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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

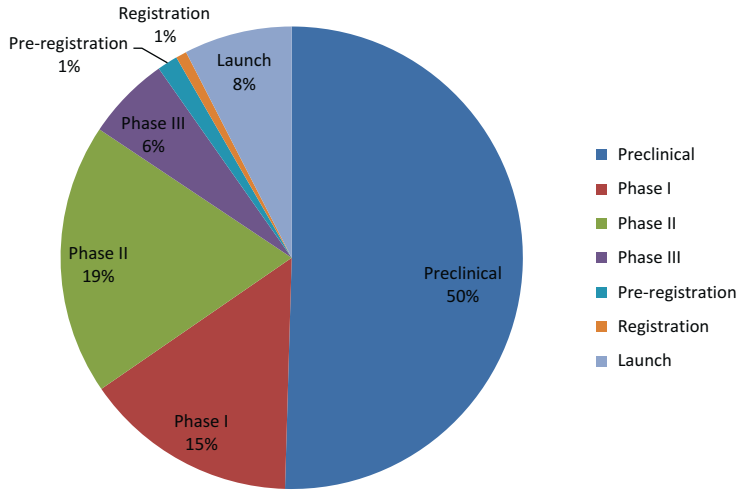

Fig. 3.1 Breakdown of drug compounds by stage of development (PharmaProjects 2010)

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.

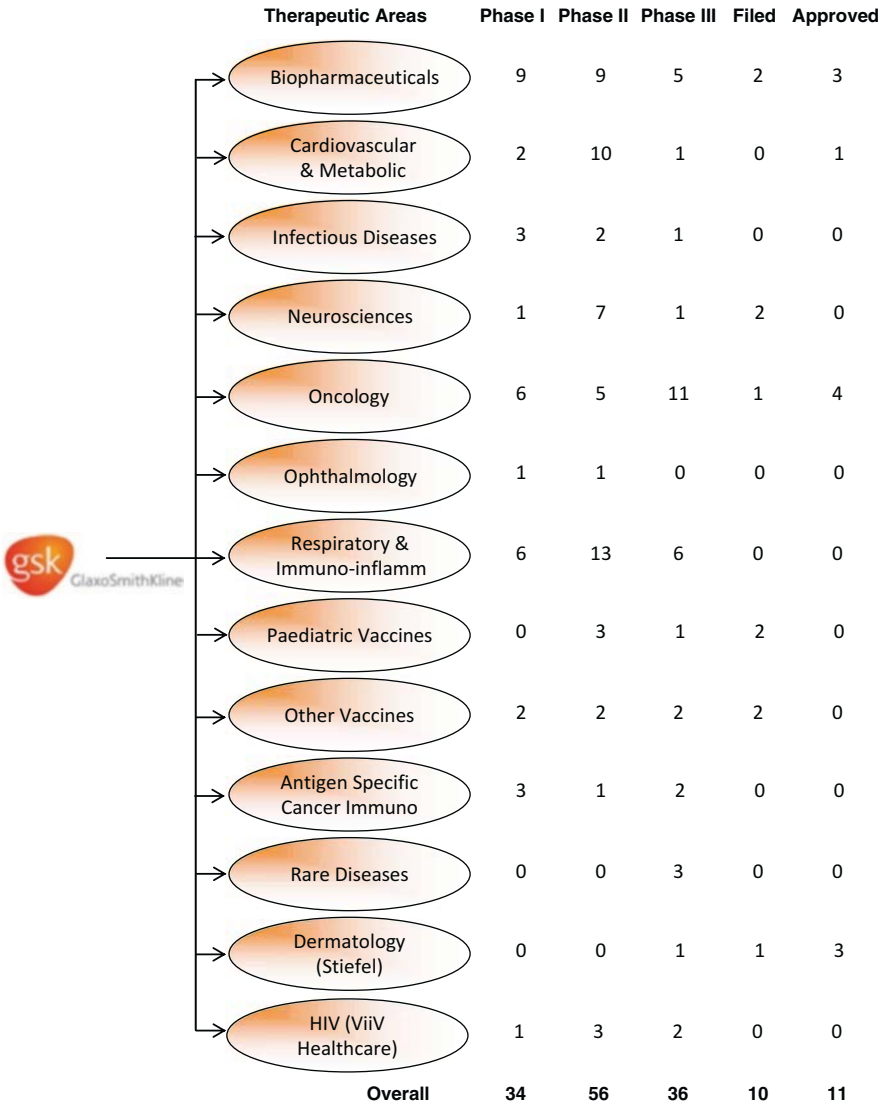

Fig. 3.2 Product development portfolio of GlaxoSmithKline (2011b)

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

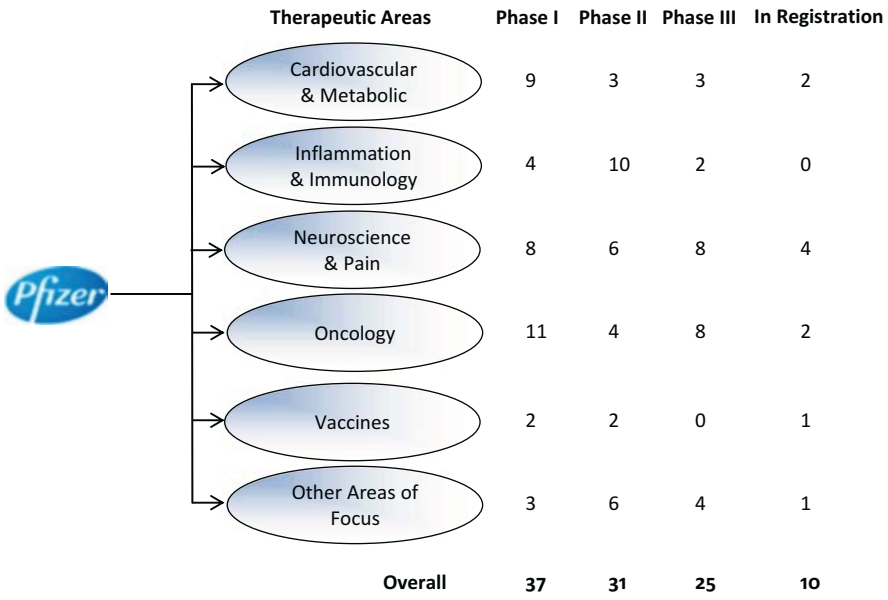

Fig. 3.3 Product development portfolio of Pfizer (2011)

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

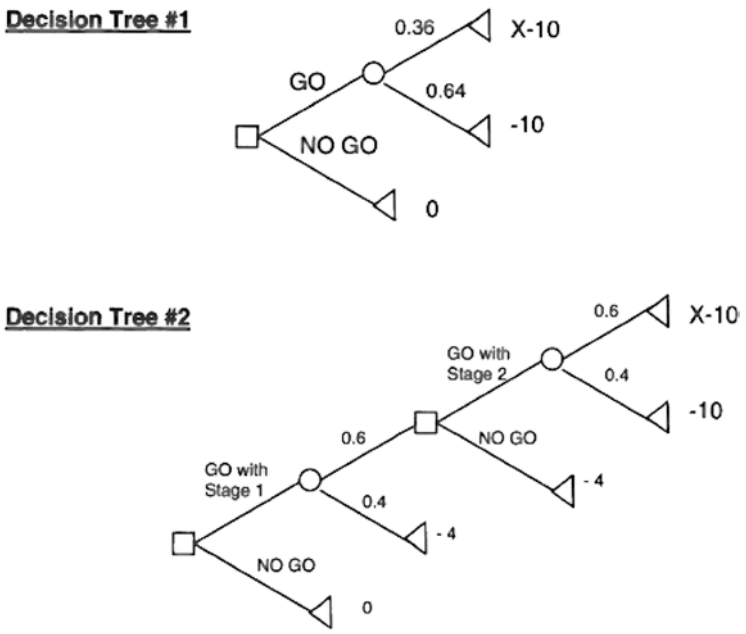

Fig. 3.4 Example decision trees (reproduced from Ding and Eliashberg 2002)

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.

3.3.1 Overall R&D investment

A key decision for the pharmaceutical firm is to select the overall R&D spend year-after-year. This then determines the number and variety of programs and therapeutic areas can be funded. While the popular business press (e.g., Jaruzelski et al. 2011) tends to report R&D spend as a percentage of sales (top players spending about 11–21 % of annual sales on R&D), these decisions also tend to be driven by competition.

Using a dynamic game, Ofek and Sarvary (2003) show that when success enhances R&D competence, the leader firm increases R&D investment relative to rivals to sustain its position with higher probability. In contrast, when success enhances reputation (such as through brand value), the leader firm tends to expend less R&D effort relative to followers. The implication to pharmaceutical firms is obvious: increased R&D competence and market reputation from commercializing a molecule for an indication can allow for "follow-on" drugs based on similar technology. In some sense, the success of a blockbuster drug may impede the development of future blockbusters as a firm looks to capitalize on possible extensions. On the other hand, the expiration of blockbuster drugs' patents may reduce the ability of a firm to continue R&D investment and eventually lead to a merger or sale to another pharmaceutical firm. Hence, strategic investments in R&D portfolios can make or break a firm's future as an independent entity.

The intensity of competition also drives R&D investment. Recent work in the dynamic oligopoly literature (Goettler and Gordon 2011) has found that competition dampens the rate of innovation compared to a monopolist. In the context of the pharmaceutical industry, a firm which enjoys a monopoly position for a given drug and indication would be more inclined to reinvest more of the profit from being a monopolist (which enables higher prices to be set). Once "me-too" drugs are introduced, the incentive to innovate in that indication is lowered as the profitability is decreased due to competitors' entry. Hence, the optimal amount of investment in R&D may depend on level of competition rather than being a fixed percentage of sales, which is often a benchmark in the industry. Further research can examine the optimality of basing R&D on a percentage of sales basis rather than in response to competitive conditions.

3.3.2 Portfolio Composition

Selecting the appropriate balance between incremental and radical innovation and having the right mix of short, medium, and long-term developments requires a "big picture" view of the new drug portfolio and how it fits with corporate objectives.

A plethora of tools exist in the form of checklists, scoring models, and mapping tools (e.g., bubble charts) to guide managers and their teams to make decisions about portfolio strategy. Day (2007) discusses the "Is it Real? Can We Win? Is It

Worth Doing?" scoring model for constructing portfolios that balance risk and reward. In particular, Day (2007) suggests that firms across industries shy away from risky, disruptive innovations in favor of incremental ones, stemming from a risk averse attitude that can hamper long-term growth. We do not focus on the extensive variations of scoring models and strategic guideposts which are available for decision making such as the Diamond model (Ahn et al. 2010; Dvir et al. 2006; Shenhar and Dvir 2007), but examine the literature on the evidence in favor of certain strategic choices.

In the pharmaceutical context, radical innovation represents investment in developing NCEs/NMEs which involve higher risk as unproven APIs can be used. Incremental innovation tends to utilize known APIs/molecules to develop drugs, such that the hurdles for regulatory approval are lower. Another dimension that differentiates radical from incremental innovation is the complexity/level of knowledge about the mechanism of action and the corresponding a priori risk of failure. Cancer drugs may be inherently more difficult to develop than anti-infective drugs, for example. Hence, Wuyts et al. (2004) define radical innovations as those which incorporate a substantially different core technology and provide significantly greater customer benefits than previous drugs.

3.3.2.1 Does Radical Innovation Pay Off?

Lee (2003) studies the US pharmaceutical industry from 1920 to 1960 and identifies two types of firms (innovators and imitators) which react differently to the radical innovation in antibiotics in the 1940s. During that period, innovators hired more biologists and other scientists than imitators, and introduced eight times as many NCEs as did imitators between 1940 and 1960. As a result, Lee (2003) concludes that "the innovators dominated in developing new drugs and the gap between innovators and imitators steadily increased."

Wuyts et al. (2004) examine the consequences of upstream interfirm agreements on the performance of radical innovation, incremental innovation, and overall profitability. They point out that the number of R&D agreements is less informative of success than the diversity of programs and repeated partnering that fosters deeper collaboration and knowledge transfer. The importance of radical innovation to long-term profitability is highlighted based on data collected from 58 pharmaceutical firms from 1985 to 1998, covering 991 R&D agreements.

3.3.2.2 What Types of Firms Have Invested in Radical Innovation?

Sorescu et al. (2003) study the characteristics of firms which introduce radical innovations and the resulting rewards. Their data set is based on a census of innovations from 1991 to 2000 from the NDA Pipeline, a database of drugs administered by F-D-C Reports, of which 380 out of 3,891 new products introduced were breakthrough or "radical" innovations, representing only 7 % of total drugs. The sample is a cross-sectional

time-series data set of 255 radical innovations introduced by 66 firms, for which complete accounting and financial data were collected. Sorescu et al. (2003) find that (1) the majority of radical innovations come from a minority of firms, (2) the financial rewards across firms have a large variance, (3) firms with better marketing and technology support benefit more from radical innovations, and (4) firms that have a portfolio with greater depth and breath obtain higher rewards from radical innovations.

Yeoh (1994) argues that radical innovations are also characterized by their speed of global introduction, with one definition suggesting such drugs demonstrate multinational approval by at least six major industrialized countries within 4 years. Yeoh (1994) demonstrates using a dataset of "global" NCEs that such radical innovations are more likely when the development is self-originated, competitive intensity is low, and the firm has prior experience in the therapeutic category.

It seems that being an innovator and investing in radical innovation can pay off handsomely. However, considering risks and commitments associated with radical innovations, a natural question arises as to the extent a firm should focus on radical innovation versus "surer bets" that are incremental innovations.

3.3.2.3 Selection and Balance between Incremental and Radical Innovation

When should firms favor incremental versus radical innovation? Ali et al. (1993) examine the effects of firm characteristics on project selection. They set up a game-theoretic model in which duopolists face two business opportunities and two alternatives strategies, i.e., a radical innovation project and an incremental innovation project. Firm characteristics such as their differential efficiencies in completing projects, differences in the degree of substitutability between the two types of products, and first mover advantages are examined. They find that beyond the project development costs and reward flows, some firm characteristics (e.g., firms' comparative efficiencies in developing projects), project characteristics (e.g., technical uncertainties), and market characteristics (e.g., potential demand substitutability between different types of new products) will all affect the optimal choice between a radical innovation project and an incremental innovation project.

Chao and Kavadias (2008) use a theoretical framework based on strategic buckets to examine the balance between incremental and radical innovation. Strategic buckets divide the R&D budget into a set of smaller subsets each of which is aligned with a particular innovation strategy, to lower the bias of project valuation tools such as NPV or real options against radical innovation due to the long-term rewards and high likelihood of failure if the entire portfolio was considered as a whole. They point out the trend among firms to move towards incremental-innovation-dominated portfolios and suggest that the right balance depends on the amount of interaction between performance drivers such as technology and market parameters (complexity) and the degree of environmental instability. Specifically, the portfolio should emphasize radical innovation when there is high complexity but low instability (as radical innovation can break away from local performance optima), and incremental

innovation when there is neither high complexity nor stability, or when there is instability but not complexity (as instability may not provide enough time for radical innovation to realize results). In the scenario where both complexity and instability are present, the balance of the portfolio depends on the parameters and does not have a clear cut direction.

Another stream of research suggests that the choice of innovation strategy is affected by a firm's position in the market. Kauffman et al. (2000) model technology development as a search problem in the space of technological possibilities. Incremental innovation is modeled as searching over small distances relative to the starting point, and radical innovation is modeled as searching over large distances. Using simulation and analytical tools, they conclude that if a firm's position is poor or average at the initial position, it is optimal for the firm to search far away (i.e., to conduct radical innovation). Once the firm finds the technological improvement (succeeds in the radical innovation), it is optimal to limit its search to a local region on the technology landscape (i.e., to conduct incremental innovation).

The key equation governing the firm's optimal search strategy is given by:

$$(1-\beta)z_c(d) = -c(d) + \beta \int_{z_c(d)}^{\infty} \left(\theta - z_c(d)\right) dF_d(\theta)$$

where d is the search distance, $z_c(d)$ the reservation price, β the discount factor, $c(d)$ the search cost, and $F_d(\theta)$ the cumulative distribution of "technology efficiency" at distance d. The firm should search at the distance with the highest reservation price.

However, DiMasi (2000) presents empirical evidence which contests this theoretical result. The firms with the most number of NCEs in the period from 1963 to 1969 continued to dominate filings of NCEs from 1969 to the 1990s. Though the percentage of NCEs that were self-originated declined from 71.6 to 60.9 % from the 1960s to the 1990s, the data does not seem to support that innovators "sit on their laurels" after initial successes. However, as a counterpoint, the increasing growth in small biotechnology firms that take on radical innovation projects, and their subsequent licensing deals with big pharmaceutical firms suggests that there may be areas in which Kauffman et al. (2000)'s theory may apply.

To summarize the discussion on radical versus incremental innovation, we note that extant literature has suggested a variety of conditions and reasons to pursue either type of innovation. It appears that the decision depends on both firm characteristics and the external environment. One opportunity for further research is to consider how to construct a portfolio that balances the two approaches. Most of the previous work focused on an "either-or" choice between incremental and radical innovation, whereas per Day (2007), the real decision is how much of each type to include in the portfolio. Achieving the right balance requires alignment with the goals of the organization. However, we suggest that firms which focus too heavily on incremental innovation may want to consider the opportunity cost of not investing in areas which promise higher returns (albeit with higher risk).

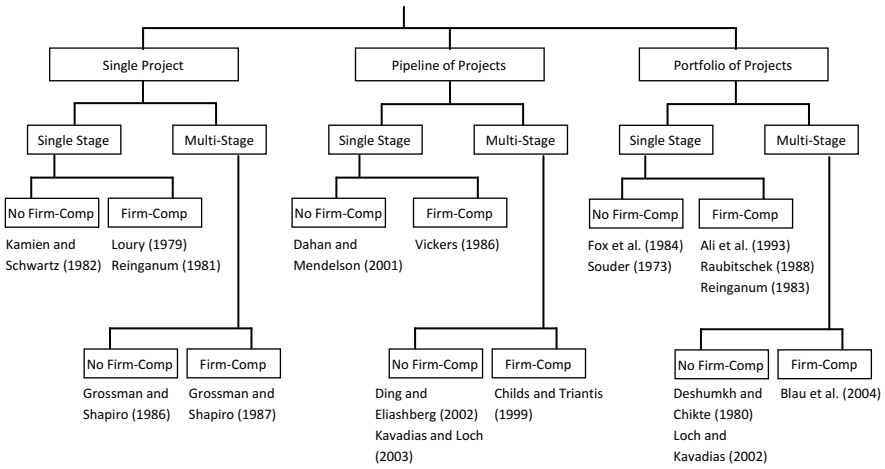

Fig. 3.5 A taxonomy of project selection problem, updated from Fig. 3.1 in Ali et al. (1993)

3.3.3 Optimal Project Selection and Prioritization

Once strategic choices are made regarding the areas and types of projects to undertake, the resulting possibilities of projects to resource still require prioritization as no one firm has unlimited resources to take on all potential projects. In this subsection, we review methods for optimal project selection and prioritization, and follow up with a discussion on interactions among projects.

Ali et al. (1993) provides a nice summary of the models dealing with project selection problems. We update their taxonomy to accommodate the recent studies relevant to the pharmaceutical industry (Fig. 3.5).

In order to accommodate a wider range of approaches, we altered the taxonomy as follows. In our taxonomy, "Single Stage" and "Multi-Stage" refer to the number of decision stages (which need not correspond to the number of stages of the drug development process). Moreover, the notation "No Firm-Comp" means no firm-level competition is modeled; it does not necessarily mean the model assumes no firm-level competition. Additionally, "Firm-Comp" means firm-level competition is modeled.

3.3.3.1 Prioritization Using Optimization Methods

The Pearson index (Pearson 1972) and Gittins index (Gittins 1979) are two widely used indices for prioritizing projects in a portfolio. An excellent summary of the differences between these indices is provided in Talias (2007), who models an R&D project as a Markov decision process.

The Pearson index is a profitability index of a project. It is defined as:

$$\text{Pearson Index} = \frac{E[\text{Net Value}]}{E[\text{Cost}]} = \frac{R\prod_{i=1}^{n} p_i - \sum_{i=1}^{n}\left(c_i \prod_{k=0}^{i-1} p_k\right)}{\sum_{i=1}^{n}\left(c_i \prod_{k=0}^{i-1} p_k\right)}$$

where R is the final reward, $c_i\ (i=1,\ldots,n)$ is the cost in stage i, and $p_i\ (i=1,\ldots,n)$ is the conditional probability of success given success at the previous stages $p_0 = 1$. It is the optimal decision rule according to Neyman–Pearson lemma (Neyman and Pearson 1933) and can be used to decide whether a project should be implemented or not by ranking all potential projects.

The Gittins index is used in a sequential selection setting (also known as a multiarmed bandit problem) in which resources must be dynamically allocated among several independent alternative projects, each divisible into stages. The Gittins index solves the problem by associating each project with a priority index and picking the project with the largest current index using the following form:

$$\text{Gittins Index} = v_i(x_i) = \sup_{n>1} \frac{E\left\{\sum_{t=1}^{n-1} \alpha^t R_i\left[x_i(t)\right] \mid x_i(1) = x_i\right\}}{E\left\{\sum_{t=1}^{n-1} \alpha^t \mid x_i(1) = x_i\right\}}$$

where $n > 1$ is the number of stages, $0 < \alpha < 1$ is a fixed discount factor, $x_i(t)$ is the state of project i in stage t, and $R_i\left[x_i(t)\right]$ is the contemporaneous reward given the state of project i in stage t. Therefore the numerator represents the expected discounted reward for project i up to n stages; the denominator represents the expected discounted time up to n stages. Hence, the Gittins index is "the maximum expected discounted reward per unit of expected discounted time" (Talias 2007). It is an example of a Dynamic Allocation Index that is updated at each decision node to reprioritize projects.

Talias (2007) suggests that the Pearson index is appropriate in a static context where selected projects will be implemented, and the rest will never be considered again. However, in a dynamic scenario, the Gittins index is more appropriate as it maximizes the expected reward accumulated sequentially.

Ad hoc linear and nonlinear programs can also be formulated using some of the above approaches as starting points, while adding constraints specific to a particular firm (Dickinson et al. 2001). These can bring more realism to the problem definition beyond a mathematical definition of optimality. Loch and Kavadias (2002) develop a dynamic programming model of portfolio choice in which marginal analysis is used to demonstrate the structure of optimal policies. The unit of analysis is not a single project but resource allocation of a limited budget across strategic programs. They provide a closed form characterization of the optimal policy in the presence of a number of project and market characteristics and provide a theoretical basis to validate managerial "rules-of-thumb" on how the optimal allocation policy would change with these characteristics.

Table 3.2 A summary of dynamic project selection studies related to the pharmaceutical industry

Study	Pipeline vs. Portfolio	Number of stage	Cost/ resource interaction	Outcome/ technical interaction	Benefit/impact interaction	Methodology
Dahan and Mendelson (2001)	Pipeline	Single	No	No	No	Analytical
Ding and Eliashberg (2002)	Pipeline	Multiple	No	No	No	Analytical
Kavadias and Loch (2003)	Pipeline	Multiple	Yes	No	No	Analytical
Childs and Triantis (1999)	Pipeline	Multiple	Yes	Yes	Yes	Simulation
Loch and Kavadias (2002)	Portfolio	Multiple	Yes	No	Yes	Analytical
Blau et al. (2004)	Portfolio	Multiple	Yes	Yes	Yes	Simulation

As an extension of the Gittins index, Kavadias and Loch (2003) set up a model in which there are multiple projects but only one scarce resource (could be scientists, lab time, budget, etc). Only one of the project can use this scarce source at a time. If the projects are independent of one another and equally affected by delays, this reduces to a multiarmed bandit problem solved by the Gittins index. However, if projects are affected differently by delays, as is likely the case in a diverse portfolio, a new policy is needed. The dynamic prioritization policy of Kavadias and Loch (2003), called the "Expected Delay Loss Index," is to work on the project "with the highest expected delay loss as if the other project was completely finished first," and prove it to be optimal if (1) the delay cost increases with the delay regardless of the performance state, (2) costs are not discounted (or, discounting is dominated by delay costs), (3) projects are not abandoned based on their performance state during processing at the scarce resource, and (4) there are no stochastic delays.

3.3.3.2 Prioritization Using Decision Trees

Another stream of literature on solving project selection and sequencing problems uses decision trees. Approaches using decision trees consist of analytical methods (e.g., Dahan and Mendelson 2001; Ding and Eliashberg 2002) and simulation methods (e.g., Blau et al. 2004; Childs and Triantis 1999). Analytical methods provide closed form solutions which suggest clearer causal relationships, but simulation methods are able to accommodate complex scenarios which give the model a more realistic flavor. In Table 3.2, we categorize the key papers mentioned above.

We define a pipeline[6] as a series of new drug developments targeting one business opportunity (a single indication). The key question revolves around the number of projects/products a firm should keep in the pipeline.

Dahan and Mendelson (2001) examine a setting in which there is only one stage of product development and multiple potential projects can be tested in parallel. They investigate the trade-off between the benefits and costs by assuming that the profits follow extreme-value probability distributions. The key result is that optimal number of projects for a pipeline is the ratio of the scale parameter of profit uncertainty to the cost per project. In other words, greater profit uncertainty or lower cost per project drive a fatter pipeline.

Ding and Eliashberg (2002) take a further step and study the optimal number of projects to be funded at each stage in a multiple stage development setting. They find the optimal structure of the pipeline (i.e., the pipeline with optimal number of projects at each stage) is determined by the cost of developing a project, its success probability, and its expected reward. Comparing their normative results with empirical practice data, they find that firms tend to have fewer projects in their pipelines than the optimal structure. Hence, pharmaceutical firms may be better off increasing the investment for a given pipeline. However, even if the optimal number of projects in the pipeline is determined, a sequencing of funding these projects may be needed if resources are scarce (which is usually the case).

Childs and Triantis (1999) conduct a simulation scenario analysis which accommodates multiple characteristics of R&D projects, including learning-by-doing, collateral learning between different projects in the program, interaction between project cash flows, periodic reevaluations of the program, different intensities of investment, capital rationing constraints, and competition. Their model considers complex interactions of multiple factors and is therefore much more realistic. However, they do not obtain analytical optimal policies. Childs and Triantis (1999) demonstrate that it may be profitable for a firm to fund multiple projects even if only one can be launched, and during the development procedure, it is possible that the firm may alter its prioritization policy significantly at different stages. The findings from the simulation model appear to fit the reality of pharmaceutical innovation fairly well.

Blau et al. (2004) propose a simulation-based approach to selecting sequences of projects in a portfolio, which maximizes the expected economic returns for a given level of risk and budget. They do not obtain closed form optimal solutions, but demonstrate an improvement of 28 % in expected return using the simulation approach as compared to a traditional bubble chart approach. The approach takes into account interdependencies among projects which is otherwise difficult to quantify in closed form.

[6]Note that the term "pipeline" is sometimes used interchangeably with the term "portfolio" in the business press. Our definitions for each of these terms are distinct and not synonymous with one another.

3.3.3.3 Interactions Among Projects

Extant literature has recognized the importance of considering project interdependencies in portfolio selection decisions (Aaker and Tyebjee 1978; Baker and Freeland 1975; Blau et al. 2004; Childs and Triantis 1999; Czajkowski and Jones 1986; Dickison et al. 2001; Santhanam and Kyparisis 1996; Weber et al. 1990; Weingartner 1966).

Gear and Cowie (1980) specifically distinguish between two types of interdependencies in R&D: *internal* and *external* interaction. Internal interaction exists when the resource requirements and benefits of a project are impacted (in magnitude and/or timing) by the selection or rejection decisions of other projects. Fox et al. (1984) further classify the internal interactions into three categories: (1) cost or resource utilization interaction; (2) outcome, probability, or technical interaction; and (3) benefit, payoff, or effect interaction. External interaction or "shocks" arises over time from overall environmental changes in social and economic conditions whose effects cut across multiple projects.

For example, if a firm could pursue two projects which require common skill sets, it could leverage the same pool of personnel, thus achieving cross-fertilization of ideas and avoiding duplication of skill sets in the organization. However, the internal interaction plays a role as changing the scope of one project affects the timing and impact of the other due to common resources. An example of external interaction would be scientific knowledge addressing potential solutions to new diseases that could either depreciate the efforts of multiple projects using older technology, or provide a new market opportunity for existing projects.

The literature on optimal project selection and prioritization we have examined thus far have focused on internal interactions, while environmental changes leading to external interactions are less commonly modeled since these can quickly lead to a proliferating number of factors and large decision trees. One solution is to use simulations to model these interactions (e.g., Blau et al. 2004; Childs and Triantis 1999). However, a closed form optimal solution may still be preferable to investigate the effect of outcome/technical interactions on project selections and sequencing and is an open topic for researchers to pursue.

3.4 Portfolio Execution Issues

While accurate portfolio evaluation and effective portfolio optimization strategies are necessary conditions for developing a successful new drug portfolio, execution is where the rubber meets the road for pharmaceutical firms. Portfolio execution translates strategies into action. In this section, we discuss four execution issues: (1) the impact of organizational design on portfolio performance; (2) how to manage the frequency of change in the portfolio and organization; (3) acquisition and licensing choices (the make or buy decision); and (4) incentive design to motivate decision makers to take actions in the firm's best interest.

3.4.1 Organizational Design

While some technologies will be acquired from other firms, a large percentage of R&D spend continues to be invested in internal projects. The key question is whether to staff a centralized or decentralized R&D organization to execute a portfolio. In Sect. 3.1, we reviewed GSK and Pfizer's approach to organizational design, which is in the direction of decentralized "Centers of Excellence" (CoE). The benefit is the focus within each CoE that is realized by reduced levels of management hierarchy. However, this directly impacts the synergies that can be leveraged across programs. For example, it is possible that two different therapeutic areas may both benefit from the same underlying molecule, and decentralization may not easily enable cooperation across units.

Argyres and Silverman (2004) examine the relationship between internal organizational structure and innovation outcomes. They find that centralized R&D facilitates more distant or "capabilities-broadening" search, generating innovations with a broader impact and drawing from previous research in a wider set of technological domains. In contrast, decentralized R&D tends to encourage proximate or "capabilities-deepening" search. There is a rough analogy between this work and that of Kauffman et al. (2000), which suggests that centralized R&D organizations are better equipped for radical innovations (since they can more easily look across domains) and decentralized R&D organizations are more suited for incremental innovations. Based on their findings, the trend of firms focusing on smaller decentralized units may result in further investment into incremental drug portfolios, which could impact long-term growth.

Further research is needed to analyze the impact of different organizational structures on new drug portfolios. We suggest that facilitating some cross-fertilization of ideas across decentralized units through mechanisms such as annual technology fairs (where people come together from different units) or a corporate-level team that maps out the synergies between units may be an intermediate step. Marketers may also have a role to play in connecting market opportunities to technologies which may cut across R&D units.

3.4.2 Frequency of Change

How often should firms change course in their portfolio strategy and execution? In today's turbulent economic conditions, personnel reshuffling from top to middle management is the norm and can give rise to frequent modifications to projects within a portfolio, and the organizational design itself (consolidation, centralization, decentralization, etc). Amburgey et al. (1993) use dynamic models of organizational failure and change estimated using a population of 1,011 Finnish newspaper firms to determine that organizational change increases the hazard of organizational failure and that there is an increased likelihood of additional changes of the same

type. While this study was based on small firms with relatively simple organizational structures compared to large pharmaceutical firms, it corresponds with the reality that firms prefer to make changes whose effects they understand. This research points out that change may or may not be beneficial to organizations and depends on the circumstances. This suggests that firms should carefully consider the history of changes made in the R&D organization and in the portfolio, to assess whether further change is likely to help or hinder overall performance.

Further research from the finance literature (Kuhn and Luenberger 2010) suggests that the right timing of portfolio revisions and adjustments is essential for long-term growth in a dynamic investment situation. This builds on work in portfolio theory such as Markowitz (1952). The key insight from Kuhn and Luenberger (2010) is that a balance needs to be struck between very infrequent portfolio rebalancing (not reacting enough to changes in the economic environment) and overly frequent rebalancing (comes at a cost). This insight is applicable to R&D portfolios in the sense that changes that are too frequent can drain organizational resources in simply managing the modifications as opposed to accelerating progress to deliver on objectives. Further research can explore how to balance the twin needs of flexibility and stability in a new drug portfolio.

3.4.3 Acquisition and Licensing

There are varying opinions in literature about whether a firm should fill its portfolio via acquiring projects from other firms. Some researchers argue that acquisitions tend to hurt innovation because they may distract managers from innovation (Hitt et al. 1990), compete for funds with existing innovation projects (Hitt et al. 1991), and trigger the exodus of key employees (Ernst and Vitt 2000).

However, other researchers argue that for some firms, acquisitions could be a tonic for innovation. For example, Prabhu et al. (2005) suggest that firms with better internal knowledge have higher ability to utilize external knowledge from acquisitions. Sorescu et al. (2007) use the term "product capital" to refer to the product development and product support assets that a firm has, and argue that firms with high product capital are better able to select the right acquisition target and deploy the acquired knowledge to gain competitive advantages.

The trend, however, points to a continuation of large acquisitions, mega-mergers, and drug licensing deals (DiMasi 2000; PharmaProjects 2010; IMAP 2011). What empirical evidence supports this trend? Higgins and Rodriguez (2006) examine the performance of 160 pharmaceutical acquisitions from 1994 to 2001, and find that on average, acquirers realize significant positive returns. They find that firms experiencing the greatest deterioration in R&D productivity are most likely to undertake the acquisition of a research-intensive firm to replenish their portfolio. They also find surprisingly, that 71 % of acquiring firms either maintain or improve their product portfolios post-acquisition, leading to positive returns. They suggest pharmaceutical firms realize gains from acquisitions because of their ability to obtain

significant information about the drug portfolio of the target firm, and appropriately value their worth thereby avoiding the "winner's curse."

3.4.4 Incentive Design

Incentives affect how organizational strategies are carried out by the people tasked with execution: managers and scientists. Most pharmaceutical firms have a hierarchical structure with a Chief Technology Officer reporting to the CEO, and a further hierarchy within the R&D organization. Given the multilevel organization, misaligned incentives can result between strategists designing R&D portfolios, and the executors, or even for the strategists themselves.

Manso (2011) examines the problem of how to motivate riskier innovation projects using a principal–agent setting and finds that substantial tolerance (or even reward) for early failure and reward for long-term success is needed for agents (such as managers or scientists) to explore riskier options. If short-term success is rewarded, then agents are more inclined to choose safer options (i.e., those which can lead to incremental innovations). In publicly held firms, a real tension exists between the short-term financial results expected by investors and the need for long-term investment to provide future growth opportunities for the firm. Manso's work suggests that incremental innovations could arise endogenously due to incentives. Thus, firms need to ensure that those responsible for strategic choices and executing on them are rewarded appropriately for their decision making, especially in the high risk world of new drug portfolios.

Chao et al. (2009) examine the incentive problem for managers allocating resources between incremental and radical innovation projects, as a function of funding authority. When funding is variable (i.e., manager can use revenue from existing product sales to fund NPD efforts), the manager is induced to focus on incremental rather than radical innovation. However, variable funding results in overall higher effort towards both types of innovation as compared to fixed funding. These authors also point out a substitution effect between explicit incentives in the form of compensation and implicit incentives (i.e., career concerns). Thus, pharmaceutical firms should carefully consider the implications of how R&D programs are funded.

There is a growing body of work relating to incentives for portfolio managers. Szydlowski (2012) focuses on a situation where a firm chooses how to allocate funding for a portfolio of projects, and a manager is responsible for multitasking across these projects. This is a commonly arising scenario in R&D departments where a person may be responsible for multiple projects. Szydlowski (2012) suggests that performance-related bonuses at the project level lead to more optimal managerial behavior than issuing firm-level equity in the form of shares. Care is therefore needed in designing incentives so that managers will undertake the right amount of effort in the right projects at the right time.

Providing the appropriate incentives to the task at hand is also a challenge faced by firms. Will a one-size-fits-all incentive system drive the right behaviors, versus tailoring the incentives according to the nature of the project? Chao et al. (2011) use principal–agent theory to determine that incentives depend on the interaction of project complexity and desired type of innovation. An organization focused on incremental innovation should set higher incentives for more complex projects. However, an organization focused on radical innovation should set lower incentives for more complex projects. This finding reconciles two differing schools of thought: the first suggests that complex problems are difficult to solve and incentives should be provided to enable managers to invest adequate effort; the second suggests that incentives in fact result in lower performance for complex tasks. Chao et al. (2011) explain this dichotomy as arising due to the choice of incremental or radical innovation (what they refer to as "search distance"). Empirical validation of these hypotheses will provide useful insights to pharmaceutical firms in designing incentives in light of projects of varying complexity and varying innovation goals.

Another critical incentive design issue is to motivate managers to kill the right projects at the right time. Simester and Zhang (2010) argue that it is difficult to reward decisions to kill projects simultaneously with rewards for success. Rewarding success may mean that an agent persists with a project even if its prospects have dimmed since its inception. Rewarding failure, on the other hand, undermines motivation for persisting to find solutions to challenging projects, as it could be "argued" that the project should be discontinued. Therefore, while a firm with a large project portfolio may prefer to kill projects with low prospects, the fact that different managers are responsible for different parts of the portfolio may jeopardize the efficient updating of the portfolio over time.

Overall, there is further ground to explore the problem of incentives and the various behaviors that result in the context of pharmaceutical portfolio management, building upon the recent research in this area. We suggest that careful alignment is required between how managers and scientists are compensated and the actions the firm would want them to undertake, to preempt "moral hazard" issues.

3.5 Concluding Remarks and Open Questions

The literature on portfolio management is inherently interdisciplinary, with work from decision theory, game theory, principal–agent mechanism design, empirical data analysis, finance, simulation analysis, and statistical theory informing this crucial topic. Extant literature has made significant contributions to the theory of portfolio valuation and optimization, as well as characterizing the empirical findings from actual practices at pharmaceutical firms. Yet, significant questions remain open for further exploration which we now outline.

Research on portfolio valuation has focused on either market-based measures (using stock market reactions to discrete events) or internal measures of value (NPV, expected utility, IRR, etc). While there is a belief that both external and internal

value measures should be highly correlated, it is still open as to the extent to which both measures are related to ex-post value. In other words, which measures have greater predictive power? Does the firm or the market do a better job of valuing a new drug? Do firms know better because they have internal know-how that gives them better insights over the prospects of various projects in their portfolio? Or is it possible that the market mechanism can efficiently price the value of various projects due to the "aggregate wisdom" of investors?

In addition, accounting for synergies between projects and pipelines in a portfolio is still an open challenge. Research such as Girotra et al. (2007) and Blau et al. (2004) attempts to model the interaction effect of multiple projects. Yet, a systematic study of how organizational capabilities, know-how, and market needs come together can enhance the understanding of valuing portfolios. Modeling external shocks that can affect multiple projects in a portfolio alongside internal interdependencies will enhance understanding of prioritizing projects in a portfolio. Using Grewal et al. (2008)'s descriptors, does the diversity from higher portfolio breadth truly counteract the positive synergy from a lower portfolio breadth with greater resources allocated to fewer areas? Are firms diversifying portfolios as a result of competitive pressures akin to a "Prisoner's Dilemma" or because this is the most value-adding strategy?

We can further our understanding of portfolio diversity by considering all sources of diversity, not just in terms of therapeutic areas. For instance, partner diversity (work with few or many other firms in collaborative efforts) and product-market diversity (potential presence in multiple geographic and product segments) can also be further investigated to determine whether portfolio risk and value are optimally traded off with such choices.

Drawing upon Grewal et al. (2008), further investigations on the key descriptors of a portfolio and the key metrics that firms should use to measure portfolios' worth needs to be undertaken.

Further implications of data visualization and presentation also need to be explored. Measurement of a portfolio's state can involve hundreds of metrics ranging from extremely granular measures at the project-level to projections in multiple dimensions at the aggregate level. The literature on managerial biases suggests that the problem of managerial decision making based on such complex data is tied to how data is presented and interpreted. Do scoring models and bubble charts, so often favored by managers, enable optimal portfolio decision making? Empirical research can investigate the biases that impact portfolio management decisions as managerial judgment continues to be a key ingredient alongside analytical methods.

For portfolio optimization, a rich literature has contrasted the merits of incremental versus radical innovations. However, the choice for firms is usually not "either-or" but how much of each type to include in the portfolio. Hence, research on optimal mixtures of incremental and radical innovations would push the frontier closer to the actual decision problem for pharmaceutical firms. While tools and frameworks exist for managing portfolio risk and return (Day 2007), an assessment of how these frameworks translate into innovation outcomes would enhance understanding of what works and what does not.

A related question is whether a pharmaceutical firm should invest more efforts into fundamental science or be opportunistic with regard to external partnerships and licensing while focusing efforts on the *execution* of portfolios as well as marketing new drugs. Recent trends suggest that big pharmaceutical firms are better suited to the operational nous required for large-scale clinical trials and marketing drugs whereas small biotechnology firms explore niche areas with a strong science-based focus. This requires further research in terms of the balance between in-house research and external partnerships, and how this depends on the firm's strategy. Acquisitions, which seem to be increasingly popular, combine new drug portfolios of the acquiring and acquired organizations and it is unclear how best to "optimize" value from two sets of portfolios which may have significant overlap.

Various papers have looked at how to prioritize projects both as a dynamic and static problem. One stream of work uses decision trees, whereas another stream examines strategic choices under competition. There would be value in bringing the streams together to simultaneously consider dynamic project prioritization given competition. In other words, pharmaceutical firms are often pursuing similar therapeutic areas and indications in parallel, and viewing the prioritization decision as a purely internal exercise may not bring enough external emphasis in the sense of the battle between portfolios of firms. Theoretical work could examine this issue as it may be difficult to empirically examine how competition affects portfolios of multiple firms.

Pharmaceutical firms are frequently changing their R&D organizational structure, ranging from centralized to decentralized units. Each camp has its advocates, yet there is insufficient empirical evidence to conclude which approach is better, or at least which types of firms would prosper under each structure. The relationship between organizational structure and incremental/radical innovation appears to be strong and requires attention so that firms can understand the optimality of the choices they make. Additionally, understanding the relationship between the frequency of change and its impact on performance is crucial as pharmaceutical firms have to manage a careful balancing act between flexibility and stability. The trend in portfolio management seems to favor more flexible and accountable drug development units, and more research is needed to evaluate this approach and how it impacts portfolio optimization.

Attention is also needed on understanding how incentives affect managers and scientists in terms of their motivation to take actions aligned with firm interests. The firm is often seen as a single entity deciding and executing strategies, but the reality of multilevel hierarchical organizations executing and adapting new drug portfolios cannot be ignored. Recent theoretical work suggests that killing projects can be challenging, and that motivating riskier radical innovation may be more challenging than expected. This may be one reason why smaller firms, which perhaps have less agency issues, are able to take larger risks than large firms. The question for investigation is whether this is in fact the optimal arrangement for larger firms.

The new center for advancing translational sciences (NCATS) created by the NIH appears to be a public-private partnership effort to promote better practices in quickly delivering new drugs to patients by overcoming current bottlenecks (NIH 2012). Given the recency of the announcement (Collins 2011), there is no existing

literature on how NCATS can facilitate experimentation in innovative approaches to develop new models of drug development and delivery. For instance, interactions across disease categories will be a critical issue as therapeutics of the future may not be limited by historical designations. The areas targeted by NCATS include therapeutic target validation, chemistry, virtual drug design, preclinical toxicology, biomarkers, efficacy testing, phase zero clinical trials, rescuing, repurposing, clinical trial design, and post-marketing research (Collins 2011). With over $720 million in annual research support, NCATS presents a new opportunity for researchers to collaborate across disciplines to address varied challenges.

As can be seen, there exist a number of open questions for future research on pharmaceutical portfolio management, both on the theoretical and empirical fronts. We hope this review of current work on the topic will spur researchers across multiple disciplines to bring state-of-the-art methodologies to address these key issues.

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