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Innovation and Marketing in the Pharmaceutical Industry

Emerging Practices, Research, and Policies

Chapter 3
Portfolio Management in New Drug Development

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Abstract The pharmaceutical industry leads all industries in terms of R&D spend. Portfolio management in new drug development is extremely challenging due to long drug development cycles and high probabilities of failure. In 2010, a pharmaceutical company like GlaxoSmithKline (GSK) spent over USD 6 billion in R&D expenditure and managed a total of 147 R&D projects across 13 therapeutic areas in different stages of development. There are a lot of challenges in deciding on how to allocate resources to these projects in order to achieve the maximum returns. For example, how to evaluate the value and risk of each project, how to choose new projects for both short-term cash flow and long-term development, how to decide which projects to prioritize and which projects to remove from the portfolio, how to design drug development unit and incentive schemes to maximize the likelihood of success, and so forth.

This chapter reviews both practice and the state-of-the-art research and summarizes the latest insights from both industry and academia. For a manager, it provides a guide to the tools they need in portfolio management in the new drug development context. For an academic, it provides a quick overview of the extant research and points out some promising research directions.

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3.1 Introduction

The pharmaceutical industry stands among a very select set of industries tasked with the dual objectives of improving human health and creating shareholder value, while being under a tight global regulatory microscope. The combination of finite patent shelf life of existing drugs, long drug development cycles of 4–16 years (Rodriguez 1998), high probabilities of failure at every stage of development (Blau et al. 2004), the escalating costs of developing and launching drugs (Munos 2009; DiMasi and Grabowski 2007), and the gargantuan postlaunch market risks (one example being the withdrawal of Vioxx®) make for a volatile landscape that pharmaceutical firms have to navigate. While all of these conditions seem on face value to be deterrents to R&D spending, pharmaceutical firms have in fact continued to invest heavily in new drug development and lead all industries in terms of collective R&D spend (Jaruzelski et al. 2011).

Munos (2009) reports that the number of new molecular entities[1] (NMEs) approved by the US Food and Drug Administration (FDA) since the 1950s has not increased commensurate with the amount of R&D spend. Part of the reason is rising costs of obtaining regulatory approval. DiMasi and Grabowski (2007) estimate that cost of developing an NME (up to approval for marketing) is about $1.3 billion (in 2005 US dollars) when factoring in cash outlays, cost of time, and capitalizing failures, while the cost of biologic drugs is only marginally lower at $1.2 billion. Garnier (2008) acknowledges that the R&D productivity has declined as a result of increasing costs and lack of improvement in output rates, possibly due to the fact that drugs that are "easy to develop" have already been invented, leaving the industry with greater challenges to continually produce a sequence of blockbusters.

There is a broad consensus among pharmaceutical firms that successful portfolio (i.e., "a collection of projects") management of new drug projects is a necessary condition for long-term survival (Munos 2009). The strategic choices for a pharmaceutical firm are to either be a low-cost generics provider or keep generating blockbusters from a portfolio of projects that provide the cash flows to support further R&D investment. Those firms which run out of cash get acquired by firms with deeper pockets, leading to cyclical waves of merger and acquisition activity (DiMasi 2000).

It is estimated that the pharmaceutical industry will lose $90 billion in branded sales over the 2010–2014, a prime example being Lipitor®, the most profitable prescription drug in history, which went off patent in November 2011 (IMAP 2011). Pfizer, which markets Lipitor®, loses a $11 billion annual revenue stream which accounted for about a sixth of its 2010 revenues. Thus, the stakes are high for firms in maneuvering to successfully replace lost revenues with new drugs coming from the R&D portfolio. Pharmaceutical firms are increasing investments in R&D portfolios in lieu of this "patent cliff," evidenced by the growth in the number of new drugs

[1] A new molecular entity (NME) is a medication containing an active pharmaceutical ingredient (API) that has not previously been approved for marketing in any form (Munos 2009). This usually excludes biologic drugs.

under development from 5,995 compounds in 2000 to 9,737 compounds in 2010, an increase of 62 % despite turbulent economic conditions (PharmaProjects 2010).

No shortage of ideas and opinions exist given the scale and stakes of new drug development on how portfolio management should be done (Garnier 2008, etc). However, some of these ideas are beliefs and experiments-in-progress. In this chapter, we present findings of multidisciplinary research on portfolio management in relation to key managerial questions. We believe, upon sifting through the research, that many important managerial questions remain open for new research (as also noted by Stremersch and Van Dyck 2009). Our goal in this chapter is to offer industry practitioners current state-of-the-art know-how that can add to portfolio management practice, and to stimulate researchers to explore topics requiring greater attention.

With the goal of having a self-contained introduction, we organize the chapter as follows. The remainder of this section will provide definitions of portfolio management and how we categorize managerial issues, review relevant facts about the pharmaceutical industry and current portfolio management practices, and close with a summary of what has been explored in the academic literature to date. We then probe deeper into specific managerial issues within portfolio management, detail the key research papers that provide useful perspectives, and summarize the insights that practitioners can take away from research. Finally, we conclude with open questions ripe for further research.

3.1.1 *Definitions and Categorization*

Portfolio management is at the heart of mapping an organization's innovation strategy to the objective and balanced selection of programs and projects to maximize portfolio value to the organization. We focus on portfolio management methods relevant to the pharmaceutical industry, drawing from both industry-specific and general literature on this subject.

Cooper et al. (1998) define portfolio management as a dynamic decision process which facilitates the evaluation, selection, and prioritization of new projects, and the acceleration, discontinuation, or deprioritization of existing projects in the presence of uncertainty, changing external dynamics and strategic considerations. This definition applies well to the ethical drug industry for which R&D portfolio management holds the key to future survival as existing drugs lose patent rights and market exclusivity.

A typical pharmaceutical firm organizes its R&D portfolio by therapeutic category (Yeoh 1994), with each category containing various medical conditions targeted by research programs (also known as indications). Since each indication can be targeted by multiple projects/compounds,[2] R&D portfolio management in the

[2] The same compound could target multiple indications. Each compound-indication combination is a separate project that follows the pharmaceutical regulatory approval process. In other words, a compound that is approved by a body such as the FDA for one indication can only be marketed for that indication.

pharmaceutical industry requires best-in-class methods to maximize value creation for stakeholders ranging from shareowners to patients.

Portfolio management can be generally classified into two areas: portfolio evaluation and portfolio optimization. Portfolio evaluation is the measurement of the state of a portfolio against specified metrics, such as value and risk. Portfolio optimization comprises the optimal selection of strategies available to the firm to fulfill the given objectives. In this chapter, we summarize the existing practices and research in both these areas and discuss open questions for further research. In addition, we also discuss execution issues that are often faced by firms when implementing portfolio optimization strategies, such as organizational structure and incentive design. We do not, however, focus on the specifics of managing clinical trials with multiple new drugs and refer the reader to Senn (2007) for a comprehensive summary of statistical methods in drug development.

3.1.2 *Drivers of Pharmaceutical Portfolio Management*

The pharmaceutical industry leads all industries in terms of R&D spend. Jaruzelski et al. (2011) report that four out of the top five global R&D spends and eight out of the top twenty global R&D spends are by pharmaceutical firms. Of these firms, six (Roche, Pfizer, Novartis, Merck, GlaxoSmithKline, and AstraZeneca) increased R&D spend from 2009 to 2010 (ranging from 0.3 to 53 % increase) despite volatile global economic conditions. This suggests that pharmaceutical firms continue to invest heavily in their portfolios with the top eight spending between $5 billion and $10 billion per year, translating to between 11 and 21 % of annual sales.

Two unique aspects of pharmaceutical innovation worth highlighting are the long drug development cycle times (from 4 to 16 years according to Rodriguez 1998) and high probabilities of failure at every stage of development (from Discovery through Phase III). Thus, the impact of last decade's R&D portfolio is felt today, and the impact of the current portfolio will be felt 4–16 years into the future. The reality for R&D leaders in the pharmaceutical industry is that portfolios have to be constructed and evaluated in the face of extreme uncertainty about technological capability, competitive forces, and market potential.

Research using historical data on returns and costs for pharmaceutical firms suggests that both returns (Grabowski and Vernon 1990, 1994; Grabowski et al. 2002) and costs (DiMasi et al. 1991, 2003) have increased since 1970. Additionally, research from the 1970s to 1990s consistently finds a highly skewed distribution pattern of returns and a mean industry internal rate of return (IRR) modestly in excess of the cost-of-capital. Per Grabowski et al. (2002), these findings support a model of intensive R&D-based competition by pharmaceutical firms to gain economic advantage through product innovation and differentiation.

Part of the reason for increasing costs comes from increasingly stringent regulations on clinical trials (e.g., The FDA Amendments Act 2007), such that an

Table 3.1 Number of compounds in therapeutic areas[a] as of Dec 31, 2010 (PharmaProjects 2010)

	Number of compounds	Therapeutic areas
A	1,442	Alimentary/metabolic products (including gastrointestinal group)
B	447	Blood and clotting products
C	800	Cardiovascular products
D	508	Dermatological products
F	1,548	Formulations
G	480	Genitourinary (including sex hormones)
H	166	Hormonal products (excluding sex hormones)
I	543	Immunological products
J	1,710	Anti-infective products
K	2,608	Anticancer products
M	1,093	Musculoskeletal products
N	1,936	Neurological products
P	94	Antiparasitic products
R	601	Respiratory products
S	410	Sensory products
T	2,330	Biotechnology products
Total	16,716	

[a]PharmaProjects (2010) reports a compound which targets multiple therapeutic areas in both areas, hence it should be noted that there are 9,717 total compounds under development, and 16,716 projects which may target the same compound for different diseases

investment close to $500 million may be required just for the opportunity to launch a drug (Blau et al. 2004) provided it successfully passes Phase III trials. Other factors contributing to cost increases include the advent of biotechnology and the shift towards treatments for chronic and degenerative diseases (Yeoh 1994). The investment figure can vastly vary depending on the level of data required by the FDA, which in turn depends on the nature of the innovation. For instance, the costs are dramatically higher for new chemical entities (NCEs) or NMEs which represent more "radical" innovation involving new active pharmaceutical ingredients (APIs) as compared to utilizing existing entities to formulate a new drug.

It is well known that only one in every 5,000–10,000 potential compounds investigated by pharmaceutical companies is granted FDA approval (which is a critical benchmark since the USA forms the single largest market for ethical drugs sales). Thus, portfolios of pharmaceutical firms usually include compounds in diversified therapeutic categories to spread the risk of failure of any given research program or project. The top 25 firms have between 43 and 304 compounds in their portfolio (PharmaProjects 2010), with the largest portfolios coming from Pfizer (304 compounds), GSK (289 compounds), and Merck (249 compounds). It is typical for the top ten firms to source 30–40 % of the compounds in their portfolio from external parties (PharmaProjects 2010).

As of December 2010, there are 9,717 drug compounds corresponding to 16,716 projects under active development or launch (the same compound targeted at different diseases counts as multiple projects). These projects can be grouped into roughly

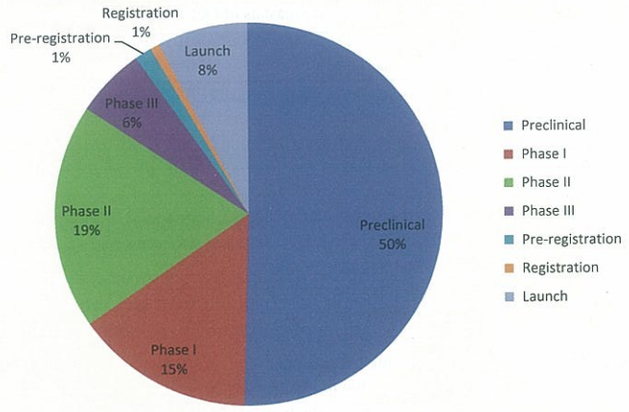

Fig. 3.1 Breakdown of drug compounds by stage of development (PharmaProjects 2010)

16 therapeutic areas/classes/groups (with differing numbers of projects in each area) as shown in Table 3.1.

About 50 % of drug compounds are in the preclinical phase, while the remainder is spread across the more advanced stages of development, as shown in Fig. 3.1.

The uncertainty of success rates by phase can be quantified using historical data. Blau et al. (2004) suggest that roughly 20 % of projects drop out after Phase I, and among the remaining projects, 80 % do not pass Phase II testing. There is no guarantee of success even in Phase III of large-scale clinical trials due to unexpected reasons that did not manifest in earlier trials. For example, from a comprehensive data base across over 200 pharmaceutical companies, Girotra et al. (2007) found 132 Phase III failures in the period 1994–2004. According to their data, a median firm (with annual sales of US$13.26 billion) experienced 6.5 Phase III failures during this time period, and one of the largest firms, Pfizer, experienced 19. Thus Phase III failures are more than infrequent anomalies and are factored into the overall capitalization of drug development costs.

3.1.3 *Pharmaceutical Industry Structure*

While our discussion thus far has spotlighted large pharmaceutical firms with a strong legacy of chemistry-based drug development, the last 2 decades have seen the advent of small research-oriented biotechnology firms that focus on a narrow range of compounds. These entrepreneurial ventures often partner with larger firms who have more access to capital and have expertise in conducting large-scale trials, under various types of legal structures (profit sharing, acquisitions, joint ventures).

Therefore, an increasing trend in larger firms is to balance self-originated and acquired compounds, leading to several waves of merger and acquisition activity in the early 1970s, late 1980s, and the mid to late 1990s (DiMasi 2000).

Acquisition activity has again picked up in the 2008–2010 period with large deals such as Pfizer's acquisition of Wyeth for $67.9 billion and the $41 billion valued merger of Merck and Schering-Plough. The trend for further acquisitions and licensing deals appears positive, spurred by low interest rates and firms' cash reserves. In particular, therapeutic areas such as oncology, central nervous system disorders, diabetes, and immunology are expected to be target areas for firms to "shop" for mid-to-late stage compounds to add to their portfolios (IMAP 2011).

As R&D productivity levels decline (Garnier 2008; Munos 2009), pharmaceutical firms are expected to pursue a combination of the following options: (1) acquisitions, (2) large horizontal mergers, (3) improve internal R&D effectiveness, and (4) increase alliance agreements (Higgins and Rodriguez 2006).

Public sector research institutions (PSRIs) such as universities, nonprofit research institutes, and hospitals constitute another type of player in the industry. Historically these institutions have focused on fundamental scientific research in drug development, though increasingly the boundary between public and private firms is becoming grey as even PSRIs file for patents to protect their intellectual property as a result of the Bayh-Dole Act of 1980 which allowed such institutes to own the intellectual property from federally funded research. Stevens et al. (2011) quantified the impact of PSRIs, stating that in the last 40 years, 153 new FDA-approved drugs, vaccines. and new indications for existing drugs were discovered from research in PSRIs. The most prolific PSRIs are the National Institutes of Health (NIH), the University of California system, and the Memorial Sloan-Kettering Cancer Center.

The NIH also plays a major role in drug development by allocating its funds across a portfolio, though it does not have the same objective as pharmaceutical firms which seek to profit from their innovation activities. Recently, the NIH has established a new center for advancing translational sciences (NIH 2012) to address bottlenecks in the drug development process, noting that drugs currently exist for only about 250 of over 4,400 conditions with defined molecular causes.

We suggest that the ensuing discussion of portfolio management applies equally well to small firms and public research institutes, though their strategies and resources may differ. In addition, while much of the discussion focuses on self-originated drug compounds, we also specifically address the topic of acquisitions and licensing of compounds.

3.1.4 *Portfolio Management Practices in the Pharmaceutical Industry*

To value portfolios, pharmaceutical firms use financial tools such as discounted cash flow (DCF) analysis or real options analysis at an individual project level. Through the course of the 1990s, pharmaceutical firms have increasing shifted

towards real options analysis (Nichols 1994), which accounts for the value of managerial flexibility in phase-by-phase decision making in drug development. To simplify the implementation of real options analysis, decision trees (Loch and Bode-Greuel 2001) are often constructed to model the choices and outcomes available, which allows for a flexible representation of risks and uncertainties.

The innovation portfolio dashboard of firms often includes metrics that indicate resource allocation/portfolio balance, process effectiveness, and performance outcomes. For instance, resource allocation can include R&D spend, human capital, distribution of projects from incremental to radical, and ratio of outside to inside sourced ideas. Process effectiveness metrics include time spent in each phase of development, and progress versus budget and target deadlines. Performance outcomes include financial measures that are only usually known after the drug is launched in the market, at which point it is managed in a business unit as opposed to research and development.

These metrics, while useful indicators of overall activity, are still at the discretion of managers who ultimately determine the appropriate portfolio management actions. Management is able to track whether strategic goals match the reality of how the portfolio is executed. Empirical evidence from Vincent et al. (2004) and Tellis et al. (2009) suggest that firm culture may be a strong driver of innovation performance. Interestingly, most of the metrics in a dashboard revolve around "hard" quantities rather than "softer" cultural descriptors.

Portfolio optimization typically involves holding a diverse portfolio of compounds and projects for large pharmaceutical firms. Bubble-chart analysis of risk versus return (Blau et al. 2004; Day 2007), strategic bucketing of various types of innovation programs (Chao and Kavadias 2008), and organizational design (Argyres and Silverman 2004) are typically used as decision levers by firms.

As an illustration, we provide a snapshot of GSK's portfolio at the end of the year 2010 in Fig. 3.2. GSK is a representative, large pharmaceutical firm with over $6 billion in R&D expenditure in 2010, translating to about 14 % of sales. From Fig. 3.2, a total of 147 projects across 13 therapeutic areas are spread across different stages of development.[3]

GSK has 34 projects in Phase I, 56 projects in Phase II, 36 projects in Phase III, 10 projects under application for approval, and 11 projects approved for launch. This totals tens of billions of dollars in investment over several years in GSK's R&D portfolio. Such a portfolio is representative of several other large pharmaceutical firms, such as Pfizer (Fig. 3.3).

To find new ways to boost R&D productivity, GSK has continually explored new organizational structures to facilitate new drug development. In 2001, GSK reorganized its new product development units into Centers of Excellence for Drug

[3]Note that pharmaceutical companies typically report their projects starting from Phase I and do not provide details about preclinical/discovery projects, since these are still in the early stage of development. This is the reason for the discrepancy between the 289 total compounds in GSK's portfolio versus the 147 projects spanning Phase I through launch.

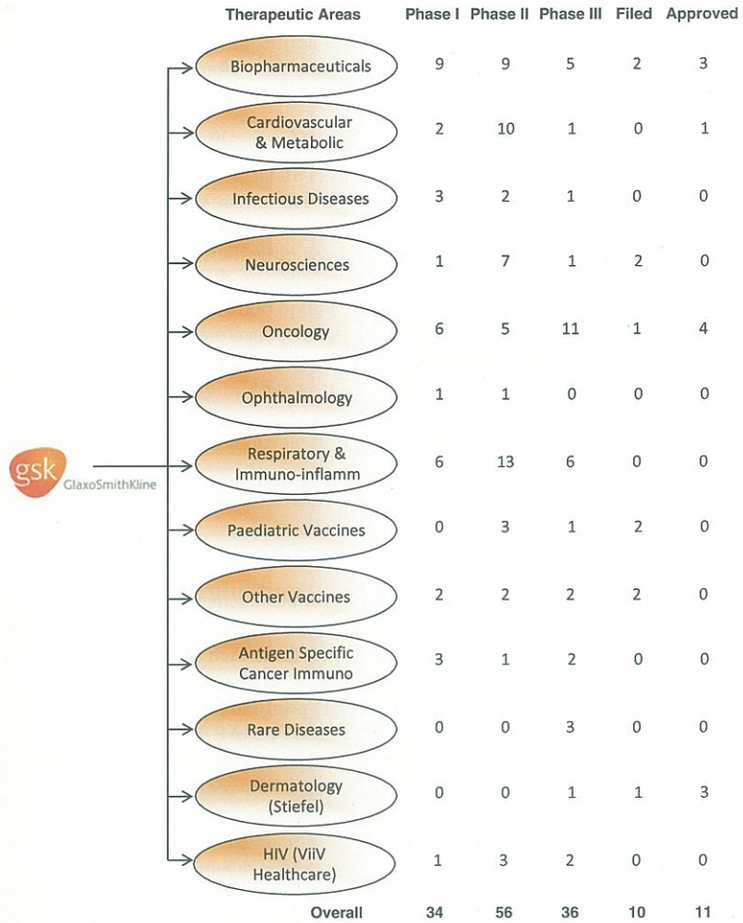

Fig. 3.2 Product development portfolio of GlaxoSmithKline (2011b)

Development (GlaxoSmithKline 2011a). GSK hoped to improve accountability and flexibility by keeping each unit small and focused (outsourcing-pharma.com 2003). A few years later in 2007, GSK launched Centers of Excellence for External Drug Discovery (CEEDDs) to marry external innovation partners and their ideas with GSK's areas of expertise. More recently, GSK has further reorganized its innovation centers into Therapy Area Units (TAUs) consisting of even smaller Drug Performance Units or DPUs (BiotechLive.com 2011). Each unit is led by a CEO with the

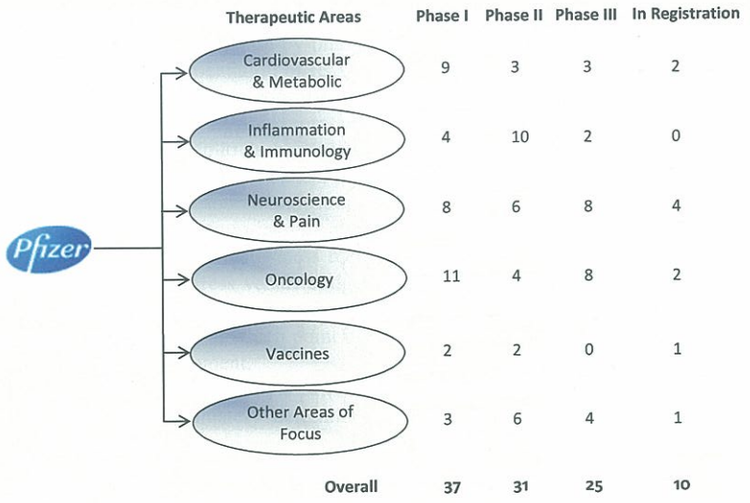

Fig. 3.3 Product development portfolio of Pfizer (2011)

authority to initiate and kill projects, with fewer management layers and increased focus on specific initiatives for scientists within a unit (Garnier 2008). Similar organizational transformations are evidenced in other firms such as Pfizer (Taylor 2009). From this example, it appears that pharmaceutical firms are still exploring optimal organizational structures to manage their R&D portfolios to combat the decline of 20 % in R&D productivity between 2001 and 2007 (IMAP 2011). Further, pharmaceutical firms are also dealing with how to minimize bureaucracy, align research objectives with incentives, and maintain balance between flexibility and control (IMAP 2011).

3.1.5 Managerial Issues Discussed in This Chapter

The remainder of this chapter covers the two major areas of portfolio management (portfolio evaluation and optimization) and discusses various execution issues in portfolio management.

To manage a new drug portfolio, the first step is to accurately evaluate a portfolio and its constituent projects. In Sects. 3.2.1 through 3.2.3, we review popular methods for evaluating the value and risk of individual projects and portfolios including decision trees, real options, and the Capital Asset Pricing Model (CAPM). In Sect. 3.2.4, we discuss managerial heuristics used in interpreting data such as portfolio measures.

In Sect. 3.3, we discuss three topics in portfolio optimization. In Sect. 3.3.1, we describe the effect of competition on overall R&D investment. In Sect. 3.3.2, we discuss portfolio composition in terms of the tradeoff between incremental and radical innovation. In Sect. 3.3.3, we discuss methods for optimal project selection and prioritization.

In addition to portfolio evaluation and optimization, we discuss four execution issues in Sects. 3.4. We separate execution from portfolio optimization based on a large literature that suggests that strategy should precede execution (Day 1990; Lehmann and Winer 2006). However, we recognize that portfolio optimization and execution can be intertwined in reality and in some cases even beneficially so, as organizations "improvise" (Moorman and Miner 1998). Thus, we suggest to the reader that clarity in portfolio optimization (which typically results from an explicit strategic planning phase) can help guide purposeful execution. Specifically, we discuss how organizational design impacts portfolio performance (Sect. 3.4.1), how to manage the frequency of change in the portfolio and organization (Sect. 3.4.2), acquisition and licensing as alternative vehicles to source new projects (Sect. 3.4.3), and incentive design to motivate decision makers to act in the firm's best interest (Sect. 3.4.4).

We conclude in Sect. 3.5 by positing open questions for future research.

3.2 Portfolio Evaluation

Managing a portfolio requires a clear definition of the metrics used for evaluation. Since the financial stakes are high in making large-scale R&D investment decisions, it is imperative to select the most diagnostic measures for evaluation. Typical metrics of interest include market value and risk of individual projects as well as entire portfolios (Davis 2002). The operationalization of value and risk are not trivial as there exist multiple ways to value innovation programs with high levels of uncertainty. Note that to produce an estimate of portfolio value, risk is often taken into account and vice versa, generating an interplay between the two metrics. In this section, we focus on methods of valuing individual projects, methods of valuing an entire portfolio, methods for measuring risk, and managerial heuristics used in interpreting data such as portfolio measures.

3.2.1 Valuation of Individual Projects

A classical approach to project valuation invokes DCF analysis. As outlined in any introductory finance textbook (e.g., Ross et al. 2003), given a set of cash flows based upon project parameter values such as cost of development over several years, projected drug sales and manufacturing costs, and the cost of capital, the NPV and IRR values can be computed and used to make decisions with a threshold rule. The

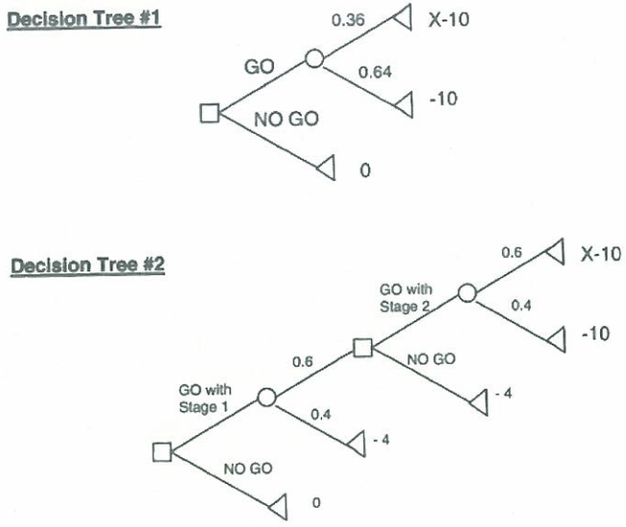

Fig. 3.4 Example decision trees (reproduced from Ding and Eliashberg 2002)

limitations of the relatively "rigid" approach of NPV are exposed in the complex and uncertain environment of drug development. There is considerable uncertainty in all costs and revenue projections, and decisions are in fact made on a stage-by-stage basis which provides considerably more managerial flexibility than NPV allows for.

An extension to NPV which takes into account the probability distributions of various parameters involves Monte Carlo analysis (Myerson 2004) to provide a distribution of possible NPVs that provides a better picture of worst, best, and expected case scenarios compared to standard DCF analysis. However, to model the phased decision-making process, methods such as real options pricing or decision trees need to be used.

While the terms "real options" and "decision trees" are sometimes used interchangeably in practice, they represent different approaches rooted in fundamentally distinct methodologies. Decision trees originate from the decision analysis literature and allow the specification of conditional probabilities of events depending on staged decisions. The payoffs are calculated from an *internal* perspective of the firm or decision maker. In Fig. 3.4, we reproduce two example decision trees in Ding and Eliashberg (2002).[4] The first tree shows a single-stage decision, while the second

[4] Another relevant example of a drug development decision tree is found in Loch and Bode-Greuel (2001).

tree shows how a phased approach can account for probabilities of success or failure along with the expected final payoff. The decision which maximizes expected value or expected utility can then be identified. This approach can be combined with Monte Carlo analysis to perform sensitivity analysis with respect to uncertain parameters.

Real options theory originates from the financial economics literature and defines value in terms of what the asset would be worth in the marketplace, not just based on its worth to the decision maker, which is a point of distinction from decision analysis (Smith 1999). Based on Black and Scholes' (1973) seminal paper on pricing call and put options, real options theory applies the principle to valuing managerial flexibility inherent in drug development projects based on the assumption that asset value over time can be modeled as a continuous-time stochastic process (Tan et al. 2010).

The key equation from Black and Scholes (1973) defines the value of an option (w) which can only be exercised at maturity date t^* for a given current asset price (x) and time (t) given exercise price c, and variance rate of the return on the asset (v^2) :

$$w(x,t) = x\Phi(d_1) - ce^{r(t-t^*)}\Phi(d_2)$$

where

$$d_1 = \frac{\ln\left(\frac{x}{c}\right) + \left(r + \frac{1}{2}v^2\right)(t^* - t)}{v\sqrt{t^* - t}} \text{ and } d_2 = \frac{\ln\left(\frac{x}{c}\right) + \left(r - \frac{1}{2}v^2\right)(t^* - t)}{v\sqrt{t^* - t}}$$

However, as Smith (1999) points out, the difficulty in solving such models when options can be exercised at any time focuses real options analyses on the evolution of a small number of stochastic factors. Smith (1999) contrasts the "dynamic complexity" of real options models with the "detail complexity" that decision trees can incorporate. In principle therefore, real options theory helps the pharmaceutical portfolio manager to factor in the potential upsides of a drug investment that may not necessarily be predictable in advance. A well-known example to illustrate this point is the development of Viagra® by Pfizer. Originally targeted at lowering blood pressure, a chance finding that it had a side effect of treating erectile dysfunction significantly boosted the drug's market potential. While not every drug may have such an upside, factoring in managerial flexibility to change course often allows for greater realism and firms have found options pricing to yield substantially higher valuations than a DCF approach (Faulkner 1996).

Loch and Bode-Greuel (2001) show that decision trees are equivalent to options pricing for risks that can be priced in the financial markets and can also capture risks that are not traded in financial markets. Thus, the downside of options pricing is the requirement for complete financial markets. However, the principle of "real options" whether modeled as a decision tree or options pricing problem brings more realism to planning for phases of development.

We now examine other approaches in the literature for project valuation. Girotra et al. (2007) measure the value of a project to the firm with the impact of its failure in Phase III. Their rationale was to use the natural experiment of a product development failure to determine the interaction effects from other projects in the portfolio. Using a combination of new drug portfolio data and stock market data, Girotra et al. (2007) show that the impact of a project's failure in Phase III is lessened when other projects targeting the same market are still being pursued by the firm. Further, the impact of a failure is also smaller if resources used in the failed project have synergies with other projects. This approach provides an *ex post* measure of a project's market value and can be a useful benchmarking exercise to compare internal valuation with that of the stock market.

Market research is one approach to developing an *ex ante* measure of project value. Conjoint analysis is a popular approach to estimate the market value of improving product attributes. Ofek and Srinivasan (2002) show that when determining the market value of attribute improvement, customers who exhibit a very high or very low probability of choosing the product should be weighted less. In addition, customers whose utility functions consist of a larger random component should be given less weight in determining market value because there is more uncertainty about their choices. We suggest that customers in this context can be interpreted broadly as stakeholders of pharmaceutical firms including physicians, health insurance firms, and patients.

We observe that the extant literature focuses either on an external measure of value (such as from the stock market, real options pricing) or internal measure of value (NPV, IRR, expected utility). An interesting research question may be to evaluate how correlated the internal and external measures are. Posed another way, does the firm or the market do a better job of valuing a new drug? Clearly, managers within a firm would have detailed insights about a project's prospects. However, due to federal regulations, data from clinical trials is publicly available information (Grewal et al. 2008) which allows the market to weigh in on the perceived value of the project. Of course, the challenging of separating a causal effect from noise in financial data is considerable and may pose a barrier that has to be overcome. Yet, since some of the key decisions for a pharmaceutical firm may involve strategic choices of therapeutic areas and preclinical resource allocations, further research can explore feasible valuation procedures that go beyond current state-of-the-art.

3.2.2 *Valuation of Portfolios*

While the valuation of individual projects can be useful, pharmaceutical firms also need to understand the total value potential of their portfolios. A common approach is to roll-up individual project valuations into an aggregate valuation.

Grewal et al. (2008) use an alternative approach, measuring the value of new drug portfolios using shareholder expectations derived from stock market-based indicators (Tobin's Q). They argue that the absence of historical performance for new drug portfolios makes it challenging to measure value, and propose four descriptors of portfolios that may be associated with shareholder expectations:

- Portfolio breadth: Number of different markets (therapeutic categories) targeted by a firm's new drug portfolio.
- Portfolio depth: Variation in the number of diseases targeted across therapeutic categories. This definition of depth is slightly different from a traditional notion in that it captures *variation* in the intensity of resource allocation rather than absolute number of diseases in a given category.
- Blockbuster strategy: Portfolio targeting a few diseases with high expected market potential.
- Stages of drug development: Earlier stages (preclinical trials, Phase I of clinical trials) and later stages (Phases II and III of clinical trials).

Grewal et al. (2008) show that shareholders have positive expectations of firms with higher *portfolio breadth* and *a blockbuster strategy*. For most firms, they find that the final stage of the drug development process is most critical for shareholders to form their expectations and portfolio depth is usually de-emphasized. However, for a minority of mostly small firms, the earlier stages of drug development process and portfolio depth are also valued by shareholders.

While the set of four descriptors is valuable to capture the taxonomy of portfolio strategies, the limitation of this research is that only 1 year of data was available from 308 firms. Capturing within-firm market value changes over time akin to Girotra et al. (2007) may add further insights. In general, the literature in the area of developing suitable descriptors to measure market value of portfolios is sparse, and future research can expand upon models and data from financial markets to construct more detailed descriptors.

3.2.3 *Portfolio Risk*

Thus far, we discussed the valuation of portfolios. However, managers are also concerned with the riskiness or spread of possible outcomes in their portfolios, and their preferences are linked to the overall strategies of the business. A small entrepreneurial biotechnology firm may place all bets on a small number of projects due to capital constraints and the desire to achieve high returns by the owner-entrepreneur. In contrast, a large pharmaceutical firm can be faced with agency issues due to separation of owners (shareholders) from managers who may be risk-averse. Thus, we may observe diversification of new drug portfolios as noted from the examples of GSK and Pfizer.

The classical measures of portfolio risk include *Beta* from the CAPM, which originates from the financial economics literature (Black 1972; Lintner 1965; Markowitz 1952; Sharpe 1964) and mean-variance.[5] These are widely used firm-level and portfolio-level measurements in the strategic management literature (Ruefli et al. 1999).

The key equation of CAPM (from Black 1972) states that under certain assumptions the expected return on an asset R_i for a given period will satisfy $E(R_i) = R_f + \beta_i[E(R_m) - R_f]$, where R_f is the return on a riskless asset for the same time period, R_m is the return on the market portfolio of assets, and β_i is the slope indicating the covariance of R_i with R_m. It essentially values an asset (e.g., a portfolio) against a set of chosen assets (e.g., a set of portfolios), and β_i is widely used as a measure of the risk of R_i.

However, the CAPM's fit to the product development setting is questioned since its assumptions are based on financial markets (Devinney et al. 1985; Ruefli et al. 1999; Wernerfelt 1985). Devinney and Stewart (1988) suggest that managers have more control over product development than financial assets, risk and return of new products may be less related than in financial assets, and that CAPM does not capture interactions among projects in a portfolio. In addition, financial economics assumes that firm-specific risk can be diversified away (Fama and Miller 1972) whereas for a pharmaceutical firm undertaking product development, the firm-specific risk component is not as easily diversifiable (acquisitions and licensing can help to some extent). Devinney and Stewart (1988) propose a generalized model that addresses these shortcomings.

Taggart and Blaxter (1992) introduce a methodology of assessing the risk associated with a firm's research portfolio by separating the technical risk and market risk components, and suggest this can be used for tracking a firm's risk profile over time. An alternative approach to yield *ex ante* measures of risk is to survey top executives (Singh 1986) or conduct market research on stakeholder risk perceptions as discussed earlier (Ofek and Srinivasan 2002).

We join Ruefli et al. (1999) in calling for further investigation of risk measures, especially tailored to the pharmaceutical drug development context.

3.2.4 *Impact of Information Presentation on Decision Making*

Assuming that portfolio valuation and risk are defined and measured, there remains the challenge of distilling the vast amount of information that exists about a portfolio such that managers can make decisions. This information can be summarized in multiple ways to support decision making (Ahn et al. 2010; Day 2007; Dvir et al. 2006). Decision making can be influenced both by heuristics managers use to

[5]The mean-variance approach to evaluate projects or portfolios is popular due to its ease of computation and interpretation (Ruefli et al. 1999).

interpret data (Hutchinson et al. 2010) and the format used to present information (Elting et al. 1999).

Hutchinson et al. (2010) suggest that managers use heuristics when making resource allocation decisions based on numerical or graphical data displays and that these heuristics create biases in some situations. Thus, it is of interest to better understand how portfolio metrics are communicated to and perceived by managers, and its impact on decision making due to "bounded rationality."

Three types of heuristics were identified by Hutchinson et al. (2010) in portfolio decision making: difference-based, exemplar-based, and trend-based. Difference-based heuristics examine local changes in allocations for each resource variable and compare those changes with related changes in the outcome variable. Trend-based heuristics involve "smoothing" the data to look for global trends. The exemplar-based heuristics look to imitate success via best practices benchmarking. The prevalence of benchmarking in the pharmaceutical industry suggests that managers should maintain awareness of a bias towards imitating the conditions leading to successful projects even in the absence of correlation between those conditions and success.

Elting et al. (1999) performed an experiment using 34 faculty members at the University of Texas MD Anderson Cancer Center as subjects, to determine the effect of different data display formats on physician investigators' decisions to stop clinical trials. The underlying data presented was chosen to have a statistically significant treatment effect so that the correct decision is to stop the trial on ethical grounds. The results indicated that showing the same information in the form of a table, pie chart, bar graph, or icon format did not result in the same decisions. In addition, the display formats preferred by the clinical investigators did not lead to the highest percentage of correct decisions. The takeaway for pharmaceutical managers is that when granular data such as results from clinical trials are subject to bias based on the format of presentation, higher level of summaries of R&D portfolios, whether presented as bubble charts, tables, or pie charts should also be closely examined to ensure the reduction of known biases.

We join Ziemkiewicz and Kosara (2010) in calling for a structural theory of visualization to understand how people derive meanings from visual structures. There is much research to be done in this area, especially as it relates to representation of new drug portfolio information, given the billions of dollars of investment at stake.

3.3 Portfolio Optimization

Portfolio optimization entails choosing (1) the overall level of investment, (2) the type of projects (incremental or radical innovation) to include in the portfolio, and (3) the strategy for optimal project selection and prioritization to fit the available R&D budget. Portfolio optimization is at the heart of portfolio management and a rich literature is devoted to addressing these questions, which we review in this section.