Executive Summary

The competitive environment in today’s biopharmaceutical marketplace is forcing organisations to be more flexible, responsive and efficient than ever before. The challenge for leaders of Life Sciences companies is to ensure that the project portfolio remains aligned to strategic intent. A key characteristic of mature organisations is the ability to ensure that the most valuable projects are selected, prioritised accordingly and receive the appropriate resources. This pressure on companies to replenish pipelines with innovative drugs that have high potential for approval and reimbursement has driven companies to revise their portfolio strategy over the last decade. Whilst it is now well understood that allocating R&D budget to projects in order to maximise the total value of the entire portfolio leads to an over-reliance on financial metrics and a narrow focus on individual products and their revenues and costs, not all companies have necessarily abandoned this model.

The key to choosing products that contribute to sustainable profitability lies in changing the business focus of portfolio management from financial metrics to a business model that maximises customer value. The challenge is how to maximise return on investment within an increasingly competitive and tough economic environment that is focused on value. The answer is to ensure that Senior Management takes a strategic view of its portfolio based on maximising value as a whole. Once the strategy is set, tactical resource allocation should align with the strategy and be followed through at an operational level where demonstrating product value and shorter cycle times are critical success factors.

This paper discusses the necessary evolution of portfolio management to respond to growing demands stakeholders and, in particular, payers expecting that value be demonstrated in order to better inform decision-making.
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INTRODUCTION

The healthcare environment is undergoing unprecedented change, with several global trends increasing the demand for care. Rapid aging of the population, greater access to healthcare in emerging markets and advances in science create opportunities to enhance outcomes for patients and healthcare providers. At the same time, cost-containment measures, healthcare reform in many countries and a shift to increasingly strict regulatory standards have created challenges.

In this healthcare industry, drug developers deal with risk every day. The question is not so much about how to avoid risk but rather how to effectively manage the risk profile of the portfolio overall. Until a few years ago, Life Sciences companies focused primarily on safety, efficacy and quality. Recently, though, portfolio managers have begun paying more attention to an emerging risk that is the need to demonstrate value amid growing pricing and reimbursement pressures. Payers in several countries are indeed turning to evidence-based medicine, using cost-benefit considerations and challenging companies to prove the value of their products.

However, while the drug development paradigm has evolved with its environment, has strategic portfolio management truly matured at the same pace to create the potential for future sustainable growth?

“If we do not take change by the hand it will surely take us by the throat.”
– Winston Churchill

A ROBUST PORTFOLIO MANAGEMENT METHODOLOGY MUST BE IN PLACE

The competitive environment in today’s marketplace is forcing organisations to be more flexible, responsive and efficient than ever before. The challenge for the leaders in Life Sciences companies is to ensure that the project portfolio remains aligned to strategic intent. Change in strategy must be quickly reflected in project priorities to optimise use of finite resources. A key characteristic of mature organisations is the ability to ensure that the most valuable projects are selected, prioritised accordingly and receive the appropriate resources, whether internally or externally sourced. This is based on the premise that a robust R&D portfolio management methodology is in place, whereby the expected value of specific R&D projects is adequately calibrated with the expected impact of technical and commercial uncertainties.

Within an increasingly challenging environment, there is significant debate in the biopharmaceutical industry directed at how to determine the critical mass in the portfolio of discovery, development and marketed products to deliver future sustainable value. Indeed, to adequately account for attrition, the discovery pipeline needs to be considerably larger to keep the development pipeline filled. Figure 1 shows a hypothetical pipeline, using industry attrition, that would provide one launch in a given year.
We have seen an alarming slide in clinical trial success rates in recent years. An analysis by the Centre for Medicines Research (CMR) of projects from a group of 16 companies (representing approximately 60% of global R&D spending) in the CMR International Global R&D database reveals that the Phase II success rates for new development projects have fallen from 28% (2006–2007) to 18% (2008–2009), although these success rates do vary between therapeutic areas and between small molecules and biologics. A recent analysis highlighted that while late stage terminations are still a concern to the industry, peaking at 53% between 2008 and 2010, the most recent year range indicates that the volume of compounds terminated in the latter, more expensive phase of development has also declined.

This erosion of productivity can be attributed to a number of factors, one of which is the insistence from payers and regulators that drug companies abandon the me-too drug development approach and focus on new treatments for unmet medical needs. The greater the unmet need, the bigger the clinical risk.
This pressure on companies to replenish pipelines with innovative drugs that have high potential for approval and reimbursement has driven companies to revise their portfolio strategy over the last decade.

Not all companies are quite yet there: some still approach portfolio evaluation by looking at their projects/assets individually and prioritising them using a benefit-to-cost metric; e.g. EIRR (Economic Internal Rate of Return), r-NPV (Risk-Adjusted Net Present Value), etc. This method is illustrated in Figure 3. We have encountered many organisations that separate portfolio management from business strategy. They allocate R&D budget to projects to maximise the total value of the entire portfolio. In our experience, this leads to an over-reliance on financial metrics and a narrow focus on individual products and their revenues and costs. The real value of an organisation’s portfolio requires a holistic view beyond financial metrics that considers not only the business strategy and fit within the organisation’s business model, but is also informed by the views of stakeholders including the payer, healthcare providers, patients, carers and patient associations.

**FIGURE 3**

*Traditional Portfolio Management Process*

Changing the Business Focus of Portfolio Management from Financial Metrics to Customer Value

The key to choosing products that contribute to sustainable profitability lies in changing the business focus of portfolio management from financial metrics to a business model that maximises customer value.

The prevailing focus of portfolio management must therefore expand to encompass more than just development of resource allocation. Resource allocation is tactical and may have been a worthy overarching focus in a simpler business environment. Today, innovative products are complex, and competition is tough and multifaceted. The challenge is how
to maximise return on investment within an increasingly competitive and tough economic environment that is focused on value. The answer is to ensure that Senior Management takes a strategic view of its portfolio based on maximising value as a whole. Once the strategy is set, tactical resource allocation should align with the strategy and be followed through at an operational level where demonstrating product value and shorter cycle times are critical success factors.

To obtain the optimum selection and balance in a portfolio, we must first understand where and how markets will develop over the medium and long term. It is therefore critical to understand the different stakeholders (payer, prescriber, patient, carer and patient associations) and their requirements. The relative importance/influence of these different customers and the weighting of their needs must be an integral part of an organisation’s strategy which is followed through to their R&D planning. The goal is to view each product’s fit within the portfolio and how this contributes to the overall return on investment. For example, if the business model is focused on secondary care and meeting unmet medical needs, the organisation requires a portfolio that ensures a leadership position versus the competition with value demonstrated through improved patient outcomes. If the business is, however, focused in the generic market, a completely different business model is required that is based on demonstrating quality and value without compromising patient outcomes.

**FIGURE 4 Identifying the Sweet Spot for New Portfolio Projects at the Intersection of High Customer Value, High Strategic Value, and Optimal Investment Intensity**

Figure 4 shows a tool to help with determining what products to pursue by looking at the intersection of high customer value, high strategic value (aligned with the strategy of the business unit or enterprise), and optimal investment intensity (the level and profile of resources invested in a new product or venture). Ultimately, optimal investment intensity is the sweet spot for new portfolio projects and depends on the specific asset and the market in which the company operates. Often a biopharmaceutical company will need to make a high level of investment to enter and dominate a new market or a new technology. For example, despite medical advances, a high unmet medical need still exists in cancer treatment, since existing therapies (chemotherapy, radiation, surgery) inflict considerable
collateral damage, whether they are efficacious or not. Because the growth and spread of cancerous tumours is a consequence of the immune system failing to recognize cancer cells as foreign, a long-time hope has been for therapeutic cancer vaccines and other immunotherapies to emerge. However, the cancer vaccine field is well recognized for high development costs and risks and until today this market has been tarnished by clinical failures (e.g., Merck KGaA’s Stimuvax) and the commercial disappointment of Provenge by Dendreon since its launch in 2010. 2013 sees GlaxoSmithKline with MAGE-A3 (Non-Small Cell Lung Cancer, Melanoma data due in mid-2013) and Amgen on T-VEC (Melanoma, Head and Neck data due in 2013) best positioned to benefit from therapeutic cancer vaccines.

Othertimes, low investment intensity is right because creating incremental value may be the right thing to do. Lifecycle management strategy objectives are not solely focused on protecting market position before the expiration of the patents covering the drugs. These also look into new ways to deliver existing molecules via new delivery routes to improve patients’ lives, either through increased adherence, reduction of side effects or improved therapeutic outcomes. The development of a patch formulation of rivastigmine is a good example. It provides comparable exposure to the highest doses of capsules (12 mg/day) with improved tolerability, allowing easier access to optimal therapeutic doses.

**Measuring the Customer Value**

From a biopharmaceutical perspective, the customer is a spectrum of stakeholders including the payer (i.e., central government, local authorities, insurance companies and individuals), healthcare providers, patients, carers and patient associations. Marketing efforts have historically focused primarily on healthcare providers as the ones who initiate treatment. However, as the focus has moved towards a need to demonstrate value in an environment of cost containment, payers have become key decision-makers and most markets have a system of health technology assessment which has driven VBP (Value-Based Pricing). Central to VBP is the development of value arguments which can be adapted to meet the needs of individual stakeholders. The value arguments should address the cost and benefits of treatment, with budget impact arguments needing to be tailored to each payer environment.

Even though the definition of value varies from one country to another, most of the models are based on VBP. The High Level Pharmaceutical Forum (HLPF) was set up in 2005 as a three-year process to find relevant solutions to public health considerations regarding biopharmaceuticals, while ensuring the competitiveness of the industry and the sustainability of the national healthcare systems. This high-level ministerial platform for discussion among Member States, EU institutions, industry, healthcare professionals, patients and insurance funds focused its work on three main topics: information to patients on diseases and treatment options; pricing and reimbursement policy; and relative effectiveness. As part of these activities, a questionnaire was submitted by the HLPF to all European Member States. The aim was to identify the demand-side benefits which are seen as important when assessing the value of an innovative medicine. The benefits identified by the Member States themselves fell into three broad categories:

1. **Therapeutic/Clinical** benefits: these refer to new medicinal products, which treat or prevent diseases with a significant unmet medical need, or diseases where existing treatments are associated with significant risks. Target populations may be broad or confined to specific populations.
2. **Quality of Life** benefits: these refer to new medicinal products, which, compared to available treatments, result in an improved quality of life. Target populations may be broad or confined to specific populations.

3. **Socio-economic** benefits: these refer to new medicinal products, which, compared to available treatments, deliver a patient benefit which results in a benefit at a societal level, for example by reducing days off work or reducing carer burden. Other benefits, for example, relating to vaccines result in reducing risk of disease in broader populations.

This, therefore, means that the portfolio strategy should include a continuous evaluation of individual product profiles during development to ensure they meet likely customer requirements and that they can compete with competitor products that are either in development or available on the market. The required profile to deliver value is usually referred to as the TPP (Target Product Profile).

In summary, customer value can be measured by assessing how a TPP caters for an unmet therapy need relative to the current therapy standards as illustrated in Figure 5.

![Figure 5: Measuring Customer Value](image)

Until the late 1990s commercial go / no-go decisions were based on clinical safety and efficacy compared with competitor products and with prices based on willingness to pay with no real economic justification in most countries. Today, this is no longer the case and value arguments are crucial. Payers are key decision-makers and commercial success depends on the ability to demonstrate value within individual payer’s environments. This has added a significant level of complexity to development since payers also require demonstration of value in the real world. Clinical development rarely creates this environment because of the regulatory requirement to demonstrate safety and efficacy within a controlled population and environment. This requires a transformative change to the drug development process to integrate real-world strategies to identify better and earlier the relative value of potential products and thus meet payer, as well as medical, needs head on. A key development challenge is to create these real-world arguments while meeting the regulatory demands and minimising delays in launch. Being first to market with a product that treats a condition with a significant unmet medical need is no longer enough. This is illustrated in the example of the NICE guidance for the use of belimumab. NICE did not recommend belimumab as add-on therapy to standard care for the treatment of active autoantibody-positive systemic lupus erythematosus, although this is a first in class compound.
Combining a Measure of Customer Value with the Traditional Portfolio Decision-Making Metrics

With the need to demonstrate value amid growing pricing pressures, the combination of a measure of customer value with the traditional portfolio decision-making metrics of strategic fit and investment intensity (as illustrated earlier in Figure 4) is required to better inform decision-making. Organisations looking to evolve their portfolio management approach need to consider critical success factors to improve the accuracy of portfolio decision-making metrics.

**CRITICAL FACTOR 1:** First overlay development success probabilities with success probabilities of managing optimally the 4th hurdle.

Most companies still use the traditional NPV metric in determining the financial value of their development compounds. The drawback of this valuation method is the enormous risk associated with clinical development. These shortcomings have led to the development of the r-NPV in light of the substantial uncertainty around safety, efficacy and quality inherent in biopharmaceutical R&D. The cash flows are multiplied by their respective likelihood of occurrence taking into account historical data on development success probabilities. Figure 6 indicates the principles of an r-NPV calculation.

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**Final draft guidance from the UK National Institute for Health and Clinical Excellence (NICE) does not support the use of belimumab for treating Systemic Lupus Erythematosus (SLE).**

The National Institute for Health and Clinical Excellence (NICE) has published a final appraisal determination (FAD) for the use of belimumab (Benlysta®) in treating Systemic Lupus Erythematosus (SLE). The FAD does not recommend belimumab, within its licensed indication, as add-on therapy in adults with active, autoantibody-positive SLE with a high degree of disease activity (for example, positive anti-double-stranded DNA and low complement) despite standard therapy.

NICE’s independent appraisal committee concluded that compared with standard care, there was some evidence of the clinical effectiveness of belimumab. However, the evidence considered did not persuade the Committee that belimumab provided enough health benefit for patients in view of how much the NHS would need to pay for it compared to standard care, as the cost of the drug in relation to how well it works is very high. As some people with severe disease currently receive rituximab, it was also considered relevant to compare belimumab with rituximab although it isn’t licensed for this use. However, there were no reliable data to show the relative efficacy of belimumab compared with rituximab, and no sound case presented to the Committee on the cost effectiveness of belimumab compared with rituximab.8
However, these development success probabilities alone are not sufficient. Demonstrating to regulatory agencies just a product’s safety, efficacy, and quality (the first three hurdles) is no longer sufficient and manufacturers must now demonstrate both clinical effectiveness (Is the new product better than currently available alternatives, including no treatment?) as well as cost-effectiveness (Is the product good value for money?) to ensure success in the marketplace. Portfolio methodologies have naturally evolved to also consider success probabilities of achieving the optimal differentiated value of a product, which will support reimbursement and an acceptable market share at a price commensurate with a minimum rate of return. As illustrated in Figure 7, if we were to compare two products of similar r-NPV, developing a product for a disease with a high unmet need or lower precedents of value would carry less risk than developing a product with a low unmet need or higher precedents of value, should the likelihood of meeting the targeted TPP be identical.

This is important since the perceived differentiated value of a product relative to the current gold standard therapy is a key factor in determining the price of a product.
\[ V = R \pm D \]

With \( V \) = Value (Price), \( R \) = Price of reference product (Gold standard therapy) and \( D \) = Net value of the perceived differentiation.

**CRITICAL FACTOR 2:** Secondly, use the price assumptions that do reflect the perceived value of the products to payers.

Indeed, more and more Health Technology Assessment (HTA) agencies will only grant reimbursement if a product’s projected cost-effectiveness falls into a more or less defined threshold for willingness to pay, e.g., £30,000 per quality adjusted life-year (QALY) in UK, $50,000 to $100,000 per QALY in US and €30,000 per QALY in Spain. Price assumption of a new product that is not based on cost-effectiveness grounds may lead to over-valuations in the r-NPV calculations. Therefore, a threshold minimum product price that meets the cost-effectiveness criterion should be used in the calculation for r-NPV.9

> **What are the Implications?**

This is of course an iterative process. Products should be reviewed regularly as they progress through the development pipeline and as soon as new (market) data become available. This approach also requires earlier consideration in the life-cycle stage, including the type of data to be collected to meet the therapeutic, QoL and socio-economic concerns described earlier.

The right combination of pharmacoeconomic data with traditional valuation methods such as r-NPV in early development phases is likely to enhance the efficiency of R&D resource use and also provide a solid foundation for communicating product value to external decision-makers further downstream, increasing the likelihood of regulatory and reimbursement approval and ultimately commercial success.

> **What are the Benefits?**

Benefits of the use of this approach for various stakeholders are illustrated in Figure 8. In particular, for Non-Generic Drug Development companies, it provides stronger incentives to prioritise and invest in drugs for those medical conditions where there is greatest need and ultimately contributes to increasing the likelihood of commercial success.

**Figure 8** Benefits of Combining a Value Index with the Traditional Portfolio Decision-Making

- **PAYER/REGULATOR**: Provides stronger incentives to prioritise and invest in drugs for medical conditions with greater needs.
- **PHYSICIAN**: Introduces better treatment options to physicians expected to consider pharmacoeconomic evaluations, contributing to reducing health related expenses while increasing the quality of patient outcomes.
- **BIO PHARMA**: Informs stop-go decisions and portfolio reviews, enabling the allocation of finite R&D resources on innovative medicines with clear benefits for patients, their caregivers and societies.
- **PATIENT**: Facilitates easier access to drugs for medical conditions with greater needs.
CONCLUSION

With payers becoming increasingly important in determining the commercial success or failure of biopharmaceutical products, portfolio managers have begun paying more attention to the need to demonstrate value amid growing pricing pressures. Organisations looking to evolve their portfolio management approach therefore need to translate payer-related strategic considerations into measures of value and overlay these with the traditional portfolio decision-making metrics of strategic fit and investment intensity.

This approach, however, requires earlier consideration in the life-cycle stage of pharmacoeconomic challenges. While payer needs should start to receive attention as early as Phase I, there are few Life Sciences companies who presently invest to this extent in pharmacoeconomic activities to support drug development and still only do this at Phase III. With the growing concern regarding budget impacts and the pricing of products by healthcare systems, such a transition is, however, imperative. A process of reassessing the pharmacoeconomic case for a drug underpinning each stage of drug development is required to contribute to the decision whether or not to proceed to the next clinical stage and, ultimately, to reimbursement and market entry. This also has a direct implication on the organisational model. We are seeing a lot of companies restructuring and reorganising to change how they deal with the increasingly complex environment. The establishment of multi-disciplinary Pricing and Market Access functions including or supported by Health Outcomes is essential in that process to develop and implement strategies that demonstrate and communicate the value of products to relevant stakeholder groups. The real challenge is getting the R&D and Commercial teams to acknowledge the importance of the payer stakeholders and resources to be invested ‘at risk’ to develop the evidence needed for market access pre-launch.
REFERENCES


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