

Executive Briefing
Therapeutic Product Expansion
– What is the Path to Success?

Catenion is a management consulting firm devoted to helping pharmaceutical and medical products companies significantly increase the returns on their R&D and Marketing investments by creating more innovative and effective strategies and organisations.

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Ulcerative colitis and additional smaller disorders. These drugs have proven efficacious because they address a fundamental aspect of disease biology – an aspect by which tumours grow or by which the immune system is activated (Fig. 1).

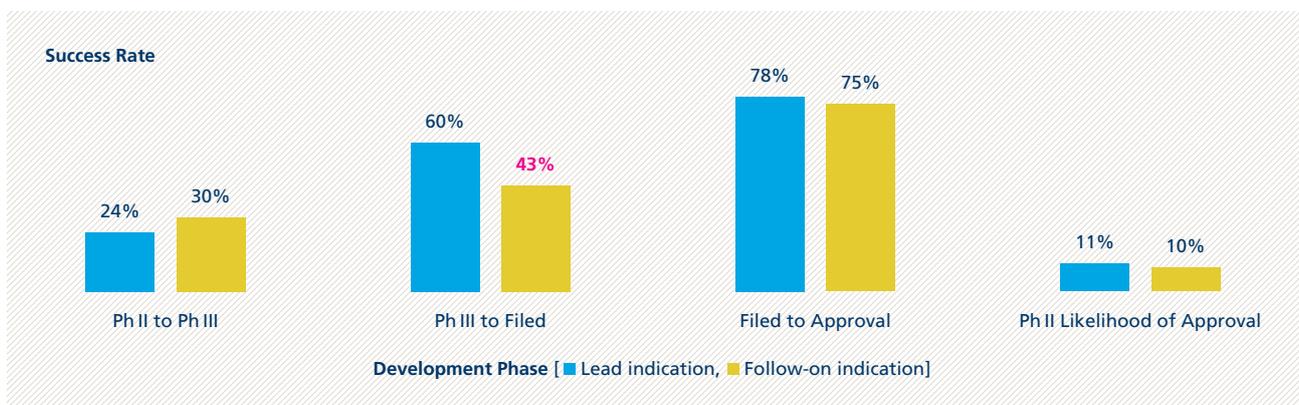
Today the combined worldwide sales of Avastin, Rituxan, Gleevec and the TNF α inhibitors top € 30 bn. There are many other examples illustrating that therapeutic expansion and line extensions have become a key lever for value creation in the pharmaceutical industry in times of increasing clinical and regulatory hurdles, payor pressure and generic competition. One can summarise six reasons why therapeutic expansion is attractive:

- Much of the initial safety risk has been resolved
- Faster development
- Increased willingness of clinical trial investigators and thought leaders to test the product in other patient populations, and very importantly in combination with other therapies

- Several regulatory risks have already been addressed such as product release, IND, and general consultations
- Marketing and sales activities are facilitated and cost effective
- Analysts appreciate the commercial potential of therapeutic expansions which in turn makes it easier for the developing company to borrow money or to find partners

Every company wants to do it, but not all succeed. Avonex, Rebif and Betaseron are IFN betas, approved in Multiple Sclerosis but have so far not been successful in other indications including Hepatitis B and C, Rheumatoid Arthritis and Human papillomavirus infections. EGFR is a fundamental growth factor receptor in Oncology. Its role in tumourigenesis has been widely described and appreciated. Nevertheless, efforts to expand Erbitux or Vectibix from initial market authorisations in colorectal and head & neck cancers into other indications such as colon, gastric, breast or lung cancer have failed (Fig. 1).

Figure 2: Clinical trial success rates in Oncology. “Lead indication” contains line extensions within that indication



Source: Catenion based on ADIS R&D Insight

The Hurdles

Historically, line extensions within an indication have shown higher success probabilities compared to the first approval setting. However, label evolution is not a quick win, especially not in other indications. Contrary to popular belief, success rates in Phase III for follow-on indications in Oncology are lower compared to lead indications (Fig. 2). Also line extensions are becoming increasingly more challenging due to high clinical hurdles, an increasing fragmentation of markets and the necessity to combine.

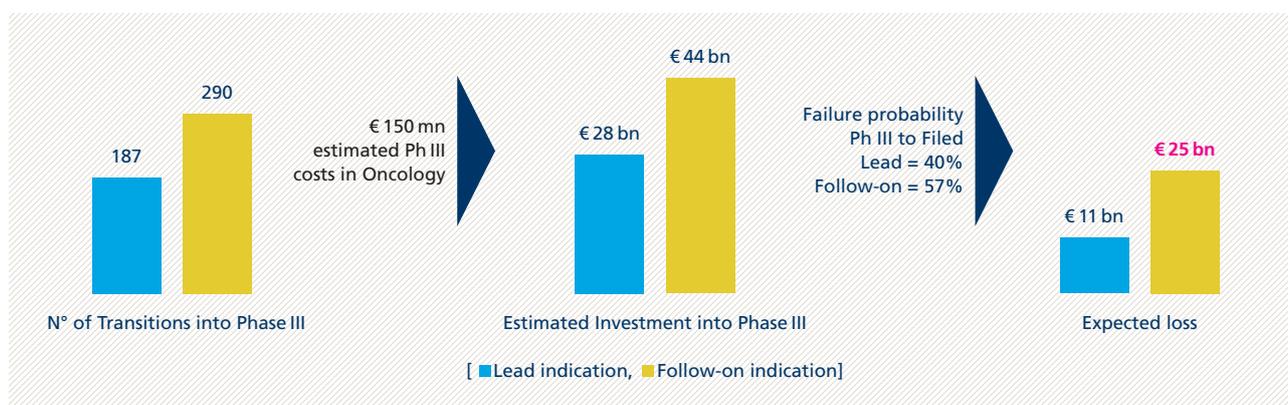
Lead indications are often selected on the basis of scientific and clinical evidence. It may not be the indication with the highest commercial potential, but where the company seeks Proof-of-Concept (PoC). Understanding the proposed Mechanism of Action (MoA) in the context of the disease biology is important. This includes an understanding of the molecular mechanisms and the generation of robust data demonstrating how a product intervenes and why it may work better in certain patient populations and subgroups. Data packages, however, are often much thinner for follow-on indications compared to lead

indications. In addition, life cycle management (LCM) activities are often driven by Commercial that seeks the “big buck” and pushes for going broad as early and as much as possible. If this mind-set dominates decision making, there is a high risk of clinical failure. Most money at risk lies in Phase III, so one should take therapeutic expansion decisions wisely.

In an analysis of Oncology drugs that have at least one indication in Phase III during the period 2003 – 2012, we counted 290 transitions into Phase III which we could attribute to follow-on indications (Fig. 3). Assuming average Phase III costs of € 150 mn, approximately € 44 bn have been invested during that period and have been at risk. If we further consider Phase III success probabilities from Fig. 2, the expected loss is € 25 bn. This is a huge amount of money and much higher than common belief would estimate.

Over the last 10 years we have worked for a variety of Pharmaceutical and MedTech companies. In our view, the most critical hurdles for a successful therapeutic expansion strategy are summarised in Figure 4.

Figure 3: Phase III money at risk in € bn for Follow-on indications in Oncology. Period of analysis 2003–2013



Source: Catenion based on ADIS R&D Insight

The Approach

Some of the hurdles mentioned are inherent to drug development and cannot be overcome easily. But we believe that a systematic expansion strategy building on a deep data analysis helps to reduce the money at risk. A therapeutic and line expansion strategy should start with the following critical questions:

- What is my option space?
- When and how much to invest?
- How to execute?

Our goal is to provide a project team or company with a detailed product expansion strategy in order to maximise the value of the entire programme. We have worked out a highly structured approach comprised of the following four elements.

Module 1: Generating and Evaluating the Option Space

The first module deals with generating strategic options beyond the initial lead indication. We have selected immunotherapies as an example, because many of these projects have a postulated broad MoA and have stirred high interest in the industry and academic community.

Immunotherapies are treatments designed to induce, enhance or suppress an immune response in patients. They have found various applications in inflammatory disorders and in Oncology. Immunotherapies such as interferons, IL-2 and TNF α inhibitors are already on the market for quite some time. More novel and more specific approaches include cell-based therapies

Figure 4: Hurdles on the way to a successful therapeutic expansion strategy of pharmaceutical products

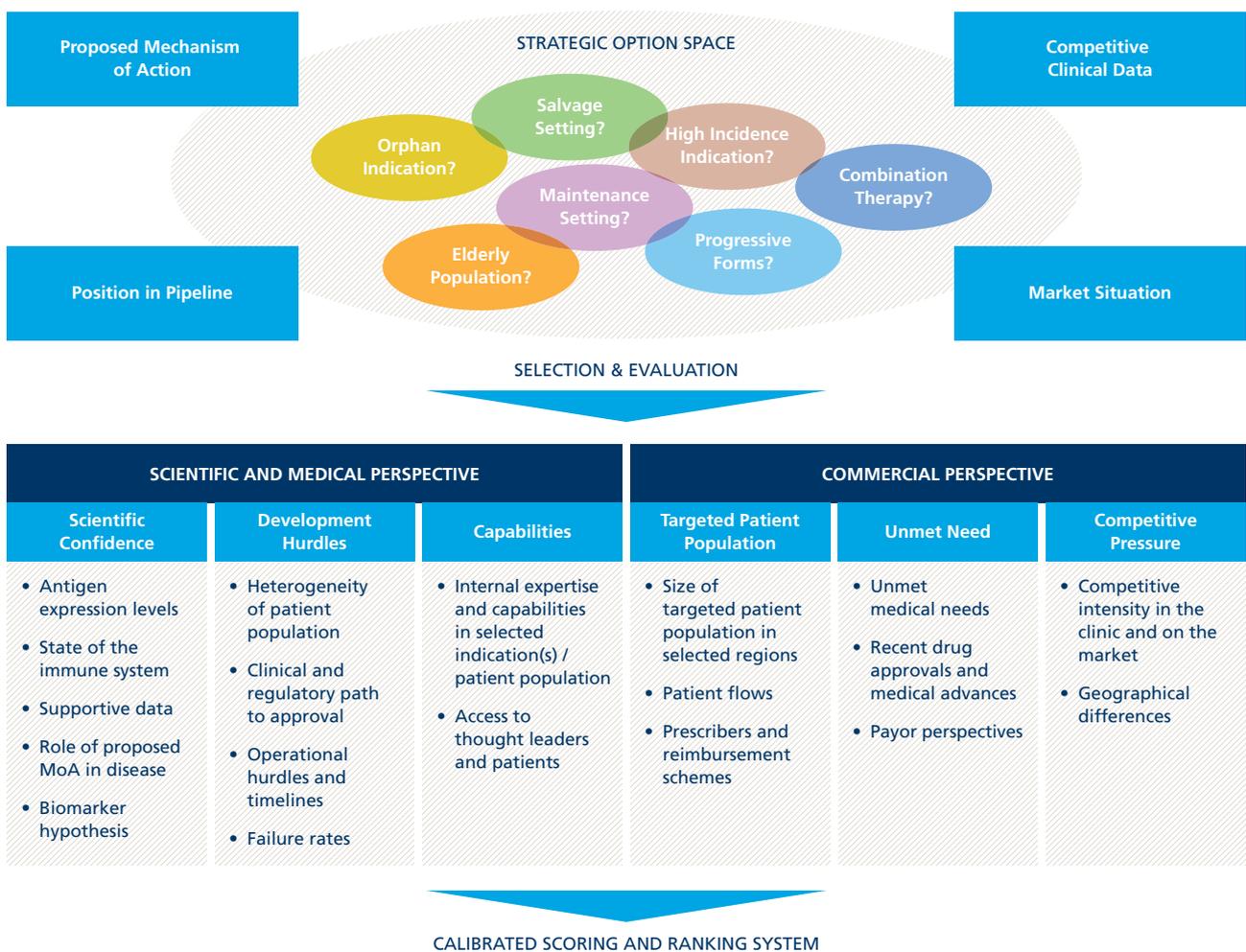
Thin Data Packages	<ul style="list-style-type: none"> • Follow-on lack breadth and depth of data normally available for lead indications e.g. target expression levels, animal models, number of relevant patients treated etc.
Disease Biology and Proposed MoA not really understood	<ul style="list-style-type: none"> • Disease biology differs substantially across patient populations even in case of platform targets/pathways such as EGFR, TNF, JAK, Dopamin etc. • Proposed MoA is not fully understood e.g. immune modulatory aspects of antibody therapies such as Cetuximab became evident long after Ph III decisions were taken.
Insufficient Capabilities	<ul style="list-style-type: none"> • Internal resources are limited leading to the necessity to “cut corners” for follow-on indication / patient populations. • Network of external experts not ideal to cover breadth of therapeutic expansions.
Wrong Timing	<ul style="list-style-type: none"> • Decision points are not interconnected and indications are viewed individually – there is no coherent therapeutic expansion strategy that aligns clinical, regulatory and financial requirements.
Mind-Set	<ul style="list-style-type: none"> • For commercial or strategic reasons, patient populations are selected that are not optimal from a scientific and medical perspective, lowering the probability of success. This includes the selection of combination partners.

(e.g. Provenge), checkpoint inhibitors (e.g. Yervoy, Xeljanz) and peptide-based immunostimulants (e.g. Astuprotimut-R, Tecemotide). Even more novel are stem cells approaches that are still highly exploratory. Figure 5 shows an example of an initial option space for an immunotherapeutic drug candidate. The four dimensions “Proposed MoA”, “Competitive Clinical Data”, “Market Situation” and “Position in Pipeline” help to systematically build that option space. Each

option should be made explicit, e.g. a maintenance setting in non-squamous NSCLC in combination with Alimta. Options may not necessarily be mutually exclusive.

Selected options are then evaluated by considering scientific, medical and commercial perspectives in more detail (Fig. 5). It is important to tailor the framework to the specific product in question. The scoring and

Figure 5: Generation and Evaluation of Strategic Options across scientific, medical and commercial perspectives



prioritisation process is driven by the intention to increase probabilities of technical success and to optimise commercial potential.

Module 2: Creating Target Product Profiles and Development Scenarios

Full-blown business cases are then created for strategic options that have scored highest in Module 1. This requires developing target product profiles (TPP) and clinical plans that meet these TPPs. The art is to create meaningful profiles that are data-driven and that address the need for differentiation, especially in an environment of increasing payor pressure. Figure 6 displays an example from an immunotherapeutic that we analysed in the context of a therapeutic expansion strategy.

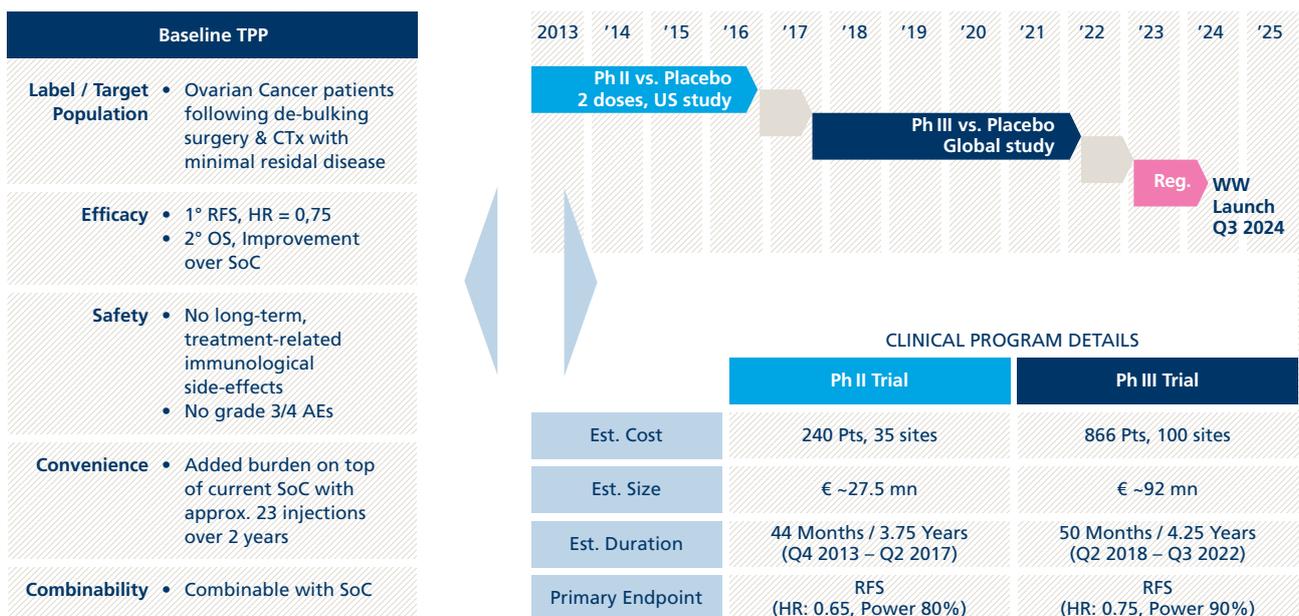
Each option can be further analysed by using our proprietary R&D Risk Assessment Software. This software allows risk assessments with a rigor and detail

that is unique in the industry. It has been generated by encoding knowledge from scientific experts as well as reviews of hundreds of different R&D projects across asset types and therapy areas. These reviews were part of Portfolio Management exercises or stemmed from asset due diligences. Our Risk Assessment turns every stone and provides project teams with a detailed risk profile of their asset (or strategic option) which can be translated into a probability of success.

Module 3: Commercial Potential and Business Case

Clinical development scenarios, cost assumptions, timelines and TPPs form the basis of full-blown business cases. In addition, key commercial parameters are added such as epidemiology, patient flows, competition at time of launch, current and future price levels, health technology assessments etc. Because point estimates are so inaccurate, our methodology creates a range of plausible scenarios that are established to embrace a

Figure 6: Clinical development plan to meet the desired target product profile



Source: Catenion, previous project example

likely true future of the project assessed. Figure 7 sums up the financial result for our immunotherapeutic example.

Module 4: Strategy & Roadmap

In a synthesis step, key financial parameters, probabilities of success, timelines, costs and capability requirements are compared across the different development scenarios to define an optimal therapeutic expansion strategy. Order, timing and investments of lead and follow-on indications are considered and put into the overall context. This includes the programme itself but also external events and company situation. Critical questions are addressed such as: when are key decision points? When are new clinical data coming in? Where are gaps? What is the financial situation of the company?

What are the consequences of therapeutic expansion for other portfolio activities? Can the organisation manage operationally? If not, what is required and what would be logical next steps?

In a final step, a roadmap is defined to implement the agreed-upon therapeutic expansion strategy.

Additional Module Partner Search

After the creation of a powerful therapeutic expansion strategy, it could be a logical next step to search for a suitable partner. Catenion has developed tailor-made methodologies and can draw on its broad network of European, American and Japanese companies. We have been asked frequently to conduct company screens for various purposes including partnering deals, asset deals and M&A.

Figure 7: Peak sales potential and project value in three different scenarios



Source: Catenion, previous project example

The Process

Setting up a programme for therapeutic expansion is a collaborative effort of a number of functions and stakeholders within the company. All relevant parties from R&D, medical affairs, commercial, pricing and reimbursement should be involved. Professional project management is a key element of our strategy projects. Our initial screening for indications / patient populations of interest is initiated by a pragmatic collection of available data and by drawing on various scientific and commercial databases. We focus on white space areas where internal personnel have not yet looked into. For Modules 1 to 4 we prepare

and conduct a series of workshops together with our clients unless a true external analysis is commissioned. The goal is to stimulate fruitful, outcome-driven discussions while minimising the additional work load. Considering time for analysis and joint workshops, the described four Modules can be completed within two to three months contingent on option space and complexity of the project.

The modular approach allows a stepwise procedure. An adapted process can also be used for MedTech projects.

What is it that sets us apart from other consultancies?

Our approach is to look deep, beyond the obvious. We are striving for scientific and commercial excellence. Our teams have a deep spike in R&D embedded in an understanding of markets and regional differences. Over the years we have gained experience working very efficiently with project teams. This includes

challenging common beliefs and perspectives. Our global network and broad working experience allows us to identify opportunities and to bring people together. We believe we bring a unique combination of scientific, commercial and strategic expertise to the table.

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