Maximising the impact of technologies on drug discovery through portfolio management

The opportunities to invest in new technologies in drug discovery are broad and extensive. Knowing where to place your investment and ensuring return on these investments is critical to ensure future success. The application of portfolio and project management (PPM) tools, along with scientific expertise, is important to ensuring transparency and alignment in applying the technologies, as well as, measuring the impact of the investment on the drug discovery pipeline. This paper will explore the application of portfolio and project management (PPM) as applied to drug discovery technologies. Drawing upon examples from systems biology, translational medicine and high throughput screening (HTS), this paper will illustrate the use of PPMs. The lessons learned, best practices developed and barriers to success will also be explored. The authors believe that the application of PPM can have an impact on applying advanced technologies to deliver quality and innovation to drug discovery pipelines.

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Pharmaceutical discovery has seen the introduction of many new technologies over the past couple of decades, including high throughput screening, combinatorial chemistry, genomics, proteomics, RNAi, as well as biopharmaceutical, translational medicine and system biology approaches to drug discovery. Each of these technologies offers the potential of delivering great promise to change the paradigm of drug discovery and bring forward new innovative drugs to patients. Each technology brings with it a high degree of complexity and the need for internal and external investments, including specialised staff and capital investment in equipment and laboratories. Pharmaceutical companies have many more opportunities to invest in these technologies than resources available. Pharmaceutical executives have to make decisions about which technologies to invest in and to what extent to invest. They have to answer the question: "Do we want to be early adopters of the technologies or be a fast follower?" The speed of scientific advancement means the fast follower approach could result in being left behind and then struggling to catch up. The risk of being an early adopter is that resources are wasted as the full potential of the technology

is realised or not. In either case it is critical for executives to understand the return on their technology investment and the impact of those investments on their discovery pipelines.

In 2004, this author[1] explored how portfolio management tools could be used in the drug discovery space. At Wyeth, this included bringing transparency to the discovery portfolio. He postulated that transparency and the use of metrics was essential to fostering and taking advantage of innovation. These approaches contributed to an increase in production and helped to manage the risk inherent in a drug discovery portfolio. The paper goes on to describe how portfolio management tools were built and implemented at Wyeth, as a way to optimise the use of budgets and resources. Finally, the use of PPM tools in decision making and prioritisation was discussed. The important concept of the need to balance, control and governance systems needed to manage the business while not stifling innovation and creativity was also described. This paper aims to describe the application of these tools to the problem of managing technology portfolios.

The approach taken to Discovery Technology Portfolio Management (DTPM) at Wyeth involved the following objectives:

- Dedicated resource providing a sound unifying structure, (standardised nomenclature, databases, resource prioritisation tools, budget control, governance, etc).
- Devise tools for determination of the impact of the technology on the success of the R&D process (metrics).
- Provide tools and data for optimisation of resources and prioritisation across all R&D areas – critical for technology groups that support multiple therapeutic areas.
- Provide data for review of suitability on a periodic basis.
- Provide an outside perspective for communication and analysis of the processes and deliverables of the managed group.

This paper will describe how these five objectives were achieved at Wyeth and how they were applied. Also, this paper will look at the above angles with respect to three examples of technologies with the capability of changing the way pharmaceutical companies discover and develop new drugs: a newly introduced capability (Systems Biology), an establishing but still new capability (Translational Medicine) and a well-established and organisationally mature technology platform (HTS). From these examples, the lessons learned, best practices and barriers to success will be described. The three examples represent three stages needed to introduce and establish technologies. The first stage involves gaining a foothold and introducing new technologies. Stage two involves aligning the Technology Portfolio, and stage three involves maintaining alignment and having an impact.

Stage 1: Gaining a foothold and introducing new technologies

The Systems Biology Group was established at Wyeth in April 2008. This group's role is to help stakeholders expand and support their Portfolios by identifying new targets and biomarkers through leveraging the power of multiple technologies in a single, integrated unit. Advances in technology, automation, software and computing have enabled this field to continue to evolve[2,3]. It is important to note that the role this group plays is auxiliary, meaning that utilisation of this resource is not required for the drug discovery at Wyeth, making it important to develop and maintain customer relationships. Generally, scientists that would like to explore new biology not found in the literature may choose to pursue Systems Biology projects. Transparency is the key to managing the relationship between the stakeholders and the Technology Group. Timelines and milestones will depend on knowledge of expertise from both perspectives. A productive, collaborative relationship will evolve when both teams play a role in this partnership as both are stakeholders in project success.

When new technologies are launched into an organisation, many challenges lie ahead. The newly established group will need to advertise within the organisation to solicit projects that are in alignment with the Portfolio. Projects will need to be designed to leverage technologies that have been established and validated first, while deferring projects that involve technologies that have not yet come on-line. As projects advance, progress should be communicated to key stakeholders. Finally, when projects complete, a critical element to success is to demonstrate that the project has added impact and value to the organisation. Portfolio Management can provide the transparency and high-level view needed to 1) help stakeholders understand which technologies are validated and ready to be utilised; 2) implement a process to ensure that vetted and aligned projects move forward; 3) develop tools to communicate and capture impact; and 4) ensure that the Portfolio is balanced.

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A process for alignment was established through documentation, scientific discussion and through multiply-endorsed documentation. A document co-endorsed by both the stakeholder and the Technology Group scientists, describing the hypothesis, decisions enabled by the work, project priority from the stakeholder's view and any expected follow-up work, is required for project initiation. The idea is to ensure proper vetting prior to project initiation and to capture the impact that the project will have on the Discovery Portfolio. The next step is to ensure that experimental detail, including resources, budget and timeline information, is agreed upon by both stakeholders. Feasibility, impact and priority are revisited to ensure that alignment is maintained throughout the process.

A dedicated team of scientists with expertise in an array of quantitative high-throughput biological tools was brought together to support this initiative. Projects on single validated platforms were sought first and those requiring a platform that was not ready to go were notified of this delay. Projects requiring multiple platforms, where some technologies were validated and available and others not were asked to engage with the Technology group to design experiments around the temporary limitation(s). Importantly, throughout the process, timelines have been met and data has been communicated regularly to stakeholders.

Portfolio Management developed tools to provide transparency in this process by 1) establishing a database to manage project data and documentation; 2) soliciting project updates to provide a form of communication and transparency; 3) ensuring that the projects maintain alignment with the stakeholder portfolios; and 4) developing a way to present the Portfolio graphically that can be used to quickly access status. For this early-stage group a decentralised governance model was put in place to ensure that the appropriate level of stakeholder buy-in exists throughout the lifetime of the project.

Finally, a primary goal for the Portfolio Manager is to ensure that the portfolio is balanced. Projects should be distributed across the areas of research and across the technologies available. Impact will need to be demonstrated early on. The portfolio should include both 'quick wins' as well as long-term projects that would have not otherwise been possible had the Technology Group not existed. For this reason, the impact and decisions that will be enabled by the work should be stated up front and captured so highly impactful projects are chosen for prioritisation. Occasionally, a project may have unrealised impact and it will be important to revisit and have a process in place for capturing the impact well after completion.

Stage 2: Aligning the Technology Portfolio

Once a technology department has been launched, a 'honeymoon' period ensues where scientists are eager to capitalise on the promise of the new competency. Many new projects are initiated and organisational expectations are high. As experience develops and the realities of implementing cutting edge science are realised, a growing disenchantment may occur even with the application of the best portfolio management tools.

It is at this point that portfolio and project managers can contribute to the success of the department by providing clear and comprehensive communication of project status. In order to maintain buy-in from the internal stakeholders of the technology, a thorough and open analysis of its alignment with the rest of the R&D process is needed followed by the implementation of corrective measures identified during this process. Portfolio managers can provide the tools and necessary transparency and independence to facilitate and then implement effective decision making.

At Wyeth, the Translational Medicine Department (TMed) came into being in February 2006 with the goal of improving the predictability of success of R&D programmes[4]. Through the discovery, qualification and implementation of biomarkers, the TMed team work to improve the translatability of preclinical to clinical work and to apply what is learned in the clinic back to the bench. Placed at this interface between Discovery and Clinical Research, Translational Medicine faces the challenge of aligning with the different needs and viewpoints of these two elements of the research and development organisation. In order to support the needs of both groups and support the R&D pipeline, Wyeth's Translational Medicine Department entered into a unique five-year, £50 million ($75 million) collaboration with a nine-way consortium comprising four Scottish universities and their associated National Health Service boards, and Scottish Enterprise[5]. The resulting collaboration was launched in 2006 as the Translational Medicine Research Collaboration (TMRC). During its first few years, Translational Medicine, in collaboration with Therapeutic Area departments, initiated a large number of projects within both the TMRC and other individual collaborations. Over the next few years Wyeth's

pipeline priorities changed and it became necessary to re-evaluate the ongoing investments in Translational Medicine.

A number of tools were developed to aid in assessing the fit, value and impact of the large portfolio of Translational Medicine projects. A data-driven scoring tool was established to facilitate impartial discussion between the various internal customers and allow consensus building. Projects were scored by a panel of internal customers from both the Discovery and Clinical branches of R&D. Four criteria were scored; Fit, Unmet Need, Value and Feasibility (**Table 1**). **Figure 1** depicts a grid plotting feasibility (risk) versus value (reward) with regions of the grid identified as risky, balanced or safe projects. Depending on the goals of the organisation and its tolerance to risk, an appropriate spread of projects can be determined (**Figures 2** and **3**). Actions can be taken to move the portfolio toward this ideal distribution and yearly re-examination of the portfolio can be used to maintain the agreed-upon project distribution.

Governance of projects initiated by a core technology department has a number of challenges compared to projects initiated within Therapeutic Area departments. As a service department, the needs of multiple internal customers spanning the organisation must be met. With a single budget and centralised resources it is simpler to have a centralised governance body with representation from the different departments that are internal customers. This allows transparency across the organisation and facilitates prioritisation of work supporting multiple pipeline projects. This form of governance also has the advantage of efficiency in that a single meeting can deal with all supported areas. At its inception, it was this form of governance that was used to prioritise resources for Translational Medicine.

A drawback to centralised governance is that individual supported departments may not feel they have adequate 'skin in the game'. This could lead to decreased support as the realities of scientific research are manifested and changes in pipeline priorities result in a loss of value for ongoing work. After realignment of the Translational Medicine portfolio, it was decided that a more direct involvement of Therapeutic Areas in the governance of TMed projects was required. Governance was decentralised to the appropriate Clinical and Discovery Therapeutic Areas.

This decentralisation increases the value of PPM leadership in these roles for its ability to assess, from a dispassionate perspective, the overall impact of any core technology deployment in terms of delivered value to the Wyeth organisation. The executive management group will have made a significant investment of resources in establishing these core technology groups. As such, they are interested in understanding whether the investment has delivered value to the organisation in comprehendible terms. The PPM group's value in this case is to extract the scientific deliverables from these groups and articulate them in terms of benefit to the business in a digested manner comprehendible to the executive management group. The added value of the PPM group here is its understanding of the interconnectivity and dependencies of projects across the organisation so supporting the articulation of value.

Table 1: Project criteria. Key players evaluate individual projects across four criteria. Averages of Unmet Need, Feasibility and Value are used in plotting charts as in Figures 2 and 3

Fit	How clearly aligned is the project with the strategy of R&D?
Unmet Need	How large and how well defined is the knowledge gap? How essential to the success of the pipeline asset is it to fill this gap?
Feasibility	What is the probability of successful delivery on time to impact critical pipeline decisions?
Value	How critical will the deliverables from the project be in informing pipeline decisions?

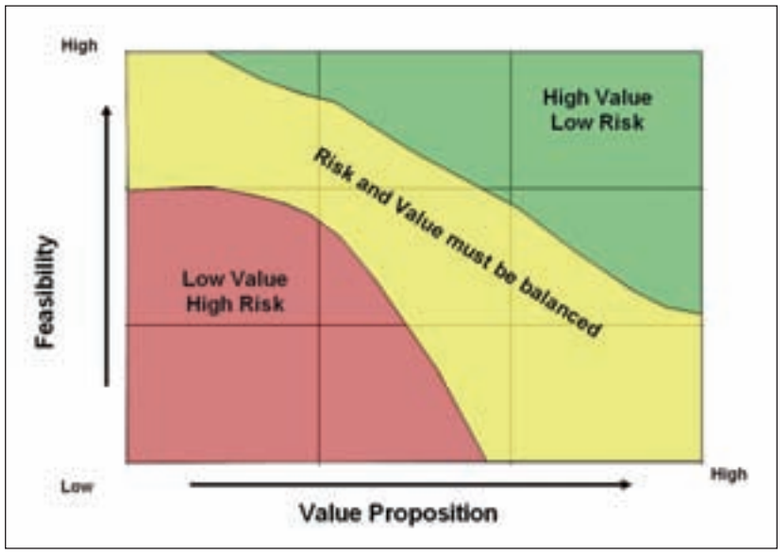


Figure 1: Risk versus reward chart

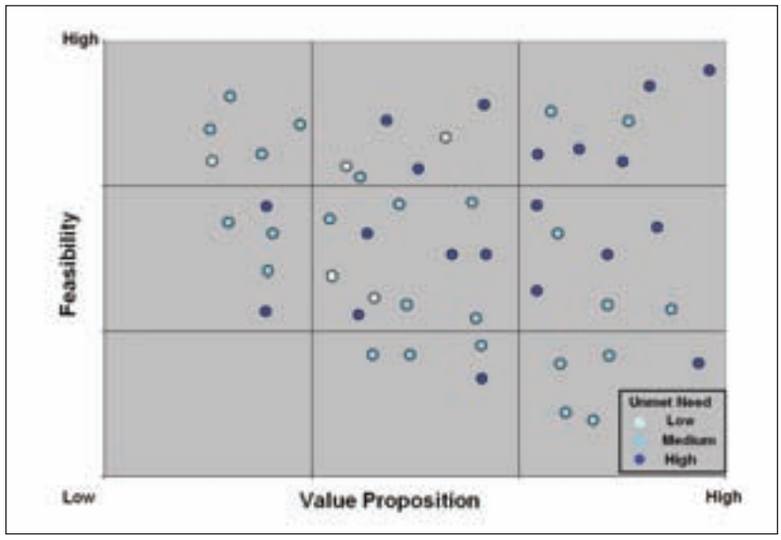
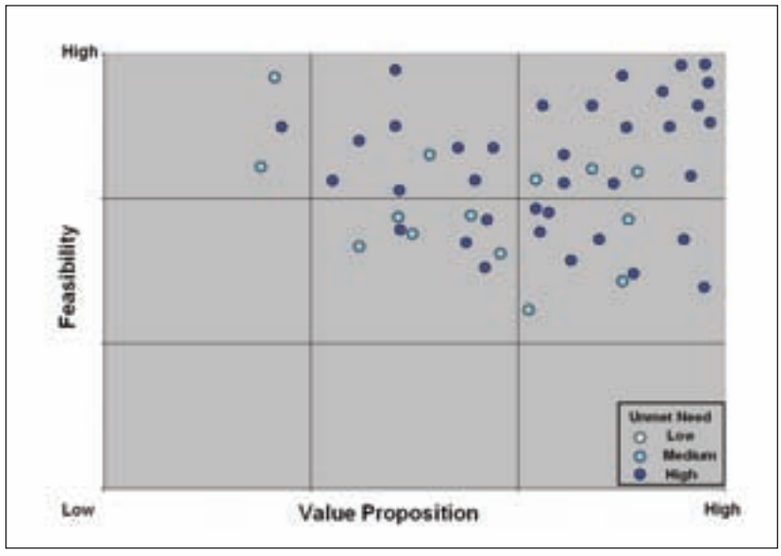


Figure 2 (above): Portfolio balancing risk and reward. Hypothetical portfolio of 50 projects in which projects of lower feasibility but higher value are balanced by projects with high feasibility

Figure 3 (below): Portfolio focused on safer projects with a higher return. Hypothetical portfolio of 50 projects in which resources are focused on projects of high value and feasibility



Stage 3: Maintaining alignment and measuring impact

The third example of the application of the PPM techniques developed at Wyeth focuses on maintaining alignment of HTS with the needs of the Discovery organisation. HTS is a core Discovery Pharmaceutical capability that enables early stage Discovery programmes to screen the entire corporate compound collection, typically comprising 0.4-1.0 million discrete compounds, in a timescale of a few weeks[6]. Established HTS functions are able to mount and complete 40-60 campaigns per annum on a steady-state basis[7].

To realise this capability, several discrete activities need to converge. These include, at-scale protein expression, the provision of live cells on a just-in-time basis, assay development, adaptation to automated operation, the provision of compounds from the corporate collection and the securing of large stocks of assay-specific reagents and consumables[8]. HTS has developed as a discrete discipline over the past 15 years. During its early years HTS underwent many of the issues described in Stage 2. Organisational expectations for delivery were unclear, and often over-sold. It constantly had to justify its existence and value to organisations which had traditionally undertaken lead identification within Therapeutic Area teams working on an iterative basis with medicinal chemistry teams. While this uneasy impasse existed for several years in many organisations, HTS ultimately became the accepted means of prosecuting early stage lead identification within almost all pharmaceutical organisations. This was accomplished by a combination of realistic expectation setting, transparency of progress and ultimately because evolving HTS capabilities in terms of assay throughputs eclipsed what could be supported within Therapeutic Area teams. To maintain close alignment of HTS and its supporting activities within Pharmaceutical Discovery, it was necessary to develop a number of communication and management capabilities. These are discussed further below.

For a core HTS function supporting multiple therapeutic areas, maintaining communication across the Discovery organisation is key. At a basic level, the HTS group ensures that its screening data sets are made available, in a standard format, to the wider organisation via a standard results database. Outside the needs of their immediate client, this allows chemi-informatics analyses within target classes and across research areas, a level of consistency not possible if screening were solely within the remit of individual Disease Area teams.

At the next level, campaign progress is made available to the wider organisation via intranet sites allowing an at-a-glance assessment of status of any one campaign. Related to this is the extraction and publication of metrics about how long it actually takes to generate a stable method fit for at-scale operation, validation thereof and securing of all key reagents necessary for prosecution of campaign, as well as the time to complete the screen itself. In an environment where the mantra has become “we screen our compound collection

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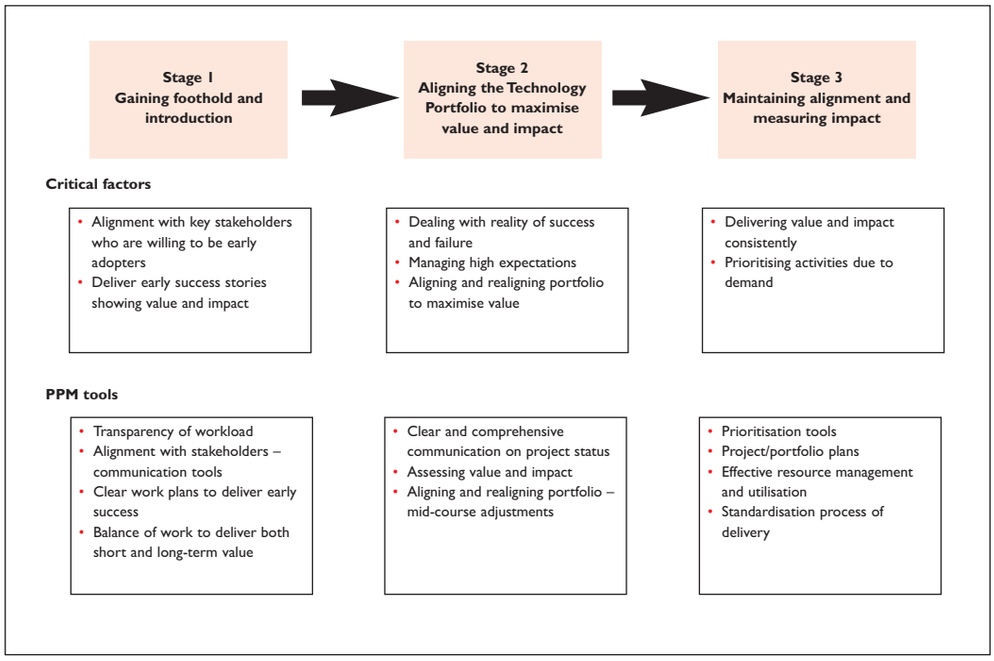
Figure 4
Stages of applying new technologies



in two weeks" it is important that the necessarily considerably longer holistic timescale for campaign completion is comprehended. At completion of the screening campaign, it is vital for continued engagement that feedback on downstream progress in lead identification/optimisation is provided to the HTS team responsible for the initial identification of the lead series compounds.

Moving to a higher level of organisation, it is important that the wider Discovery organisation is aligned behind providing the necessary internal resources required to establish an HTS campaign on site. Clearly the nature of the resources will vary by the specific instance of campaign but typically these internal resources will include the ability to express functional protein at scale, the provision of large numbers of live cells on a just in time basis, the development of a tractable and robust HTS assay methodology and the availability of the necessary automation assay lines for assay validation and operation. Clearly many of the above activities represent projects in their own right. Only following the successful completion of each of these activities can the HTS activity itself commence. For best use of finite resources, it is important that the Research Executive can take a balanced view on the tractability of the component elements behind the proposed HTS campaigns. The establishment of a cross Research Area management committee to shepherd the development of new campaigns as well as ensuring that the necessary resources are in place to support the downstream output from the campaigns themselves is an approach that has demonstrated considerable value. In addition, manufacturing resource planning techniques are now being developed by some of the leading HTS practitioners with the objective of developing more effective campaign scheduling through the use of sophisticated supply chain manufacturing planning and communication techniques[9]. While these are ostensibly software projects, their successful implementation requires significant change management implementation and effective communication across disparate groups within Discovery and potentially third party suppliers. This is a role which PPM groups across the industry could become intimately involved with in the future.

Outside the immediate communication requirement, PPM contributes to the overall governance of installed capability/technology groups at an organisational level. The organisation has made considerable investment in the capabilities of such core groups and it is important to comprehend in a consistent manner whether the investments are delivering what is required of them

This works at a tactical level by providing a simple and clear picture of the overall status of the portfolio within the HTS cycle and activities downstream from it. At a more strategic level, the aggregate view of the portfolio across multiple Research Areas allows the Research Executive to take a

holistic view of overall portfolio progress and undertake capacity planning as the balance of absolute number of assays or target types varies with time. This allows timely investments to be made in additional capacity or new capability for the benefit of the whole Discovery organisation. A holistic view of the projected forward order pipeline allows the Research Executive to take a holistic view on competing priorities for resource.

The case for technology PPM tools

As described above, three examples of implementing new technologies into the Drug Discovery Process were illustrated. Three stages of implementation were described: Stage 1: Gaining a foothold and introducing new technologies; Stage 2: Aligning the Technology Portfolio; and Stage 3: Maintaining alignment and measuring impact. Each of these stages has significant challenges and there are critical factors that are needed to be successful. The cases also describe and illustrate how project/portfolio management tools have been developed and applied for each of the three stages. The tools used vary based on the needs of each stage. These are summarised in **Figure 4**.

During Stage 1 it is important to ensure that there is alignment of activities with key stakeholders who are willing to apply the technologies early and often untested. It is also important to have early success stories. These 'quick wins' are critical to show the value and impact of the technology. PPM Tools bring transparency to the application of new technology. This is important to ensure there is alignment and buy-in of stakeholders. Clear project plans and project management is also important to focus on early success and 'quick wins'. Finally, PPM Tools should be aimed at ensuring a balance of work to deliver both short and long term value.

In Stage 2, the 'honeymoon period' is over and with early success comes a high expectation of the value a technology can deliver. As experience is gained, the reality of implementing cutting edge science is encountered. There is a risk that stakeholders may become disenchanted with this reality. In Stage 2, PPM Tools should be focused on clear and comprehensive communication of the status project and workload. This is important to ensure continued buy-in and to minimise disenchantment and manage stakeholder expectations.

PPM tools are also important if mid-course adjustments and re-prioritisation is required. These adjustments to the portfolio are needed to ensure that new technologies continue to deliver value and impact.

Finally, in Stage 3 the technologies become mature and accepted and there is a high expectation of the value and impact a technology can deliver. In Stage 3, PPM tools are important to maintaining alignment through communication with stakeholders. The focus of applying these tools at this stage should be effective resource utilisation and to prioritise activities. Also, as the technology matures PPM Tools can also drive appropriate standardisation of processes.

Conclusions

This paper has addressed the issue of how multiple strands of a complex research organisation are managed at Wyeth. We have established a Technology PPM capability with dedicated and experienced resources to provide visibility, alignment and the means of assessing impact of major capability investments within the organisation. We have described how this capability is deployed across developing, mid-term and established organisational capabilities each of which faces its own unique challenges.

Within Wyeth, PPM plays an important part in terms of organisational transparency in that, by articulating capabilities in a comprehendible manner, it sets realistic expectations for performance of key core groups, for example, the HTS functions. This is especially important because of the cross functional nature of the work of these functional groups.

In terms of alignment, we have shown that PPM has developed appropriate tools for undertaking portfolio review exercises to realign the Translational Medicine portfolio with internal focus changes of the business. Such exercises require the collection and analysis of the underlying data in a highly consistent manner. It would be difficult to undertake such an exercise on a consistent basis if multiple groups were running the analysis. Analysis by a central independent resource results in more impartial decision-making.

Additionally, holistic views of the capacity and capabilities of core groups such as HTS can be undertaken in the context of the overall portfolio demand profile such that focused investments can be made in a timely manner.

Finally, PPM capabilities have allowed us to develop appropriate tools supporting the need to define value, to appraise capabilities holistically and to assess portfolio fit. It is important that such tools are employed on a consistent basis which again argues for the central role of a PPM group. DDW

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