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).

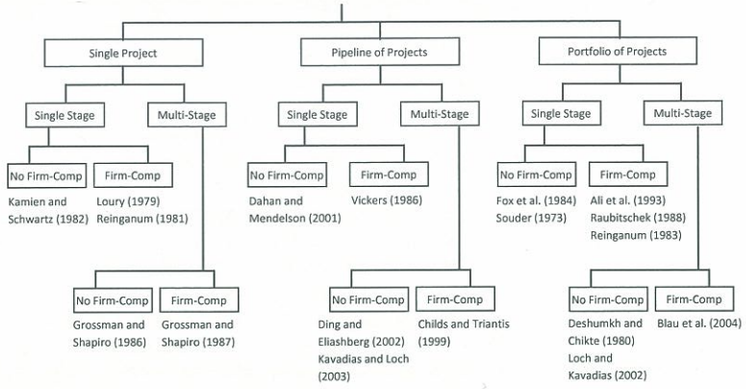

Fig. 3.5 A taxonomy of project selection problem, updated from Fig. 3.1 in Ali et al. (1993)

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.

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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.

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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Chapter 4
Grassroots Innovation: A Promising Innovation Paradigm for Pharmaceutical Companies

Ulrich A.K. Betz, Nuno Camacho, Michael Gerards, and Stefan Stremersch

Abstract Pharmaceutical firms face a period of unparalleled turmoil. Major societal, technological, and regulatory challenges require firms to quickly respond to a rapidly changing environment. In particular, the issue of how to improve R&D productivity is considered *the* key challenge faced by the pharmaceutical industry nowadays. The core thesis of this chapter is that grassroots innovation programs—structured processes aimed at stimulating employees in all corners of the organization to contribute to innovation efforts—may be an essential complement to pharmaceutical firms' more traditional and top-down stage gate processes. However, academic research to guide pharmaceutical firms in the implementation of grassroots innovation is scarce. This chapter discusses an in-depth case study of a grassroots innovation process (*Innospire*) at Merck KGaA, Darmstadt, Germany. The process design and implementation was based on theoretical derivation, to facilitate the transfer of knowledge to other firms and contexts. Hence, we also discuss our

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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.