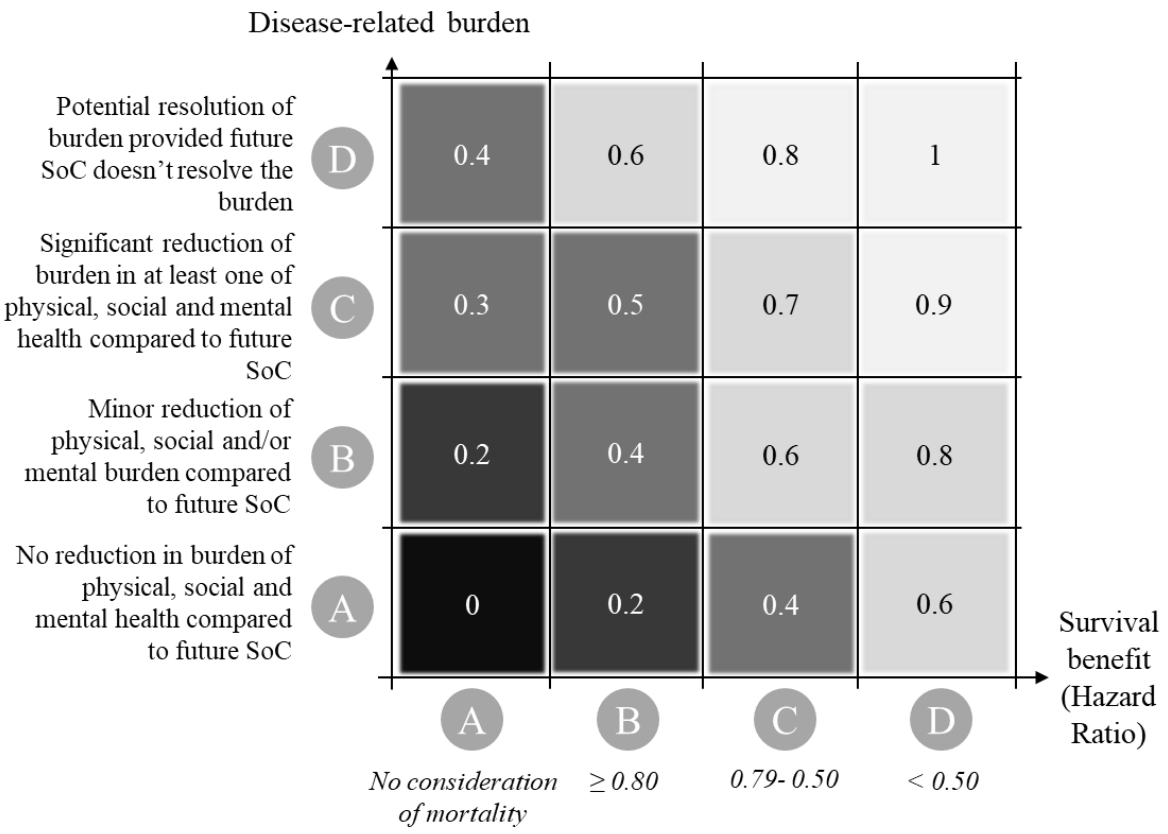

Figure 2: Combined scale to measure the reduction of mortality and disease-related burden with illustrative values due to confidentiality.

The lower bound was defined as an asset that does not provide any reduction in the burden of physical, social, and mental health or a reduction of mortality as measured by the Hazard Ratio. The upper bound was defined as an asset that provides a potential resolution of the disease burden and a mortality reduction of more than 50 %. The difficulty of this particular objective was two-fold. First, the value of an asset must always be assessed by the extent to which it reduces an unmet medical need. A simple assessment of the unmet medical need would not allow for distinguishing assets in the same indication. Second, the reduction of the unmet medical need must always be based on the future standard of care. Hence, the assessment has to consider the severeness of the disease, the future standard of care by the time the asset is launched, and the potential to reduce the remaining mortality and disease-related burden by the asset itself. The same difficulties were encountered with other scales such as the reduction of side effects. To have it describe a value on its own, independent of other scales like the disease-

related burden, it must measure the degree to which it provides an individual benefit to the patient, i.e., a reduction of the patient's burden. This provides an independent value even if assessments might be correlated, e.g., the smaller the addressable disease-related burden, the less likely it is to have significant treatment side effects that could be reduced. Combined scales helped ensure preference independence in such complex assessments (Marsh, et al., 2016).

It must be recognized that it is very challenging for different asset teams to consistently evaluate a wide range of assets in different indications based only on scales and descriptions. There must be a common understanding of methodological requirements, e.g., independence concepts, and coordinated communication between asset teams. Hence, a system of fundamental objectives champions was installed. For every fundamental objective, one person with relevant scientific knowledge and experience was nominated who served as both a consultant and a referee to the assessors. The champion would support the assessors with their assessments, answer remaining questions, describe the scales in more detail, and provide feedback on the difficulties. Furthermore, the champion would ensure a consistent evaluation of the various assets against the objective and challenge any remaining biases so that the scales worked properly. Especially when using ordinal scale metrics as interval scale metrics, there is a risk for biases when the scores are at the boundaries of the steps. In addition, using the mortality scale mentioned above as an example, the hazard ratio could also be interpreted based on the estimated ratio itself and a confidence interval. However, these additional complexities were not displayed within the scale so the fundamental objective champion needed to spot and correct outliers.

3.5. Eliciting objective weights

As stated above, objective weights were elicited in a facilitated trade-off process. The trade-offs were discussed with the seven decision-makers individually. Due to the difficulties and

challenges of trade-offs, the interviews were guided by two or even three decision analysis experts in 60-minute sessions. One interviewer always led the discussion while another expert used an online decision support tool developed by RWTH Aachen University in Germany, the Entscheidungsnavi (www.entscheidungsnavi.com), to display the scales and all implied trade-offs of the statements of indifference to the decision-maker (Von Nitzsch, et al., 2020). The Entscheidungsnavi, or decision navigator, provides different graphical presentations and can display the implications of a statement of indifference on different sets of assets and has proven valuable in recent applications (Höfer, et al., 2020). This helped create realistic examples and improve the decision maker's understanding of the logic (for a detailed description and graphical illustration, please see von Nitzsch et al., 2020). Using this approach, all decision-makers were able to follow the logic and express their preference through the trade-offs. Further, the discussion became more efficient with every statement of indifference so that all interviews with all five trade-offs could be finished within 60 minutes.

The definition of the scales was of utmost importance for the trade-off discussions. Only if the scales are detailed enough and described such that decision-makers can easily come up with realistic example assets for every step is the trade-off discussion doable. In other words, the decision-makers must be able to meaningfully describe what they would be willing to sacrifice in one objective to increase the achievements in another. To support the decision-maker in reflecting on these trade-offs, the interviewer must be experienced in decision analysis techniques. Furthermore, the interviewer must possess extensive industry knowledge and ideally knowledge of the company's historical and current assets to help the decision-maker identify the right assets for the trade-offs. For example, one decision-maker described two assets with different evaluations in two objectives. The decision-maker stated indifference between these two assets. Considering the pre-defined scales the evaluation of the two assets yielded assessments in "innovation" and "market attractiveness" of 0.8 and 0.4 for one asset

and 0.6 and 0.6 for the other asset. Hence, the objectives were to be equally weighted. To ensure that the trade-off is meaningful and realistic, the interviewer had to support the decision-maker with more examples of assets that would be equally valuable to the decision-maker based on this statement. The Entscheidungsnavi supported this need by graphically displaying the characteristics of the assets in terms of fulfillment of the objectives. It was important for the decision-makers to see these. Multiple decision-makers expressed that the exercise made them aware of their preferences. The combination of industry knowledge and a decision support tool that can graphically display the implications of trade-offs has proven very valuable to ensure that the decision maker's preferences are correctly reflected in the decisions. Hence, detailed scales based on deep reflection are indispensable. Furthermore, the visualization and the feedback discussion were critical for the acceptance of the results with a view to the long-term and regular use of the methodology.

3.6. Aligning on objective weights

Having worked out the individual objective weights of the different decision-makers, the challenge was still to align on a single set of objective weights as a company. In an MCDM process, consensus on objective weights is not a necessity. If the ranking of alternatives does not change with different weights, aligned decisions can still be made. However, there was an explicit desire to have agreed objectives weights. These could be communicated to the organization to make the prioritization of assets tangible and help asset teams shape asset development plans in line with portfolio strategy. There are two ways to reach consensus: behavioral approaches that require group interaction and mathematical combination methods. We chose a group interaction and applied what can best be described as a variation of the Nominal Group Technique (Delbecq, et al., 1975). Compared to methods like Delphi, which are anonymous, the open interaction between decision-makers was actively desired. Once all

sets of objective weights were collected individually, the decision-makers each received feedback on the result. See Figure 3 for an illustrative example.

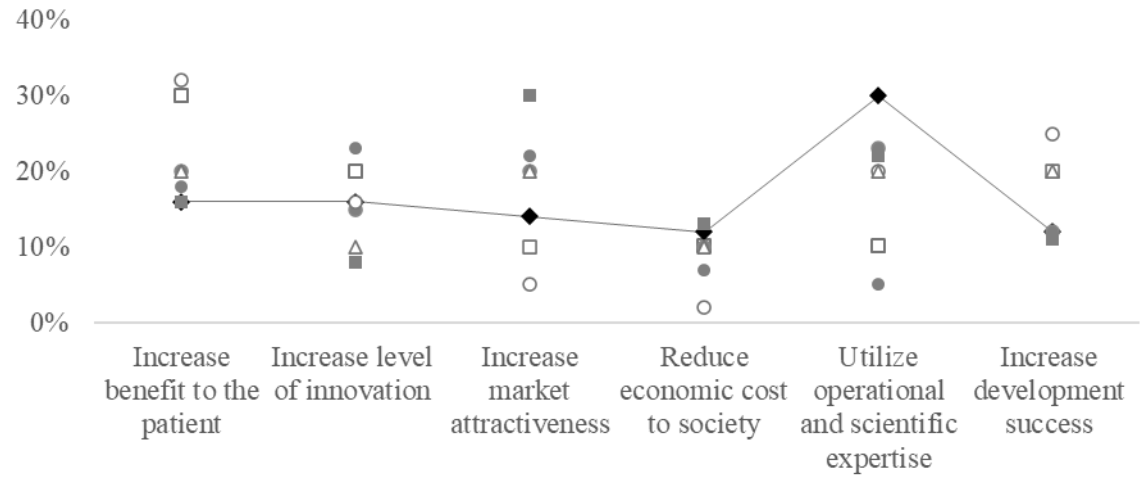

Figure 3: Illustrative output of individual trade-off discussions as fed back to decision-makers. Black diamonds represent an individual's weights as compared to the group.

Each decision-maker was informed in advance about the extent to which their individual preferences deviated from others in the group. Hence, the decision-makers could prepare before the open discussion and reflect on the reasons for their deviation. In the following group discussion, all objective weights of the different decision-makers were shared to create transparency within the group. This transparency made it easier to have open discussions, e.g., about how much they were willing to sacrifice the traditional desire to have high chances of success to be able to work on more differentiated products that have a greater benefit to patients and society. These trade-offs had not been openly discussed in the past. The discussion of the reasons behind diverging preferences helped clarify a common understanding of the corporate strategy. Although there were multiple decision-makers, there was a common desire to agree on what is best for Bayer Pharmaceuticals. This was clearly stated at the beginning of the process, referring again the original decision statement. Overall, we experienced a collective desire to cooperate within the group. Hearing and understanding reasons for deviating objective weights helped to break down even the strongest initial reservations. In particular, openly

agreeing that innovation often contrasts with development success, but that innovation still is an important strategic preference, increased the overall commitment to the set of preferences. In the end, the decision-makers jointly agreed to a common set of objective weights.

3.7. Assessing the early-stage assets

All assets in the entire early-stage portfolio were assessed by the respective project teams using the scales decomposing the fundamental objectives. MCDM's good practice is to check the consistency of the analysis, e.g., consistency in how assets are evaluated and scales are interpreted (Marsh, et al., 2016). To this end, the established system of fundamental objective champions was of great value. An illustrative example of an evaluation for two drug candidates is shown in Figure 4, which shows the relative strengths and weaknesses of the assessed assets with value contribution by fundamental objective.

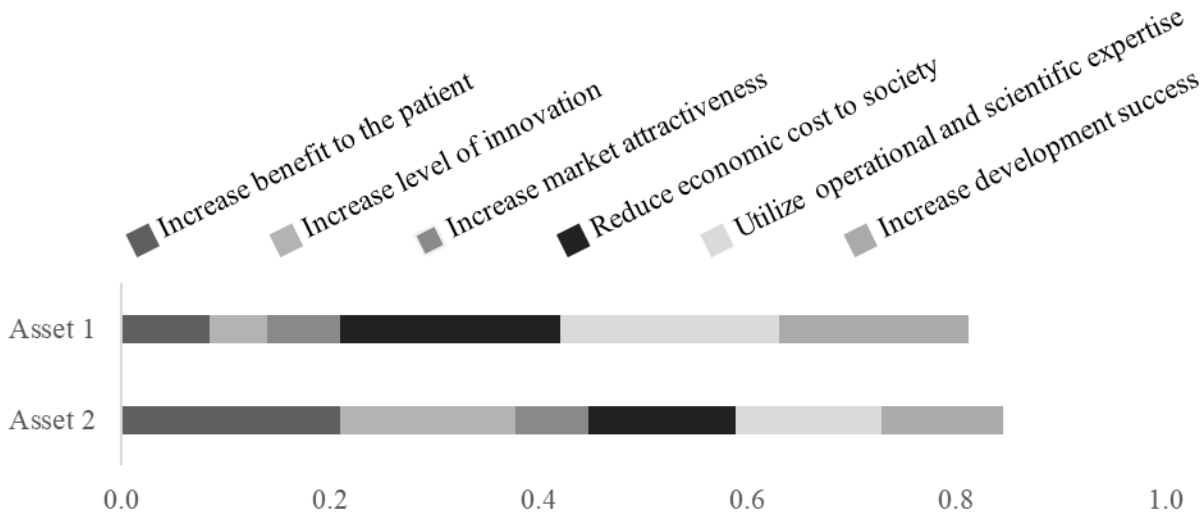

Figure 4: Illustrative evaluation of two drug candidates and their aggregated values.

Angelis et al. already concluded that there is a trade-off between the availability of data and the ability to drive and inform drug development decisions (Angelis, et al., 2020b). Interestingly, this challenge did not come up and there was little discussion around the individual evaluation of the different assets. These discussions had all happened when creating

the scales. We experienced that having discussions on the scales early in the process resolves later discussions on individual asset evaluations to a great extent. The asset teams, as a result, were genuinely trying to do their best to be objective. They understood that the challenge was to be consistent across assets. Furthermore, the thorough reflection of the scales and the communication between the teams as facilitated by the fundamental objective champion enabled efficient assessments. Each asset assessment required about 1-1.5 hours of discussion, granted with some preparation from the project leader and their team.

3.8. Impact of integrating the decision process

The decision-makers had aligned to a set of fundamental objectives and their weights. Hence, the drug candidates were easily rank ordered and the strengths and weaknesses of the assets could be discussed. In Figure 5, illustrative outputs are presented showing how individual drug candidates in the portfolio performed against two objectives at a time. These types of depictions helped to facilitate understanding of the source of value in the discussions.

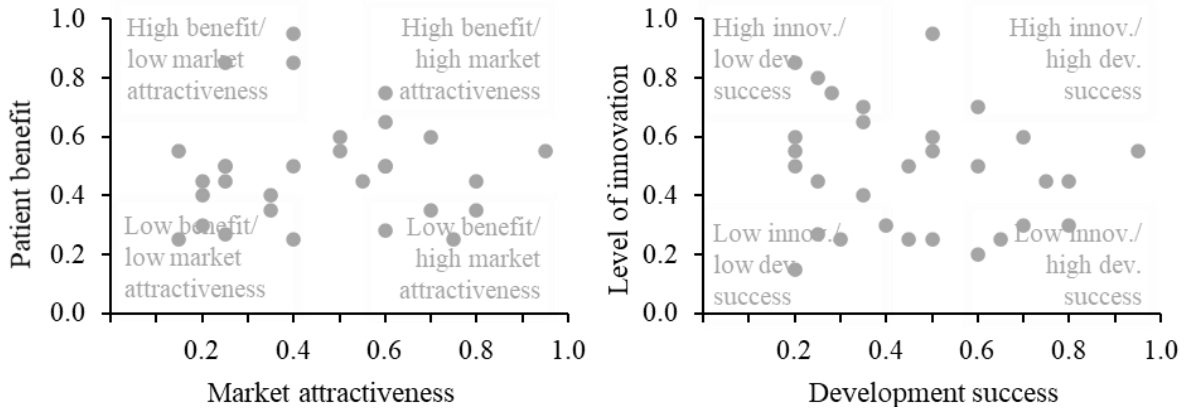

Figure 5: Illustrative example of outputs derived from the MCDM evaluation of individual drug candidates.

Ultimately, resources were allocated across the different early assets, prioritizing the most valuable and eliminating less-valuable projects. A shift toward more innovation became immediately evident. The objective to increase innovation was now clearly communicated and operationalized from a high-level fundamental objective down to specific means-objectives

such as focusing on new modalities and new mechanisms of action. Doing this required a reflection on scales to understand what innovation for an early-development asset means and how to distinguish levels of innovation. The value of innovation could be measured and a structure and a forum for making the necessary trade-offs was established. Hence, choosing an innovative asset over another could now be justified and led back directly to corporate values.

4. Discussion, limitations, and conclusions

When dealing with long-term decisions with high uncertainty about potential outcomes such as early-stage pharmaceutical decisions, a clear process and structure are needed as a guideline for efficient high-quality decision-making. In contrast to established methodologies from the literature on pharmaceutical development decisions, the work presented here demonstrates that this guideline can come from the reflection on and communication of the business's fundamental objectives. Instead of being led by data that happen to be available on the technical determinants of an asset, the evaluation of an asset should be driven by the objectives that truly matter. Especially when outcomes are uncertain, data is ambiguous, and the asset itself is not fully characterized, transparency can be created by starting with a clear picture of what is to be achieved. Decision-makers can then discuss fundamental objectives and their individual preferences so that they align to a strategy. Once that strategy, i.e., the guidance for prioritization, is fully communicated throughout the company, the evaluation of assets becomes a question of scientific rigor and consistent assumptions that, in the end, define the outcome of the strategy. Consequently, decision-makers decide based on a set of fundamental objectives that they believe to be the company's value drivers rather than based on a methodology they distrust. This creates transparency and now, as we have seen in this concrete example, supports innovation in early-stage pharmaceutical decisions by increasing its relative weight when making decisions.

Further conclusions can be drawn from this practical application. The efficiency of the decision-making process can be improved by separating discussions about scientific expectations from strategic discussions about preferences and objectives. When assets are assessed across pre-defined scales by expert teams, the separate decision discussions become very focused on objective weights. Displaying the impacts of certain objective weights on the ranking of assets in the portfolio can then uncover motivational biases. Sharing the individual preferences of decision-makers about the objectives transparently creates a mutual understanding and facilitates decision-focused discussions. In other words, by understanding the different viewpoints, decisions can be made in the interest of the company. We observed the benefit of using the Entscheidungsnavi as a decision support tool. Future research needs to investigate how decision support tools enhance the process of communication with the whole company even more.

As a concluding consideration from this application, the limitations related to methodological choices need to be addressed. We need to acknowledge the fact that more interventions are needed to generalize our conclusions and to understand whether the limitations have different or more significant implications for other applications. For example, there were at least two obvious concepts to consider in applying MCDM methodology: multi-attribute value theory referring to riskless decisions and multi-attribute utility theory for decisions with uncertain outcomes (Dyer & Sarin, 1979; Keeney & Raiffa, 1993). The initial intent was to apply utility theory because of the large number of uncertainties in early development. Utility theory would require, e.g., the assessment of drug candidates for different scenarios describing the future market landscape and competitor developments as well as the technical success of the asset's development. Also, the likelihoods for these scenarios would need to be assessed and utility functions elicited describing the risk attitude of the decision-makers about different objectives. However, the application in practice needed a more pragmatic approach. To begin with, the

time and effort required to conduct multiple assessments for drug candidates and to identify and align the decision makers' utility functions for different objectives were not feasible. In addition, the approach was perceived as too academic and opaque because an assessor cannot see the results of an evaluation based on the scale but only after an additional manipulation through the decision-makers' utility function. Furthermore, with regard to the quality of a decision, the assumptions on common utility functions are often not the limiting factor, but rather the quality of information used for assessing alternatives across the objectives (Keeney & Von Winterfeldt, 2007). Consequently, the choice was made to structure the decision as a riskless choice, i.e., a decision with certain outcomes. The decision is about exploring innovative technologies, targeting the right indications and markets, addressing societal needs, and working effectively on drug candidates that provide clinical evidence. The outcome of this decision is not uncertain, it is determined by the characteristics of the assets that are chosen. This workaround might be a limitation of the approach, but it enabled the decision-makers to quickly grasp the criteria they deem relevant to their decision. In this respect, the combination of methods is understood as "a theory informed approach" (Ackermann, et al., 2014).

Irrespective of uncertainty, there are parameters in the value model that can be varied and the impact on the decision investigated. For example, a slight variation in the preference weights, which determine how much value of one objective can be offset by a different one, can have a significant impact on the decision. Although the group of decision-makers agreed on a single set of weights, the effects of applying each individual's set of weights were examined. Performing a sensitivity analysis to determine how much the value of an asset changes when a different set of weights is applied served as a robustness check. In addition, assets that ranked highly regardless of the weighting of the group members could be allocated resources with confidence. A similar analysis for different parameters of the model can be performed to create more insights. However, within the time of the project, a full probabilistic sensitivity analysis

was not conducted. Nevertheless, we recommend conducting a sensitivity analysis to ensure the robustness of all modeling steps. See, for example, Montibeller et al. who provide a guide to simulating the impact of various potential modeling concerns in prioritizing health threats (Montibeller, et al., 2020).

A different limitation stems from the set of fundamental objectives and scales. Acknowledging that risk-related objectives are difficult to include in MCDM, the objective "Increase development success" was still considered (Parnell & Miller, 2016). In an ideal expected utility based MCDM approach, the development success would be modeled probabilistically, reflecting assessments of the drug candidate for all different development outcomes. However, in addition to the already discussed reservations, there was a desire to include development success explicitly as a fundamental objective. Choosing this structure indicates that development success, i.e., developing the current drug candidates in the R&D pipeline to products, is part of a set of six different fundamental objectives with a relative priority that can easily be communicated. Thus, with regard to concepts of preferential independence, the value of, for example, the degree of innovation to the company should not depend on whether an asset is successfully developed and commercialized. The value should come from the innovation that is explored by developing the asset to learn about technologies for future applications. This thinking reduced the focus on uncertain development outcomes that led to incremental development steps in the past and paved a path to true innovation. Further, we agree with Ralph Keeney and Detlof von Winterfeldt (2007) that with a reasonable set of fundamental objectives an additive model can be the right choice for practical applications and could even incorporate pieces that are not truly additive. Objectives can be included in this way as long as the decision-maker understands the reason (Keeney & Von Winterfeldt, 2007). Besides the objective of increasing development success, some scales could raise questions as well such as the separate assessments of disease-related burden and side effects. For example,

for diseases with high unmet medical need and severe disease-related burden, patients might be willing to accept a different level of side effects than patients with less severe disease. Therefore, the scale developed for the evaluation of side effects was used to assess the relative impact on the expected standard of care. Thus, it was examined whether the burden for the patient improved or worsened compared to the expected standard of care, with some gradations. If treatment was associated with headache, this might be perceived as a worse burden when treating a skin rash compared with a cortisone crème, but not when treating cancer with chemotherapy. However, it must be acknowledged that there are more methods of measuring side effects and different opinions on how to evaluate different gradations of side effects across indications. For example, side effects could also be assessed separately by indication based on independent benchmarks such as the common terminology criteria for adverse events (U.S. Department of Health and Human Services, 2017).

The understanding and endorsement of decision-makers describe another constraint or condition for the use of this approach. This approach requires top-down portfolio management, i.e., decision-makers must proactively provide guidance. Therefore, the objectives must reflect the decision-makers' beliefs about the company's value drivers and reflect their preferences for objectives weights. With changing personnel in leadership positions, continually reviewing the framework and ensuring that the model still reflects the current beliefs of the decision-makers is a must. Further, the longer the system is in place, the more asset teams will try to structure their asset development to achieve a high score in the framework. While this is often a benefit of the approach if teams make their decisions in line with the decision maker’s guidance, it can also lead to distortions. Asset teams might overvalue their assets to make them appear more attractive, or focus too much on defending and discussing weak scores that are not as important from a strategic perspective. In either case, fundamental objective champions need to take

ownership of the process. They need to lead the discussion and be accountable for applying debiasing measures and ensuring the buy-in and endorsement of the decision-makers.

Acknowledging these limitations, the approach is useful for several reasons. On the one hand, the approach enables holistically exploiting and sharing and distributing the knowledge across the company. On the other hand, it allows for creating value by efficiently linking strategic corporate objectives with operational aspects. Reflecting on corporate objectives and developing scales to measure what is fundamentally important to the company will allow companies to overcome a low-innovation bias inherent in long-term decisions based on cash-flow models. This study showed that reflecting on and identifying the value-drivers of a company enable concrete trade-offs on the level of fundamental objectives so that the corporate strategy can be aligned, communicated, and implemented.

The observed alignment and efficiency of the process are attributed to the clarity of the decision-making back end and the transparency and reflection of the decision frontend, i.e., value-focused thinking. However, the clarity and transparency were also a result of the enormous effort put into the communication of the approach and the breadth of people involved from various corporate functions. The development of the scales to measure the fundamental objectives, for example, was facilitated by a sequence of individual meetings with expert teams across the company. Furthermore, the methodology was explained to the asset teams in various disease areas to support their assessments. Hence, to ensure that the process leads to the described positive outcomes, the importance of communication and of involving a diverse set of people from asset teams to decision-makers cannot be overstated.

In summary, in decision situations of high uncertainty, reflecting on the fundamental objectives of the business can create the transparency and clarity needed to commit confidently to long-term innovation. Therefore, we encourage practitioners to apply Decision Analysis methods

and researchers to further develop methods customized for the needs of the pharma industry. Bayer Pharmaceuticals supports this approach as its future way of making early-development portfolio decisions. In the end, the attention to fundamental objectives will sustainably affect decision-making, leading to higher quality decisions in a more efficient process. In the same way, clarity on objectives can be used to guide decisions in other pharmaceutical companies as well.

Appendix

The questionnaire we used

The wish list:

What is in the best interest of Bayer in developing the portfolio?

What do you believe is the desired outcome for Bayer in portfolio decision-making?

When do you believe the company should be satisfied?

What would be your wish for Bayer's portfolio from a wizard?

Current status:

What disturbs you when you consider the current status of the portfolio?

What aspects of competitors' portfolio decision-making are better than yours?

General values:

What values do you consider to be important for Bayer that could be relevant in this decision situation?

Which philosophy and vision does Bayer have that should be reflected in portfolio decision-making?

What attitude would you like to see from the project owners?

External requirements:

What kind of commitments does the company have to external stakeholders?

What kind of responsibilities does the company have to society?

The comparison of alternatives:

In which aspects do the early-phase development projects differ from each other?

Which criteria are fulfilled by a perfect early-phase development project?

How does the current early-phase portfolio differ from the perfect portfolio?

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