Horses for Courses

Portfolio Management Methods for Different Stages of Drug Development

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“Horses for courses” is a term used in horseracing parlance to mean that certain horses run better on certain courses. It is a colorful way of stating that the proper tools should be used for a given task. As an example, one would not manage a portfolio of commercial buildings in the same way as a portfolio of stocks, or a portfolio of high risk experimental drugs. Similarly, within a pharmaceutical R&D organization, discovery programs are very different from the lower risk, shorter term and capital intensive late stage projects. These portfolios differ in terms of cost, timing, risk and assessment of value of the opportunity. They also differ in the components being managed and evaluated – e.g. biologic targets or a family of molecules for a specific disease. In this paper, we discuss some of the different portfolio management approaches that can be applied to the various types of pharmaceutical R&D portfolios.

What exactly is portfolio management? A simple definition is “a process for making optimal funding decisions across multiple opportunities”. A richer definition is “a systematic process to achieve maximum value and manageable risks within R&D portfolios, driven by proactive decision-making based on project assessments and strategic goal alignment” (see figure 1).

Figure 1. Summary of typical R&D portfolios, by key activities and portfolio elements.
The focus here will be on R&D portfolios in the pharmaceutical/biotechnology industries for small molecules and biologics. These guidelines can be easily extrapolated to medical devices.

A. Different Portfolios within the R&D Pipeline

Since each stage of drug development typically has its own budget and strategic goals, the development stages described below can be thought of as separate portfolios. Within each portfolio, there are distinct “portfolio elements” that are evaluated and compared, and for which funding decisions are made.

1. Research/Discovery Stage. Initially, biologic targets that play a role in disease states are identified and validated. Then chemical compounds or biological molecules are tested against these validated targets. Molecules meeting specific scientific criteria are selected, and structurally altered to improve their desired properties (lead identification and optimization). These lead molecules have the right characteristics to indicate possible clinical efficacy in at least one, and often many, disease states. Thus, the elements of the Research/Discovery portfolio are biologic targets and lead molecules.

2. Early Development Stage. The portfolio elements in Early Development are individual molecules that may be effective for treating many different diseases. During this stage of development, the critical decision of which specific indication(s) to pursue is made. Furthermore, safety and initial efficacy readings are demonstrated following a battery of tests in vitro, in animal models (in vivo) and finally in humans. It is also at this stage that the Target Product Profile (TPP) is developed as a clinical standard to assess safety, efficacy and tolerability in clinical trial results for the chosen indication. The demonstration of initial clinical efficacy at a safe dose is often described as clinical Proof of Concept (PoC), usually Phase 2, and marks the end of Early Development.

3. Late or Full Development Stage. The Full Development portfolio is comprised of molecules that have demonstrated PoC, i.e. safety and initial efficacy readings in humans for a specific disease state. The longest and most expensive of the hurdles remain - the pivotal trials - in which the molecules are tested in larger patient populations and for longer periods of time to show safety and efficacy with both statistical and medical significance. The hurdle of obtaining regulatory agency approval also needs to be overcome in this stage.

4. Life Cycle Management (LCM). The Life Cycle Management portfolio is comprised of molecules that have already been approved by the appropriate regulatory agencies, and have been manufactured, marketed and used to treat patients in at least one disease. LCM portfolio elements may include:

- Additional indication(s) for the same molecules
- Post-marketing clinical trials (Phase 4) for the purposes of expanding the label
- Different formulations for the molecule, typically to increase patient convenience
- Different delivery systems or administration regimens for the same molecule
The risks for LCM projects are typically lower since safety and efficacy have already been established in the lead indication.

B. Key Project Characteristics

At the project level, there are typically four key characteristics of analysis and evaluation. (See Figure 2)


2. Timing. Years to reach key milestones such as start and finish of clinical trials, product launch, and patent expiration/loss of exclusivity.

3. Risk. Technical factors that can derail the opportunity such as safety issues, lack of efficacy, drug/drug interactions, unwanted side effects, and manufacturing hurdles. For commercial risk - see Value below.

4. Value. Typically incorporates market size, market share (incorporates competitors on the market and in development), and pricing (Average Sales Price \{ASP\} & reimbursement) to obtain potential sales. Commercial risk (value uncertainty) is caused by uncertainty in size, market share, pricing due to lack of knowledge, changing competition, or other uncertain events.

Figure 2. Summary of differences in project characteristics (cost, timing, risk and value) throughout the development stages. The outlined cost, timing and risk estimates reflect general benchmarks, and there certainly will be exceptions that fall outside the range.

<table>
<thead>
<tr>
<th>Development Stages (Portfolios)</th>
<th>Research / Discovery</th>
<th>Early Development</th>
<th>Late or Full Development</th>
<th>Life Cycle Management</th>
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<tbody>
<tr>
<td>Cost</td>
<td>~ $5-20 M</td>
<td>~ $20-50 M</td>
<td>~ $50-400 M</td>
<td>~ $50-500 M, variable depending on type of LCM</td>
</tr>
<tr>
<td>Timing</td>
<td>~ 4-7 yrs</td>
<td>~ 2-4 yrs</td>
<td>~ 3-5 yrs</td>
<td>~ 2-7 yrs, variable depending on type of LCM</td>
</tr>
<tr>
<td>Risk*</td>
<td>&lt;10% after molecule selection</td>
<td>~ 25%</td>
<td>~ 40%</td>
<td>~ 60%, variable depending on type of LCM</td>
</tr>
</tbody>
</table>
| Value                           | • Generally not possible to estimate value via the classic metrics of market size, market share, and pricing  
• Possible to develop high level proxy of market size  
• Difficult to estimate market size, market share, and pricing  
• Possible to develop proxies for the above  
• Market size, competitors & market share, ASP & reimbursement fairly well understood since TPP¹ is known  
• Market size, competitors & market share, ASP & reimbursement typically very well understood (but largely dependent on type of LCM) |

(*) Risk = probability of reaching the next development stage
C. Portfolio Management Approaches

Let us now introduce two general approaches to portfolio management that have been successfully utilized in pharmaceutical/biotechnology companies.

1. Financial Portfolio Analytics. This approach is financially based and relies heavily on the four project characteristics of cost, timing, risk and value. The overall value of each project is expressed by the commonly used financial metrics of NPV, ENPV, Productivity Ratio and EIRR (see definitions of these below). Cashflow is also critical to a pharmaceutical company’s survival and therefore projected annual cashflow measures and low projected cashflow years are also important metrics for portfolio management. Key insights can be drawn by the following types of portfolio level analysis performed using these financial metrics (see figure 3):

- Prioritization or rank ordering of all projects based on desired metrics.
- Optimization of the portfolio based on chosen constraints. For example, what is the portfolio of projects with the maximum ENPV, when constrained by a certain fixed budget, with the inclusion of all core therapeutic area projects and a selected business development opportunity?
  - Efficient Frontier is a powerful optimization technique that deserves special mention. It determines the best mathematical portfolio of projects that produces the greatest return on investment for each level of resources (capital or human resources). Since the resources constraint is often “soft”, it helps management to know how much value can be realized by finding additional resources.

![Figure 3. Examples of outcomes that are generated for the Financial Portfolio Analytic approach, illustrating prioritization, tradeoffs, optimization (efficient frontier) and balance.](image-url)
• **Balance** means achieving a correct number of projects of a certain type, or a correct percent of portfolio resources committed to each category of projects (“correct number or percent” is typically defined by portfolio or corporate strategy). Portfolio balance of projects by phase of development, therapeutic area, launches per year, level of technical risk, and high vs. low innovation are among the common balance metrics.

The Financial Portfolio Analytics approach has been widely used in the life sciences industry.

2. **Multiple Objective Decision Analysis (MODA).** The classic Financial Portfolio Analytics approach relies entirely on financial metrics, and thus it is a *single objective* approach (that of financials). The MODA approach to portfolio management integrates multiple, often competing objectives, for assessing the value of the opportunities.

These objectives or criteria can be financial in nature, as discussed above. They can also be non-financial in nature i.e. address unmet medical needs, fill projected revenue gaps, align with corporate strategy etc. The MODA process involves identifying the desired objectives, arranging the objectives into a hierarchy, developing a measure and value function for each objective, assigning weights to the objectives (see Figure 4), and then mathematically combining values and weights to produce an overall value for the opportunities. Then prioritization, optimization and portfolio balance analyses can be applied to derive key insights.

*Figure 4. Multiple Objective Decision Analysis (MODA) example showing objectives, the measure and value function of one objective (Time to Transition), and the weighting (%) applied to the objectives. Typical MODA outputs are not shown here.*
The MODA approach is especially useful in situations (earlier development) when the classic elements of analysis – cost, timing, risk and value – lack accuracy or are even non-existent, and so other useful criteria are factored into the analysis. This methodology is only recently gaining prominence in life sciences portfolio management.

There are multiple MODA approaches, but one favored by KROMITE (and successfully implemented with several global pharmaceutical clients) is Value Focused Thinking. A thorough description of this process is beyond the scope of this paper, so please refer to KROMITE’s white paper and/or book chapter.

D. Different Portfolio Processes for Different Portfolios

Let us now integrate the above discussions into how different portfolio management approaches should be applied to different types of portfolios. Each development stage portfolio has different portfolio elements, as well as different project characteristics of cost, timing, risk and value. Therefore, each portfolio needs different analytical methods. The following recommendations for the type of portfolio analytic approaches to be used for different portfolios stem from the collective experience of KROMITE and industry best practices (see table 1 and figure 5).

### Table 1. Summary of the portfolio level decisions and portfolio management approaches most appropriate for the type of portfolio.

<table>
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<th>Types of Portfolios</th>
<th>Decision Type at Portfolio Level</th>
<th>Recommended Analytics</th>
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| Research / Discovery      | Level of resources to each program; resources often means scientists’ efforts | • Incorporation of MODA to scientific reasoning  
|                           |                                                                      | • Possible to include aspects of strategic guidance/objective and market potential    |
| Early Development         | Resources and budget based on molecule development strategy          | • Focus on MODA  
|                           |                                                                      | • Prioritization, optimization, and balance are recommended                           |
| Late or Full Development  | Prioritization of indications for given molecule                     | • Focus on MODA  
|                           |                                                                      | • Prioritization, optimization, and balance are recommended                           
|                           |                                                                      | • Dependencies need to be modeled                                                   |
| Life Cycle Management     | Resources and budget based on indication development strategy       | • Focus on Financial Portfolio analytics  
|                           |                                                                      | • Prioritization, optimization, and balance are recommended                           |
1. Research/Discovery Portfolio. Most Research/Discovery portfolio decision-making is driven by scientific tests and reasoning. A systematic MODA approach can augment the science to include aspects of strategy or market potential in a consistent way. For example, such non-scientific objectives can be incorporated for prioritizing which biologic target should be used to start a program, or which lead molecules should progress to the next stage. Scientific evidence is always the key driver, but it generally serves as a filter, rather than a rating on a scale. Filters often do not have the ability or sensitivity to differentiate amongst different biologic targets or molecules.

2. Early Development Portfolio. The MODA approach is ideally suited for Early Development portfolios where less is known about the molecules, and thus there is more reliance on non-financial objectives. This process will encourage consistent assessments of cost, timing, risk and value, despite an incomplete understanding of the molecule. It will also lead to the qualification and quantification of the non-financial objectives. Application of prioritization, optimization and portfolio balance analytics are recommended. Optimization is especially useful when dealing with multiple potential development strategies per project, or when potential business development (BD) opportunities are included in the analysis.

   During this stage of development, decisions need to be made of which indication(s) will be pursued from amongst all the potential choices. Here, MODA again has proven to be very effective. One also needs to keep in mind that when multiple indications are pursued with the same molecule, potential dependencies amongst these indications need to be incorporated in the analysis. These dependencies can include safety risks, target engagement, formulation cost and risk, regulatory approval, marketing costs and market access.

3. Full Development Portfolio. By the time the project has reached this stage, a dramatic reduction of unknowns has provided more clarity regarding both costs and rewards. This improvement in financial clarity and the substantial increase in cost-at-risk (due to expensive Phase 3 trials) lead us to recommend the Financial Portfolio Analytics approach. Portfolio objectives for this stage are financial in nature, such as achieving a level of revenue in a troubling year, or fitting large and “lumpy” costs into a constrained budget.

   Furthermore, the ever-present eye towards maximizing short and long-term value for the shareholder supports a financial method. Uncertainty and financial measure uncertainty drivers should be included.

   Portfolio prioritization, optimization and balance should be used to gain insights to effective funding decisions. Again, as in the case with Early Development, optimization is very useful when dealing with multiple development strategies per project or inclusion of BD opportunities.

4. Life Cycle Management Portfolio. Typically these projects, by their very nature, can be combined with the Full Development projects, and thus should be scrutinized by the methods as appropriate for that stage of development.
The three portfolios as defined (Discovery, Early Development, Full Development/LCM) will typically have their own separate R&D budgets and potentially different strategic objectives, although hopefully aligned with the corporate objectives. Typically, funding decisions should be made independently within the context of each type of portfolio. However, allowance for balancing the various budgets (and resources) amongst portfolios should be considered, if the pipeline flow demands it. The very important topic of dealing with dependencies amongst the portfolios is beyond the scope of this paper and will be explored in another KROMITE paper.

To conclude, let us reiterate the importance of utilizing the proper type of portfolio analytics for a given portfolio situation. Effective portfolio management is about making quality decisions based on accurate and consistent project attributes, and logical and transparent portfolio processes. The use of an inappropriate methodology can lead to misinformed, low quality R&D funding decisions. The pipeline of R&D projects is the future life-stream of a company - and involves hundreds of millions if not billions of dollars in annual R&D spend (for mid and large pharmaceutical companies) with up to hundreds of projects - so much is at stake. To remain competitive in the current environment of escalating R&D costs, a dearth of “low hanging” unmet medical needs, high regulatory hurdles, and increasing loss of patents for major drugs, the importance of effective portfolio management decision making cannot be overstated.
Financial Definitions

• NPV = Net Present Value, a sum of discounted cashflows over a stated time horizon
• ENPV = expected NPV, a probability-weighted average of all possible NPV outcomes
• Productivity Ratio = ENPV divided by expected development cost (EDC), a measure of ROI
• EIRR = expected internal rate of return, IRR associated with risk-adjusted cashflows

Abbreviation Key

• ASP = average sales price
• B/U molecules = back-up molecule
• BD = business development
• EDC = expected development cost
• IND = investigational new drug application
• LCM = life cycle management
• MODA = multiple objective decision analysis
• NME = New Molecule Entity
• NPC = total risk-adjusted development cost
• PoC = proof of concept
• R&D = research and development
• TPP = target product profile

References


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