

Therapeutic Expansion

Jan Hendrik Sitz and Markus Thuncke at Catenion point out that therapeutic expansion has become a key lever for value creation in the biopharmaceutical industry in times of poor R&D productivity

On 6th May, 2009, Roche announced the approval of Avastin for the treatment of *glioblastoma multiforme* – the fifth approved indication for the angiogenesis inhibitor – after it had initially been launched in metastatic colorectal cancer in early 2004. After an early forecast from October 2004 predicted sales of \$1.2 billion by 2012 (1), by 2005 Avastin had already surpassed this figure with sales of \$1.4 billion (2). According to Roche, 2008 sales were \$4.9 billion (3), and recent forecasts anticipate Avastin to become the industry's biggest selling product by 2013, with sales of \$8.1 billion in 2012 (4). Genentech's own forecasts for the US range from \$6.7 billion (probability adjusted) to \$10.2 billion (unadjusted for probability) in 2015 (5). Whereas one might be tempted to explain this huge difference in forecasts for the same product over time with the inherent difficulties of predicting the future, there is another factor in play: a tremendously successful lifecycle management programme with multiple therapeutic expansions. Roche/Genentech's anti-VEGF-R antibody exemplifies a common theme in oncology and other therapeutic areas. It is efficacious not only in the original indication, but has successfully been developed in several additional tumour indications, showing the expansion potential of the drug.

The example of Avastin illustrates how important strong lifecycle management, after obtaining the initial approval, has become in an industry that is wrestling with poor R&D productivity and more demanding payers and regulators. In addition, a more aggressive generics industry and the rapidly evolving field of biosimilars further increase the pressure on originators to realise as much value as possible during the precious years of market exclusivity.

DEFINITION OF LIFECYCLE MANAGEMENT

The term lifecycle management (LCM) means different things to different people – therefore, a clear definition is needed.

As illustrated in Figure 1, LCM in the biopharmaceutical industry comprises a continuum of measures, ranging from relatively small modifications of the drug product with limited effort and risk, to demanding developments – in terms of time, costs and risk – of an existing drug in a new indication. Some people even include modified versions of existing molecules in LCM. However, here we will focus on what is arguably the biggest lever for value creation – therapeutic expansion, defined as the development of existing products for approval in new indications.

TRUE VALUE ADDED?

As one countermeasure against the ongoing R&D productivity crisis, many companies have put a strong emphasis on LCM activities, often establishing 'lifecycle teams' that replace the classical project development teams, once initial approval has been obtained. However, classical LCM measures, such as reformulations, new dosages or fixed-dose combinations, are increasingly viewed as attempts to secure their incomes at the expense of other stakeholders in the healthcare environment, such as payers or even patients. Hence, healthcare systems are reluctant to accept and to pay premium prices for such products, and the impact of such measures in prolonging lifecycles of drugs is questionable in a future where health technology assessment – by authorities such as NICE – will be increasingly adopted by payers across the globe.

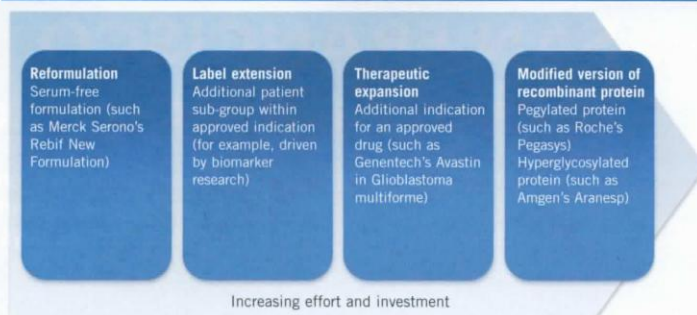
Therefore, LCM measures have to prove their value to patients and the healthcare environment in a similar way to true new molecular entities (NMEs). It is crucial to developers – whether small biotechs or Big Pharma players – that they both maximise and fully exploit the potential of a drug early in its lifecycle. These two aspects can be combined in following a therapeutic expansion strategy, as shown in the example of Avastin.

A prerequisite for such a strategy is the therapeutic expansion potential of the drug based on the mechanism of action (MoA) and the targeted disease pathway. Drugs addressing a mono-causal genetic disease such as phenylketonuria (for example, Biomarin's Kuvan, which reduces phenylalanine levels in these patients) are most likely to have only a very limited expansion potential into other indications, or none at all (although niche drugs can still become 'nichebusters' based on the unmet need, the therapeutic benefit and respective price, as Genzyme's Cerezyme exemplifies).

WHEN TO KICK OFF LCM ACTIVITIES

A critical parameter for a therapeutic expansion strategy is timing. To avoid significant delays of approvals for additional indications after the initial product launch, therapeutic expansion has to be integrated into the project plan early on, ideally during the pre-clinical phase, where studies in animals set the basis for

Figure 1: The lifecycle management armamentarium



targeting the right indications. During development, a clear strategy should define order and timing of primary and secondary indications.

The decision for a development in additional indications is always a risky investment, as the development may fail, or it may even harm the product in the primary indication. The overall risk should still be much lower than developing NMEs, as important safety and possibly efficacy hurdles will have been cleared by the primary indication. However, in most companies, development resources are limited, and it is therefore not an option to pursue all potential indications in parallel. 'Let's try everything' approaches, without a sound scientific basis and a clear strategy, usually lead to poor results.

HOW AND WHERE TO INVEST IN LCM

In order to tackle the challenge of selecting and targeting the right indication with the right timing, most value can be created by using a portfolio management approach.

A number of dimensions should be looked at in order to understand the probability of success and the potential value of a product in an additional indication:

- It all starts with a significant unmet medical need in the targeted indication(s).
- Scientific confidence in fulfilment of the targeted unmet need is another key dimension that can be captured through a thorough risk assessment for each targeted indication. This also helps to determine the optimal starting point; if conceptual risks are high and no proof of concept (PoC) has so far been obtained for the molecule and its target, it may be a safer strategy to first develop the drug until PoC in an indication that is best supported by current data. However, even in such a case, the expansion should be planned early on in order to avoid losing valuable time after obtaining the first PoC. As discussed above, therapeutic expansions into additional indications after a first PoC should have a much higher probability of success than a completely novel therapy. Nevertheless, risks may still be significant, particularly if the targeted indication is substantially different from the PoC indication. This is illustrated by a

number of examples, such as Biogen Idec's Avonex, the leading interferon beta in multiple sclerosis; this has been developed without any success in six additional indications and in an inhalable formulation.

- Another important factor is a positive differentiator versus the current standard of care and other existing treatments. This differentiator should relate to a benefit for the patient and the healthcare system. Without such a differentiating advantage, pricing and market share will be compromised. In some cases, superiority over existing treatments may even be required for approval or reimbursement.
- When contemplating an additional indication, most companies will look at the attractiveness of the targeted indication, determined primarily by the market size in terms of numbers of drug-treated patients, price level, and competitive intensity.
- In particular, for products that are on the market already, or at least in full development – when significant data on product properties are available already and where uncertainty about external factors is less than for a preclinical project – an additional basis for decision-making should be a full-blown business case. This should include a sales forecast and an 'expected net present value' calculation. Creating and calculating different scenarios both for the product profile in the indication of interest and for external factors in the marketplace help to deal with uncertainty around key factors.

EFFECT OF THERAPEUTIC EXPANSION ON THE PRIMARY INDICATION

In order to calculate the real value of an additional indication or label to the company, a potential effect on the primary indication needs to be taken into account. This effect can be positive or negative. If the product has been or is planned to be launched in a niche indication first, and later in a mass market, there may be a significant negative impact by the second launch. In such a case, the achievable price in the mass market is likely to be much lower, so the marketer may have to drastically reduce the price in the primary indication. Overall, this effect can lead to a negative contribution of the second launch on the franchise. In contrast, an

additional launch can also contribute positively to market share and sales in an established indication, as exemplified by Avonex again. In 2002, Avonex became the only one of the three available, close-to-identical beta-interferons that could actively be marketed for clinically isolated syndrome (CIS), an early form of multiple sclerosis (MS). Because the majority of CIS patients progress to definite MS, this exclusive label for Avonex was an opportunity to capture patients early on, which is likely to have contributed to Avonex's commercial success. Avonex was able to exploit its unique position for four years until 2006, when Bayer Schering's Betaseron/Betaferon was also approved for CIS.

STRATEGIC FIT AS A KEY DRIVER FOR LCM DECISIONS

Even the most promising indication for an existing or new drug may not become a success story if it does not fit strategically with a company. Most obviously, capabilities in several areas to develop the product in an additional indication are required. The less related the therapeutic expansion is to the primary indication, the more demanding this may be, and not every company will have the expertise to make a product a success in two very different therapeutic areas, as Biogen Idec and Genentech/Roche managed to with Rituxan in non-Hodgkin's lymphoma and rheumatoid arthritis.

In contrast, sometimes the relevant question is not 'are we able to develop this?', but rather 'do we really want to go in this direction?'. This is nicely illustrated by the deal agreed by Roche and Aspreva for the development of CellCept in autoimmune diseases in 2003. Roche granted Aspreva the exclusive worldwide rights (excluding Japan) to develop and commercialise CellCept in all autoimmune disease applications. This deal allowed Roche to stay focused on CellCept's primary area, transplant rejection, and still fully exploit the potential of the drug in autoimmune diseases.

USING EXTERNAL PARTNERS TO DRIVE LCM

Indication- or therapeutic area-specific deals like the one on CellCept are also an option if resources are limited, and a company cannot or is not willing to take

the risky investment into an additional development (large Phase III studies can easily cost more than \$100 million). This may often be the case for smaller pharmaceutical and biotech companies. For these players, the development with cooperative groups or academic centres becomes an attractive option – be it to develop a secondary indication that a small biotech cannot fund, or to pursue a very broad programme in a vast number of indications that even a major player could not afford to run in parallel. A strategy of involving co-operative groups to a large extent has allowed Genentech, in the case of Avastin, to pursue more than 25 different tumour types in over 130 trials. Avastin’s approval in non-small-cell lung cancer and breast cancer depended primarily on cooperative group-sponsored studies. Development with cooperative groups has several pros and cons:

- Reduction of costs for the company by cooperative groups sponsoring trials
- Facilitation of recruitment to large studies
- Increased awareness for the product by exposing a large number of thought leaders and physicians, which helps to penetrate the market quickly after launch
- Increased credibility of trial results

About the authors

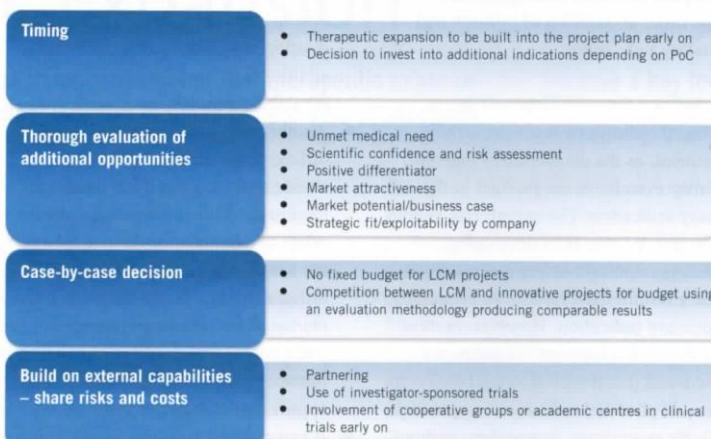


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Figure 2: Critical factors for a successful therapeutic expansion strategy



- Disadvantage of a partial loss of control over study design, operations and use of results

Particularly for smaller biotech companies, heavy and early involvement of cooperative groups could be a strategy to fully exploit a drug candidates’ potential when internal resources are scarce.

LCM IS A MULTIDISCIPLINARY EFFORT

Setting up a programme for therapeutic expansion addressing the topics outlined

above is a collaborative effort of a number of stakeholders within a company – for many projects, all relevant functions from research, through development and marketing, to regulatory will be involved. To ensure proper decision-making and appropriate funding of both novel and LCM projects, it is essential to integrate major LCM projects, including therapeutic expansion, into the normal portfolio management process. LCM projects should be reviewed and prioritised together with the overall R&D portfolio to allow for a fair competition between projects and indications and for an optimal use of resources. The points discussed in this article and summarised in Figure 2 will help LCM projects to receive appropriate attention, and companies to keep all relevant measures during the entire lifecycle of a drug product in focus. Used in this way, LCM becomes an important measure to create value in times of decreasing R&D productivity.

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