Editorial: De-risking novel therapeutic development – time to stop blaming the molecule?

Emerging therapeutic discovery and development companies need to ask awkward and difficult questions about the clinical utility, cost–benefit and revenue potential of their molecules even before making commitments to a specific clinical development strategy. The temptation is to either avoid the questions altogether or leave the task of addressing them until it is too late to change course.

Failures in early stage development are an inevitable, perhaps necessary, but also a costly consequence of the discovery-based approach to drug development. Rational drug design and *in-silico* tools were expected to overcome many of the failures of traditional hit and miss approaches. They have made a significant contribution particularly for ADME (administration, distribution, metabolism and excretion) and toxicity prediction, but the ability to evaluate with any certainty the physiological behaviour of a specific molecule in population *in vivo* is still a long way off. This is made more complicated where a number of related but distinct clinical applications are available for a given molecule.

It is plain that significant information about a drug candidate's physiological and biological characteristics is required before testing a clinical hypothesis and committing to a clinical development strategy plan. But here is a conundrum – you will have to invest significant development resources to identify early efficacy for a defined indication – yet there could be a number of indications for the product that need to be explored. How can you spread your risk but at the same time ensure that sufficient resources are allocated to clinical testing that will yield data of the required scope and scale?

In fact, in making a commitment of resources to a specific indication you are not just placing a bet on the clinical utility and efficacy of the candidate, but also on the market opportunity in the target clinical niche, its reimbursement potential and on the health economic cost–benefit.

The exit costs that arise from betting on the wrong indication are very high – particularly for a small biotechnology company aiming to partner products at Phase II.

QUESTIONS

Is there a lesson here? Can the odds on these bets be improved? Here are three important questions that need to be addressed early on – certainly before proceeding to the clinic – particularly when there are a number of options with regard to its intended use in the clinical setting:

- How would this product fit into current medical practice?
- Is there a convincing cost–benefit that will enable it to be fully reimbursed and priced to reflect its value?

- For the key indication options that can be identified, what is the sales potential?

If these cannot be answered – even if it is necessary to makes some stretch assumptions about the putative therapeutic – then what are the grounds for believing the drug can succeed commercially?

Gain a deep understanding of medical practice

Let us start with current medical practice. Take a novel treatment where there are alternative clinical utility hypotheses for applications, as is often the case. One example might be in the treatment of early stage primary tumours, later stage primary tumours and for secondary metastases, eg for breast cancer. There is potential for the drug to be assessed for clinical effectiveness against each of these but which one should resources initially be directed at?

The risk-spreading approach being advocated here is to look at all three in parallel. Detailed decision trees for diagnosis and treatment regimens need to be prepared, using published national guidelines coupled to information directly from physicians, who will not necessarily follow an identical approach to national recommendations. Interviews or focus groups with a number of key opinion leaders can yield valuable information. Further market research such as telephone interviews may also be justified to test the clinical hypothesis and the willingness and interest from physicians and other stakeholders to adopt the drug.

Using this information a clear 'map' of current clinical practice for each key market can be prepared from which the fit of the putative therapeutic agent can be clearly evaluated against existing and evolving treatments, diagnostic procedures, subpopulations of patients and, importantly, the work-flow of the healthcare system in which it will be used – be it primary or hospital care. This initial mapping exercise can help identify a number of early critical issues: is there a real fit for the products in the key territories being targeted? Do competing therapies already occupy strong positions in the target niches? Will major changes to clinical practice be needed before it can be adopted? Significant challenges to achieving high levels of adoption and sales are highlighted early on. The information may also help to identify the right partners to take the putative molecule to market and to identify clinical applications for the molecule that were previously unconsidered.

Early evaluation of reimbursement potential and pricing strategy is valuable

A second fundamental is to gain an early understanding of the two related issues of reimbursement potential and pricing strategy. The default strategy should be to price the product based on its intrinsic benefits and the value it could bring. It follows that the hypothesis needs to be tested that the product could improve on current treatment – that it could lead to better outcomes in terms of the medical benefit to the patient, and with regard to expenditure of the healthcare system's resources. This needs to be implicitly incorporated into clinical development programmes.

The product must be able to show that the benefits are outweighed by the direct and indirect costs of treatment. True, at this stage you may not have an optimised molecule in your hand or have spent millions of dollars on clinical trials, but a basic health economic evaluation should still be conducted using models and assumptions for the putative drug under a defined set of indications. Based on an understanding of its value, a set of indicative prices can be established – you cannot judge the revenue potential of the molecule until you have these.

Estimate the revenue potential early on

The third question of sales potential falls into place from the two questions above. The basic sales calculation of the 'price multiplied by volume equals sales' is the starting point. Careful stratification of patient groups against each indication under investigation, coupled to data concerning the prevalence and incidence of the disease within these groups, as well as expected growth rates for the disease, can be used to establish the potential patient population. For an early stage drug it is important to extrapolate to the point where the drug will be launched and the revenue stream over the following 10–15 years. There are a number of variables that will make the total market much smaller than implied by the simple calculation of price multiplied by incidence. Competitors will launch alternative therapies and some visibility of these will already be apparent before their launch. There will be a range of adoption rates in different territories and the level at which your marketing partner promotes the product will also be critical. All these factors can be modelled early on using spreadsheet-based sensitivity analyses.

Going through these approaches will provide clarity on the 'wish list' of properties for the therapeutic molecule and identify the extent to which these can be met for each indication area of interest. It will also identify areas for improvement that can be relayed back to medicinal chemistry, as well as helping to set priorities for further commercial, scientific and clinical development.

CONCLUSIONS

Investing in assessing these questions at an early stage for a number of possible intended therapeutic indications – even before the lead molecules have been fully optimised – could significantly reduce R&D and clinical costs, and create major shareholder value by focusing on the right drug candidates. Timing is critical – the lesson must be to ask these awkward and probing questions as early as practicable to avoid the development of products aimed at the wrong market and without sufficient clinical utility and benefits.

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