Shaping Pharmaceutical Strategy
Recombinant Portfolio Management
– Recognising and Enabling Innovation
Catenion

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Catenion's "Shaping Pharmaceutical Strategy" Series

"Recombinant Portfolio Management – Recognising and Enabling Innovation" is
the third commentary in Catenion's "Shaping Pharmaceutical Strategy" series. While each
stands on its own and can be read independently, readers will get the full benefit if they
are familiar with the basic ideas discussed in the first two commentaries.

The first commentary, "Elements of Winning Strategies in R&D", introduces the concepts
of 'productivity-led' and 'creativity-led' values & beliefs and resulting R&D Business
Models.

The second commentary, "Recombinant Innovation Management (RIM) – How to Stimulate
Breakthrough Innovation within Large R&D Organisations", discusses how large com-
panies can become more 'creativity-led' and prone to breakthrough innovation without
giving up the obvious advantages of the 'productivity-led' systems and structures.

This third commentary in the series, "Recombinant Portfolio Management – Recognising
and Enabling Innovation", focuses on how Portfolio Management can act as the central
'switchboard' function within an R&D organisation and can help stimulate and capture the
value of breakthrough innovation. It offers a balance between the various different driv-
ers and requirements of 'productivity-led' and 'creativity-led' corporate strategies at the
organisational and project levels.

"Although it may be admirably suited for a few specialized copying applications, the Model 914 has no future in the office-copying-equipment market."

Arthur D. Little report from 1959, commissioned by IBM,

on the future prospects of the first xerographic copying machine

"I think there's a world market for about five computers."

Thomas J. Watson (IBM Chairman), 1943

Portfolio Management has Become Standard Practice in the Pharmaceutical Industry

Portfolio Management has become standard practice in Pharmaceutical R&D over the last decade. Most companies have implemented processes and systems with varying degrees of sophistication and rigour across the entire R&D value chain from Early Discovery to Late Development, both for internal opportunities and as part of due diligence and licensing activities for external opportunities.

The goal of R&D portfolio management is to maximise the economic or strategic value of a pipeline by prioritising resource allocation within and across projects, indications, therapy areas or entire business fields. This prioritisation of resource allocation is usually achieved by trading off the three dimensions of risk, return and strategic fit. The importance and relative weights of the three dimensions are dependent upon a given company's preferences (utility in 'portfolio speak'). As such, portfolio management is a central piece in the arsenal of 'Managed Research' tools and practices because it translates corporate strategies into actions at the level of therapy areas and projects. All this is often accompanied by incentive systems that align individual actions with portfolio and corporate goals.

While portfolio management is primarily a process, it also comprises a number of tools and methods along the dimensions of risk, return and strategic fit. Companies use those tools and methods to varying degrees of sophistication – from simple qualitative scoring schemes to more complex stochastic modelling.

Methods to evaluate the risk dimension range from simple traffic-light scoring systems for the main risk categories (technical, clinical, regulatory, and market) to more sophisticated in-depth risk profiles for each project.

The return dimension is usually assessed by defining target product profiles (TPPs) that serve as a basis for evaluating the levels of addressing unmet needs, competitiveness, treatment patterns and epidemiology. These then become inputs into forecasting models that range from simple judgement-based systems to very sophisticated algorithm-based systems (neural network computing that analyses correlations between a variety of factors and market share being the latest 'rage'). For clinical projects, the risk and return dimensions are routinely collapsed into risk-adjusted net present values (rNPVs) by using decision trees, often with benchmark success probabilities. There are several variations on this theme, such as Monte Carlo simulations or Real Options Valuation.

Strategic fit is normally defined in terms of indications or therapeutic areas. More refined approaches delve one or two levels deeper, describing the preferred patient populations, drug formats, drug targets, chemical space, innovativeness etc. Especially for in-licensing purposes, many companies generate in-depth descriptions of strategic fit.

All these tools and methods are embedded in a process that is usually driven by a portfolio management group as a preparation for an annual or bi-annual review and resource allocation meeting. This preparation can require an intense process of project and opportunity evaluations that can last a few weeks for early stage projects, but also several months for an in-depth review of advanced clinical projects. In the subsequent 'Portfolio Board' meetings, a cross-functional committee of senior managers then prioritises and allocates resources to projects, indications or therapy areas.

The Benefits and Limitations of Portfolio Management in its Current State

Ideally, portfolio management links resource allocation within R&D to long-term value creation at the company level. This is one of the explanations why net present value (NPV) systems have gained such popularity; they are based on the same discounted-cash-flow logic that is also being used for the valuation of an entire company.

The more immediate benefits for R&D organisations lie in the resulting transparency and comparability to be found around the project prioritisation and resource allocation process. Past intuitive and judgement-oriented decisions made by senior managers have now become subject to objective challenging by the relevant expertise within a company. There are considerable additional benefits which occur in the organisational dialogue stimulated during portfolio management processes. This dialogue often proves to be as valuable as the actual numbers created.

Despite all these undisputed benefits of portfolio management, there are some serious limitations that have led to persisting scepticism and frustration among both portfolio reviewers (portfolio management groups and senior management) and reviewees (project leaders and operative scientists).

The most serious downside is that all portfolio management systems have to deal with investment decisions under conditions of huge uncertainty. These must often be made with little or no available supporting data. Commercial or other rigorous evaluations work best when there is an existing market or dataset from which assumptions and extrapolations can be drawn. Forecasting product performance up to 25 years into the future is no easy task, especially when having to factor in breakthrough innovations that will shape or create new markets. Incremental innovations that enter into an existing market with well described features are much more amenable to forecasting.

Although the R&D risk domain around a project or approach can be described and captured more adequately than commercial potential, it is extremely difficult to predict how this risk will translate into a project's probability of success. Therefore, many companies use industry benchmarks as a baseline. The validity of these benchmarks, however, is a matter of concern as they tend to fluctuate greatly, depending on the source and respective year. Risk-adjusted NPV models are highly sensitive towards changes in success probabilities. A serious loss of confidence and trust in portfolio management can result, if resource allocation decisions solely depend on the source of the attrition benchmarks employed in a model.

In many companies, portfolio management places significant emphasis on TPPs even in the early stages of R&D. However, in those early stages the main goal may be to explore as many therapeutic options as possible (especially within areas like oncology and immunology). The unwanted consequence of using a TPP too early and too strictly can be that valuable options are discarded for the sake of forecasting or evaluation accuracy.

Another limitation is linked to the perceived nature of portfolio management groups in the organisation and among senior management. Sometimes, these groups have the reputation of being decision analysis 'number-crunchers', but have only few ties at the working level and into the tacit knowledge pool of the organisation. All too often, these well-intended groups have very little impact on decision-making by senior management and are not proactively involved in the 'steering-wheel triad' of strategic planning, resource allocation and people management.

Given these shortcomings, decision-making may, in the end, have to rely on the eloquence of project champions, personal preferences and beliefs of senior management as well as organisational politics. However, there is something else – a much more fundamental complication that is linked to the nature of the 'productivity-led' R&D business model that portfolio management has been developed to serve.

Portfolio Management in the Context of the Prevailing 'Productivity-led' Business Model

Driven by technological promises and stock market pressures, the pharmaceutical industry has perfected a 'productivity-led' R&D business model over the last ten to fifteen years. In this model, human creativity and the search for breakthrough innovation have been replaced largely by an attempt to industrialise and automate the discovery process. Management principles, such as top-down strategic direction setting, incentives linked to process productivity, specialisation and 'centres of excellence', have led to innovation patterns that are more predictable than those arising in a 'creativity-led' model. The price to be paid for these more predictable innovation patterns, however, is that most resulting innovation is of a more incremental nature (demonstrated by the rising percentage of 'incrementally modified drugs' and pure lifecycle management products). Often, such 'productivity-led' organisations tend to struggle in dealing with potential breakthrough innovation and risk. Due to their often non-quantifiable characteristics, the unknown risks involved and their lack of fit with company strategy, potential breakthrough innovations rarely get funded in a model in which 'centres of excellence' have to achieve their productivity goals (see Text Box 1).

In this 'productivity-led' paradigm, portfolio management delivers what it is supposed to do: it de-prioritises unknown risks and is fully aligned with the strategic planning, culture and incentive systems of companies focused on manageable, incremental innovation. If breakthrough innovation occurs, it is often in spite of rather than because of the ruling management system.

A fundamental redesign of portfolio management must therefore go hand in hand with a review of the overall R&D business model, focusing on the central 'steering-wheel triad' of strategic planning, resource allocation and people management.

How the 'Productivity-led' Organisation Deals with Risk

– Text Box 1 –

The overall risk level in the pharmaceutical business has increased across the board due to a number of factors. – These factors include rising regulatory requirements, the increasing hurdle to add therapeutic benefit in many indications and the heightened focus on the risk-benefit ratio. Notably, there are very different types of risks.

Many pharmaceutical R&D organisations operating within the logic of the 'productivity-led' mindset shy away from taking on too much risk when operating outside of their areas of expertise, while accepting more risk when they are operating within their 'comfort zone'. For example, more complex therapies, such as gene therapy or monoclonal antibodies, are predominantly left to the biotech sector or academia which then explores them until pharma feels that the concepts are at a level where the perceived risk is low enough to warrant internalisation and an investment within the logic of an NPV-based portfolio system.

In oncology, for example, most large companies driven by the promising advances in targeted therapies are trying to leverage their small molecule capabilities. On the other hand, more complex approaches such as cell-based therapies, vaccination, payload-monoclonals or gene-therapy have largely been ignored. The only exceptions are monoclonal antibodies that have recently been added to the arsenal of some 'Big Pharma-approved' technologies, largely driven by the commercial success of trastuzumab, rituximab, and bevacizumab. Nevertheless, the result of this late adoption stance leaves a few biotech companies sharing the basic technology rights and in-licensing by large pharmaceutical companies has become extremely competitive and costly as more companies are chasing a few late-stage opportunities. The question remains, whether some large pharmaceutical companies should be willing to take on more unknowns risks that may eventually develop into the next 'monoclonal antibodies'.

Recombinant Innovation Management (RIM) has been Designed to Stimulate Breakthrough Innovation within Large R&D Organisations

The ultimate goal for any R&D organisation is to combine the sometimes conflicting strategic and organisational requirements of 'creativity-led' and 'productivity-led' business models in such a way that breakthrough innovation is enabled, but not at the cost of decreasing productivity. This is difficult since this combination can not be achieved without significant tension. Yet it is exactly this tension that the most successful companies use to their advantage. Recombinant Innovation Management (RIM) is a systemic approach that has been designed primarily to help large 'productivity-led' organisations create a business model that maintains productivity while opening up spaces for creativity and breakthrough innovation. The 'recombinant' in RIM refers to the fact that most breakthrough innovations have an element of recombining existing problems and solutions from seemingly unrelated fields of knowledge across epistemological and organisational barriers. RIM addresses the main elements of the R&D Business Model – the 'steering wheel triad' of strategic planning, resource allocation and people management, as well as the underlying structures and processes.

Recombinant Portfolio Management

Portfolio Management within the context of RIM has been designed to address the main limitations of most existing portfolio systems, namely:

Their 'productivity-led' bias towards risks that are well-known within core competence areas

Their detrimental effect on nurturing options in Discovery and Early Development through excessive formalisation and restricted focus

The nature of many portfolio management groups that often struggle to make a real impact on decision-making

The following sections will discuss how Recombinant Portfolio Management addresses the above-mentioned limitations by redesigning a few fundamental processes and structures around strategic direction setting, project and portfolio evaluation, resource allocation, and the organisational setup of portfolio management groups.

A Balanced Approach to Strategic Direction Setting

Recombinant Portfolio Management begins by asking an organisation to answer the strategic questions of "How much risk and innovation do we want to take on in our portfolio?" and "How should we balance more long-term innovation goals with the short-term need to demonstrate productivity?"

Thus, planning within Recombinant Portfolio Management requires the formulation of explicit innovation goals in the different categories from breakthrough to lifecycle-management with dedicated resources for each category. Sceptics may argue that it is impossible to plan for potential breakthrough innovation and that dedicated resource buckets make little sense. This argumentation ignores that one critical element in catalysing breakthrough innovation is the formulation of stretch goals and challenges. By necessity, these challenges will be somewhat vague and more related to the field and to unmet needs than to any specific approach. Another vital element is to leave enough unplanned space and resources for unexpected discoveries that can occur anywhere and at any time during the planning cycle. The critical point is to reserve a budget for the further exploration of these unexpected discoveries.

Within Recombinant Portfolio Management we strongly support taking on selected unknown risks in the form of exploratory projects. No strategic analysis in the world can replace the learnings that can come out of such short exploratory activities. Once strategic direction has been established, ideally through a mixture of top-down planning and bottom-up initiative, the actual project and portfolio evaluation process needs to be tackled.

Assessing a Project's Location on the Innovation Continuum

When commencing the evaluation process, it is necessary to look at each project in more than one dimension. Projects may usefully be viewed as positioned on a continuum between pure incremental and pure breakthrough potential. Some will be purely incremental, e.g. the fifth entrant into an established drug class, while others will exhibit pure breakthrough characteristics, e.g. the first drug with disease-modifying characteristics for a given disease. Some projects will be located somewhere along the continuum, addressing unmet needs in an incremental fashion in known markets and with known risks and at the same time providing opportunities for breakthroughs in other indications with unknown potential and risks. The breakthrough nature of a project could be elucidated by answering the following questions:

- How different is the proposed approach to existing approaches?

- Where is this particular approach located on the bibliometric and industry S-curve?

- Can the approach potentially lead to a large step in addressing unmet need?

- Would the approach compete largely with or within existing drug classes or does it have the potential to expand the market?

- Does the approach require novel clinical endpoints that are not yet included and accepted in regulatory guidelines?

- How many additional therapeutic or other options does the approach create beyond the initial indication application?

This classification step would have to be performed at each review cycle and for all projects. An early hypothesis may turn out to be unsubstantiated later. On the other hand, new observations may show unanticipated breakthrough potential.

The Portfolio Process for Projects Located More Towards the Incremental Side of the Innovation Continuum

If it is found that a project is located more towards the incremental end of the innovation continuum, a 'normal' path through the portfolio management process will be sufficient to capture the three dimensions of risk, return and strategic fit.

This 'normal' process typically consists of a number of basic building blocks: defining target product profiles (TPPs), assessing risk, generating decision trees and calculating values or commercial potential, followed by a qualitative review of strategic fit and alignment with goals. The resource allocation then follows portfolio priorities by trading off the three dimensions risk, return and strategic fit at different aggregation levels from R&D phase to indication to therapy area.

While the basic building blocks of this system stay the same during the different R&D phases, the specifics depend on the availability of data in a given phase. In Discovery or even Early Development, a commercial assessment might be linked more to the attractiveness of the indication than to a particular compound. The TPPs in Discovery and Early Development should capture all relevant options and not force-fit projects. At Catenion, we have developed specific 'Options Space Maps' (OSMs) for this purpose. The focus here lies on documenting the different therapeutic options and the required data, resources, milestones and timelines to realise any of the options. Once a project has passed proof-of-concept, a standard TPP may suffice. All this can be mapped out in a simplified decision tree structure.

Assessing R&D risks is another crucial building block: leading companies try to capture consensus on what defines high-risk versus low-risk outcomes for each activity in the R&D process. This can then be incorporated in a qualitative or semi-quantitative scoring system allowing the discussion of risks compared to the baseline benchmark risk (always questioning the validity of the benchmarks as a first step).

Whether or not to translate the results of a risk assessment into probabilities in decision trees is quite controversial. In our experience, the calculation of NPVs or rNPVs in Discovery makes little sense; their use in Early Development can be debated and after proof-of-concept they are in general tremendously helpful. Because of the long timelines and the risk adjustment, most early stage projects will appear only marginally attractive in an rNPV model. Some companies use Commercial Value (not risk adjusted) to circumvent this problem or they try to apply Real Options Valuation techniques (see Text Box 2).

Another crucial question is how to best assess commercial potential. Lifecycle sales forecasts are required for NPV models, but what to do if NPV is not the parameter of choice? The methods range from purely qualitative descriptions of markets and their competitive pressures to epidemiology- and competitiveness-based peak sales calculations. There is no one-size-fits-all best practice; all of these methods have their pros and cons and each company will have to find an approach that their decision-makers feel most comfortable with.

Thinking in (Real) Options

– Text Box 2 –

How useful is Real Options Valuation (ROV) for pharmaceutical R&D? – ROV is based on applying the principles of financial options valuation to real assets. There are numerous examples of options in real asset investment decisions. These include the "option to abandon or delay" a project, the "option to increase capacity" in manufacturing and so on. Many R&D projects have option characteristics, as they contain multiple staged phases and investment commitment can be spread over time, several decision points and milestones. When ROV is used in an appropriate manner, it can bridge the gap between the worlds of hard numbers and business intuition. In this case, the option value of a project can lead to an investment even if the traditional NPV is negative.

While the mathematics involved can be complex, the underlying logic is easy to grasp: an option gives its owner the right, but not the obligation to buy the underlying project asset (a project's expected cash flows). The option value has significant upside (based on the risk and resulting volatility of the underlying cash flows), while the downside is limited to the price of the option (investment in the project until next learning milestone). The value of the option relative to the static NPV mainly stems from two sources: the volatility of the project's cash flows (where an increase also increases option value) and the point in time until the final investment decision can be deferred (time to switch from exploratory research to full-blown investment, where a long timeline increases the option's value). The logic that an increase in risk (=volatility) increases project value is new and counterintuitive to most managers who were trained to minimise uncertainty.

There are two factors, however, that limit ROV's applicability to pharmaceutical R&D projects. One is that ROV works best in situations with market-priced risk. Ideally, the asset would be traded on the stock/derivatives market. This is certainly not the case with a typical pharmaceutical R&D project. The other factor is complexity, as a typical pharmaceutical project will contain multiple embedded options (an option on an option on an option, etc.). This poses significant challenges for financial analysis.

In a nutshell, at Catenion we would not recommend to use the ROV as a financial tool, but to try to implement some of the more qualitative principles especially for the evaluation of potential breakthrough projects:

• Uncertainty and risk can increase value if investment is spread over several learning milestones rather than dedicating large sums at once.

• Creating and nurturing options follows a different timeline than that of the normal portfolio review and planning cycle.

• Flexibility to take decisions as learning milestones are met is key.

• Stopping exploratory projects if learning milestones are not met is as important as nurturing them in the initial start-up phase. Options proliferation is to be avoided.

All this requires a lot of portfolio management discipline.

The value of stretch goals even for a project that appears incremental should also not be underestimated. The whole concept of RIM relies on the fact that breakthrough innovation can be stimulated but not predicted. An organisation should always be willing to set stretch goals for all projects, but as described below, will need to be able to rapidly recognise breakthrough innovation and enable growth of these projects, when breakthrough happens. The setting and management of stretch goals is a vital part of the portfolio management process for all projects.

The Portfolio Process for Projects Located More Towards the Breakthrough Side of the Innovation Continuum

Once a project qualifies as a potential breakthrough based on the simple self-assessment questionnaire described above, the idea initiator could seek a 'sponsor' among senior managers, who in addition to their normal budgets would ideally also have a dedicated budget for 'exploratory breakthrough projects'. Once a 'sponsor' has bought into the idea, a more formal evaluation process would be run by the portfolio management group. This process would critically rely on the following factors – borrowing heavily from the qualitative insights derived from ROV (see also Text Box 2):

- An in-depth review of the scientific confidence in the approach (including a bibliometric analysis)

- An assessment of the potential step-increase in addressing unmet need

- A thorough competitive assessment

- A qualitative description of the target markets, if feasible

- An assessment of all strategic and operative R&D risks

- The generation of an 'Options Space Map' (OSM) including a decision tree to describe all therapeutic options, a systematic risk assessment, likely timelines and required resources

- The definition of 'learning milestones' and description of how uncertainty will be reduced at each milestone including a short description of how investments can be spread over those learning milestones

- An 'incubator structure' required to get the project started (if there is no natural 'home' for it within one of the therapeutic areas)

- The idea could then be presented by the initiator and the sponsor to the Portfolio Committee. This senior management group could allocate resources either internally or externally based on the financial budget that they have.

- The process could be applied with varying degrees of sophistication until projects reach a suitable milestone where they can then converge into the 'normal' innovation management process.

Organisational Implementation of Potential Breakthrough Projects

Ideally, potential breakthrough ideas will be generated everywhere, at all levels throughout an organisation and at any point in the value chain. In the spirit of the 'open innovation' model, external opportunities must also be included in the process. The most unlikely places will be the most promising, because breakthrough innovations tend to follow a pattern of matching and adaptation across organisational and epistemological boundaries in an unpredictable fashion.

In some cases, these projects will not quite fit into the logic of a 'centre of excellence' structure. 'Incubator structures' can serve an important role during the initial start-up period of such breakthrough projects. These 'incubator structures' would ensure that projects are matured until they have reached a level where they can be funnelled back into the normal innovation management process.

Recombinant Portfolio Management as a 'Knowledge Brokering' Function

How can the impact of portfolio management groups be increased? In addition to adapting and complementing processes and systems, an area that probably represents an even bigger lever is the appropriate staffing and structuring of portfolio management groups. Recombinant Portfolio Management has two objectives: one is to support senior management and project teams with all aspects related to data-driven decision-making, the other is to serve as a catalyst, stimulating cross-functional idea generation and verification. By definition this is what a 'Knowledge Broker' would do: mapping an organisation's knowledge space and seeking areas with high 'Recombinant Innovation' potential. Who would be better suited than a portfolio management group to catalyse this?

The selection of the right people for such a group is essential. Portfolio Management should not be a last resort for those that have not been successful in other functions or are close to retirement. Following one of the fundamental principles of RIM, Recombinant Portfolio

Management should have its own share of 'T-shaped' people: with a deep knowledge spike in a few areas with high relevance for the job at hand and a very broad mind and overview of as many different areas as possible. Ideally, the deep knowledge spikes within the group would be complementary, not overlapping. Also, a high level of trust and respect from their peers is essential for portfolio group members to gain access to the relevant knowledge pool of an organisation.

Again, following the principles of RIM, the group members are encouraged to work on two areas in parallel: one within their field of expertise and one outside of their field of expertise. By doing this, the mental and organisational processes necessary for recognising potential breakthrough innovation across boundaries are facilitated.

Within Recombinant Portfolio Management, the same processes that are applied to the internal pipeline are also applied to external opportunities. This implies that Business Development/Licensing does not have its own project assessment group, but is served by the central portfolio group.

Catenion Value Proposition

Recombinant Portfolio Management is an essential part of RIM – a systemic approach designed by Catenion to help large R&D organisations reach their full innovation potential.

Catenion has a longstanding track-record of designing and implementing portfolio management systems for all R&D phases from Target ID to phase III (our team has evaluated more than 400 individual project opportunities over the last few years). The systems encompass all best practices required to assess risk, return and strategic fit.

We have developed specific tools, templates and processes required to evaluate potential breakthrough innovations. The right combination of the 'normal' and 'breakthrough' processes and systems define Portfolio Management within RIM – 'Recombinant Portfolio Management'.

Finally, and most importantly, we do not believe in a 'cookie-cutter' approach to implementing Portfolio Management. Our philosophy is to integrate and to build on existing client processes and systems in a truly 'recombinant' manner rather than to force-fit everything into one framework.