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potential to grow

A true understanding of the challenges of niche markets is needed for companies to achieve worthwhile returns

Four emerging pharmaceutical market strategies delimited by uniqueness of positioning and type of competition were identified in the article, 'If the Shoe Fits' (January/February 2010 edition - see: www.pmlive.com/shoefits). This next article in the series concentrates on the top right quadrant of the grid depicted in that opening feature, describing situations where a product, with unique positioning, has a competitive advantage on outcomes. This is the case, typically, for orphan drugs and other first-in-class "niche" therapies.

For a long time, the pharmaceutical industry was not required to prove superior outcomes to generate large surpluses: companies were paid above the amount required to sustain the economic viability of their product portfolio. Today, severe pressure on healthcare budgets means payers can no longer provide huge sums each year for products that, in many cases, do not even have curative value.

In July 2010, the National Institute for Health and Clinical Excellence (NICE), covering England and Wales, turned down Takeda UK's Mepact (mifamurtide) for the treatment of children, adolescents and young adults with

osteosarcoma, a rare and often fatal form of bone cancer. The committee agreed that, based on the evidence available, the incremental cost of the drug was, at best, £50,000 (€60,000) per Quality Adjusted Life Year (QALY) gained and, at worst, more than £100,000 (€120,000) per QALY gained, and therefore well above its cost-effectiveness threshold. While the decision generated fury among patient associations and medical experts, this may be an indication of future prospects for such markets.

BLOCKBUSTER POTENTIAL

Although orphan markets only represent five per cent of total industry sales, the potential for growth is an important consideration. The numbers of market authorisations keep increasing, with the European Medicines Agency (EMA) having set up specific incentives in its Orphan Medicinal Products regulation of 1999 (10-year market exclusivity, accelerated processes for granting approval, fee reductions and technical advice). In the US, 14 applications a year have received approval from the Food and Drug Administration under the Orphan Drug Act in the last decade. But this is only the beginning, since most rare diseases still have no labelled treatments. In this field, off-label use is the rule rather than the exception; only 50 designated orphan medical products exist in the EU, compared to several hundreds of rare diseases currently being treated with questionable effectiveness.

However, the possibility of getting approval for multiple indications offers the potential to turn these "niche" products into the blockbusters of the future. This is partly why big pharma is turning to orphan markets by acquiring patent rights from much smaller biotechs and setting up dedicated teams to undertake their further development. For example, Pfizer recently struck a deal with Israeli Protalix Biotherapeutics and GlaxoSmithKline signed an agreement with Dutch firm, Prosensa. Besides, with $40bn-worth of brand sales going off-patent for the first time in 2010 and 2011 combined, big pharma has no choice but to seriously consider other options. The emergence of viable rare disease focused biotechs, such as Genzyme, Actelion and Alexion proves that financially sound business models can be built upon these markets.

Many current top sellers were originally considered niche products. Novartis considered Gleevec a niche product when it was first launched in 2001. It is now Novartis' second best selling drug ($4bn of sales in 2008) since receiving approval for ten additional indications. Other examples are Johnson & Johnson's Remicade and Topamax.

Indication extension is vital for expanding such markets. In a recent article, Mark Fishman, president of the Novartis Institutes for BioMedical Research (NIBR), stated: "if we understand the mechanism in a narrow niche indication then of course we hopefully will be able to extend it out to other diseases which share underlying mechanisms."

The specific features of orphan drugs, such as unique positioning and limited outcome competition, have long granted them an exceptional status in payers' minds. Low patient numbers and the absence of alternative treatments mean that orphan drugs have not been on their main focus, despite concerns about their cost-effectiveness. However, with increasing cost pressure as more expensive drugs arrive on markets, combined with payers' budget restrictions, this is no longer the case. With constant pressure for healthcare payers to reduce their pharmaceutical budgets, it is doubtful whether these niche markets will remain "safe havens" for the industry.

Indeed, governments are scrutinising the rare diseases/exceptional drugs component of their national budgets, realising that while the budget impact of treating a single individual is negligible for the healthcare system as a whole, figures quickly add up.

Times are changing; Sweden has refused to recommend 30 per cent of EMA approved orphan drugs for use and in England, NICE has started to set up a review process for orphan drugs, which is something long resisted as they are very unlikely to meet the £20,000-30,000 QALY threshold. Italy, France and the Netherlands have started implementing strict registry policies for such drugs. France's Haute Autorité de Santé (HAS) is requesting a post pricing and reimbursement registry for Shire's Elaprase, while the Dutch authorities have decided that future reimbursement of Shire's Replagal will depend on the overall results of its pharmacotherapeutic evaluation, cost prognosis and effectiveness study in three years' time.

GREATER ATTENTION

Governments and social security systems are clearly giving greater attention to the cost-effectiveness of these products than in the past. A research paper presented at the European Conference on Health Economics (ECHE) in Helsinki in July 2010 compared access schemes for orphan drugs across the world and stated that today "most healthcare systems assess cost-effectiveness of drugs for reimbursement decisions" while "regulations for reimbursement of orphan drugs in the case of off-label or compassionate-use are heterogeneous". Heterogeneity of regulations is further reinforced by the existence of varying national epidemiological definitions of a rare disease alongside those of the EMA. For example, to qualify as rare, a disease must have a prevalence rate under 1/50,000 in the UK, while in Sweden it must be under 1 in 10,000. These are much tighter thresholds than the EU's 1/2,000.

Therefore, the industry will have to adopt new strategies and provide healthcare systems

with more than 'better than nothing' drugs. But reviewing cost-effectiveness of orphan drugs poses serious difficulties both to payers and the industry. In the current situation, methodological and statistical hurdles are such that everybody admits the impossibility of achieving the same quality of cost-effectiveness assessments as with other types of drugs. Because cost-effectiveness studies consider the extra (incremental) benefit of a drug compared to treatments currently used, provided they exist, they need to have good data on the existing situation. Yet orphan diseases are, by definition, so rare that baseline data necessary to conduct a study is simply not available. This is the rationale for better coordination on data collection, an effort promoted by inter-governmental organisations and supported by rare disease patient forums such as Eurordis. Indeed, it is in the interest of the industry to encourage the development of transnational cooperation in order to increase the statistical power of rare disease studies.

The emergence of personalised medicine provides new opportunities for orphan drug development and funding. As Dr Kathrin Roll from the Institute for Health Economics and Health Care Management in Munich stated at the ECHE meeting: "personalised medicine will lead to a subdivision of the patient population into smaller groups. This might increase the numbers of authorised orphan drugs that qualify for schemes that promote authorisation and reimbursement of orphan drugs." Indeed, payers are more and more conscious of the benefits of personalised medicine and are thinking of new ways of funding it. In the Netherlands and England, insurers are devolving bundled budgets for providers to choose the best treatments for their patients. For the industry, this means opportunities for new markets but also more competition. And with the advent of pharmacogenomics, industry should make the most of these new means to better convince payers of the effectiveness of their products for targeted sub-populations.

> "The emergence of personalised medicine provides new opportunities"

STRATEGIC IMPLICATIONS

In the short term, companies need to optimise their pricing strategies by taking into account payers' budget constraints and conducting cost-effectiveness studies with larger data sets and new pharmacogenomic tools. In other words, they will have to prove that their new technologies can produce real outcome improvements. While evidence may be a challenge, those that can produce sound data will already have a competitive advantage.

Companies entering these markets should take into account the large gaps between disease prevalence and drug use. Prevalence alone does not suffice, as delays of up to four years have been observed between market authorisation and actual adoption by patients. This is the crucial difference between market authorisation and market access: a recent study conducted by the Italian National Centre for Rare Diseases shows that of the 50 orphan medicinal products approved by the EMA in the last decade (covering 30 conditions and potentially benefiting some 1.6 million people), availability varies between all in Austria to a mere two in Latvia.

This is why these markets require industry to change its business organisation. While primary care markets rely on commercial teams on the ground, niche markets require investment in establishing valid clinical trials, working with patient advocacy groups to ensure these costly treatments are actually reimbursed by payers and, last but not least, by increasing disease awareness. Indeed, in many instances, rare diseases remain undiagnosed. Industry should work with patients' groups and providers' associations to promote educational programmes.

In the long term, companies will have to adapt to each payer's specific concerns with made-to-measure market access strategies at all levels: national, local and even provider level. They should be more conscious of future changes in overall healthcare funding mechanisms such as current decentralisation trends at regional level in France, or at the insurer/local provider level in England and the Netherlands. Evidence of this can already be seen in the emergence of so-called "risk sharing schemes" for very expensive drugs, which are the result of negotiation between the payer and the pharmaceutical company on who bears the risk of the technology not achieving its goal (the 'no cure, no pay' principle). For example, in Scotland, Bosentan for Pulmonary Arterial Hypertension (PAH) is only funded if there is observed improvement in a six-minute shuttle walk test three months following treatment initiation; if not, the drug is withdrawn.

However, though the adoption of such schemes is spreading in cancer treatments, it remains to be seen whether they are sustainable for rare diseases. Indeed, the cost-effectiveness gains achieved by both parties sharing the risk might well be outweighed by the very high per capita administrative costs associated with the follow-up of the patients involved.

With payers more conscious of costs of rare diseases and big pharma's growing interest in niche markets, the era of large product surpluses is likely to end. To succeed, approval from the regulatory authorities is no longer enough; pharmaceutical companies will increasingly need to convince payers of the cost-effectiveness of their products. This implies shifting resources from traditional commercial teams to pinpointing subgroups of patients and providers, investing in data collection and cost-effectiveness expertise and being more aware of payers' constraints.

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