Stem cells:Layout 1 26/6/09 13:34 Page 9

STEM CELL THERAPIES

assessing the commercial opportunity

Restructuring and reorganisation is routine and relentless in the pharmaceutical industry, with a future focus essential for effective strategic decision making. In recent years, small molecule blockbuster drugs have taken a backstage role compared with the attractions of biologics with their perceived lower risk from generic competition. Now, as the biologics market matures, branded products face familiar challenges in patent exclusivity and price as biosimilars begin to reach the market. As the industry looks for its next generation of products, targeting small, highly defined patient groups with very high unmet medical needs could allow demonstration of cost-effectiveness, even with very highly priced interventions. Stem cell research may provide new therapies to meet these needs. While there are many technical issues still to overcome, we consider the challenges in assessing the commercial attractiveness of opportunities in this rapidly emerging area.

By Su Webber, Andrew Millest and Mark Williams

The pharmaceuticals industry is under pressure: the 21st century is bringing new challenges such as the looming loss of exclusivity on blockbuster drugs. Generic competition and generic substitution by payers in some markets is striking at the heart of the traditional pharmaceuticals business model. Pricing pressures and the difficulty in obtaining approval from bodies such as NICE have effectively introduced a fourth hurdle into the approval process for new prescription medicines. At a time when regulators are demanding ever more rigorous pre-approval safety data, requiring longer and more expensive development (with clinical R&D costs around $1 billion) and eating into effective patent life, research and development productivity is declining[1]. Despite the pressures to deliver new patented medicines, it is vital for pharmaceutical companies to understand at an early stage in development the factors likely to affect the commercial success of stem cell therapies before committing time and resource.

Biologics are attractive due to the relative ease of candidate drug identification compared with small molecules, ability to target disease processes currently untreatable by small molecules, and the potential to bring new highly priced drugs to market relatively quickly using standard development pathways established from experience with small molecule drugs. The success of drugs such as Herceptin™ has also shown how some biologics

Stem cells:Layout 1 26/6/09 13:34 Page 10

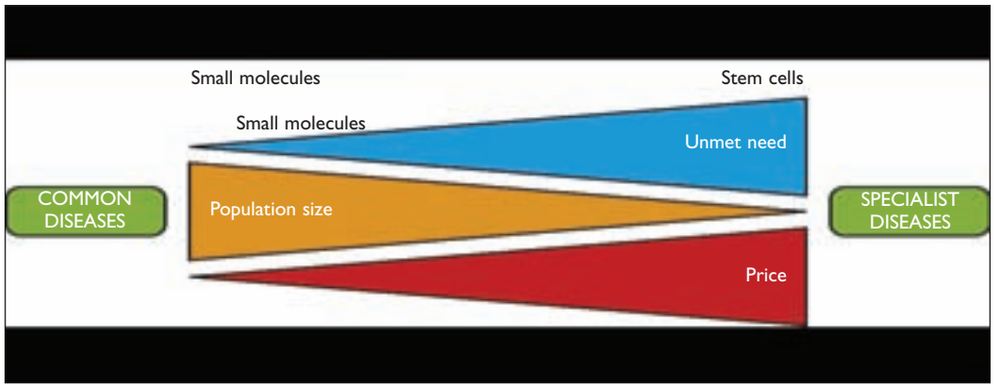

Figure 1
Interaction between market size, unmet need and price potential

can be targeted to defined patient groups, thus providing support for reimbursement. The attractions of biologics precipitated a headlong rush by major pharmaceutical players into acquisitions, strategic alliances and mergers. The $46.8 billion Roche acquisition of Genentech in 2009 is the latest major consolidation in this area.

One perceived attraction of biologics was the reduced potential for generic (biosimilar) competition due to factors such as the estimated $300 million start-up cost for production facilities for antibodies[2], the technical challenges associated with biologics, and unclear paths to biosimilar approvals. However, with peak sales of branded biologics estimated at $112 billion and US biosimilar sales estimated at $4.9-12.6 billion by 2015, branded biologics look set to face the same generic pressures as small molecule drugs[2]. Biosimilar competition has already emerged in Europe with five epoietin-alpha biosimilars approved[3]. Pressures in the USA are also set to increase, with two draft bills introduced to Congress in 2009 that could provide a pathway for biosimilar approvals and may also see branded biologics' patent exclusivity reduced to between five and 14 years[4,5].

In January 2009, Teva and Lonza announced a joint venture to develop, manufacture and market a portfolio of biosimilars, bringing together a major generic house with an established biologics manufacturer[6]. The branded biologics market is beginning to appear like that for small molecules, with several biosimilars likely to compete for the same patient pool, price becoming increasingly important and traditional generics companies raising the competitive pressure.

Traditionally, the pharmaceuticals industry has focused on developing treatments for relatively common diseases such as hypertension and diabetes, where high sales volumes in large patient populations, as well as price, are key factors in determining the commercial attractiveness of a new drug (**Figure 1**).

However, new specialist treatments such as eculizumab for paroxysmal nocturnal haemoglobinuria, which has an incidence of only 1-2 cases per million, costing approximately $400,000 per patient per year, highlight the potential for highly priced therapies in rare diseases or specialist settings. This potential has been recognised, with at least 300 companies worldwide investigating stem cell therapies in at least 70 different indications[7], and major companies such as Pfizer, GSK, J&J, Novartis and Roche investing in stem cell research programmes or collaborations.

The regulatory environment for stem cell therapy is still developing, but the established burdens and costs of demonstrating safety, efficacy, manufacturing quality and proving cost-effectiveness are expected to apply to stem cells just as they do to traditional drugs and the impact of these factors on clinical commercial success needs to be considered. In addition, with a view to the future, although the levels of investment needed to develop and commercialise, a stem cell therapy may prove an initial barrier to generic competition; the lesson emerging from biosimilars is that branded stem cell therapies may not enjoy long-term protection from competition and this threat needs to be factored into investment decisions.

Beyond the many technical issues still to be resolved, it is clear that key questions for stem cell therapies are how to analyse the commercial value of small highly specialised diseases and the uncertainties that may impact on the probability of a successful new product launch.

How should the commercial potential of stem cell therapies be analysed?

The potential commercial value of a stem cell opportunity is affected by various factors, the most

Stem cells:Layout 1 26/6/09 13:34 Page 12

common being the sales forecast, research and development costs, and costs of sales and marketing activities.

The impact of these, and other factors, can be taken into account through calculation of the product Net Present Value (NPV) (**Figure 2**). The NPV provides an estimate of how much overall value, as opposed to peak year sales (PYS), at today's prices and costs, a product brings to a company and is a standard method to evaluate the potential contribution of new clinical candidates or licensing opportunities.

NPV does not by itself account for the probability of launch or failure of a product, but this can be taken into account by calculating the risk-adjusted NPV, which provides vital information when making investment decisions such as clinical phase changes or building manufacturing plants. For example, a product with forecast PYS of $300 million but with a 75% probability of launch could be a more attractive investment than a product with $1 billion PYS but only a 20% probability of launch.

Making good assumptions around the probability of a successful launch is difficult, even for small molecules and biologics, where there is a wealth of historical data and development experience on which to draw. For example, an analysis of Phase III success rates at the top 10 (by market capitalisation) pharmaceutical companies indicates that biologics have a greater probability of launch than small molecules (**Table 1**). However, this type of knowledge is lacking for stem cells and the risks associated with investment choices may be very different for these new therapies than for traditional drugs.

Just as NPV estimates require accurate and realistic assumptions to be made, sales forecasts, R&D and sales and marketing budgets are all built on assumptions; by definition, all of these assumptions are subject to uncertainty. It is important to understand the uncertainties associated with stem cell therapies, not just from a technical perspective, but also to incorporate into uncertainty analysis modelling to determine which factors have the greatest impact and to assign credible probabilities to the range of possible outcomes before making business decisions.

At present, the range of uncertainties and risks associated with stem cell therapies are much less understood than for small molecules and biologics. However, some factors that could be evaluated to allow development of robust assumptions for forecasting and NPV calculations are discussed below.

Stem cell therapy may only be suitable for very high unmet need settings, which will restrict the size of the eligible patient population. In these settings, social pressures from patients may increase pressure on authorities to approve and reimburse stem cell therapies, but in a regulatory environment in which safety is becoming more important, it is unclear if there will be different efficacy hurdles compared with traditional drugs, or a greater acceptance of risk for stem cell therapies.

Unlike traditional drugs, stem cell therapies may need to be produced on demand; this may restrict the number of centres that can offer treatment, thus limiting patient throughput. In addition, specialist surgical, medical or imaging skills may be needed to deliver stem cell therapies into specific tissue sites, placing further restrictions on

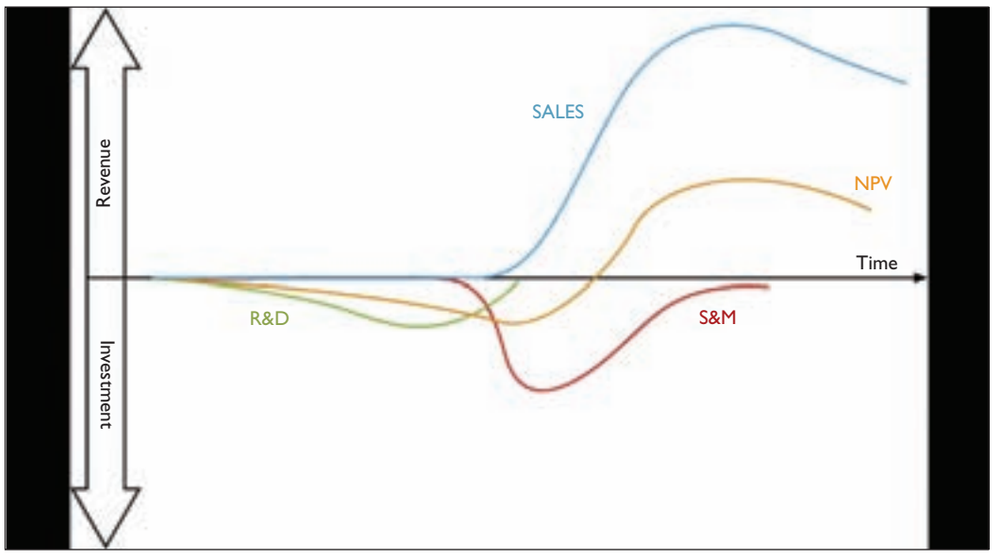

Figure 2
Relationship between costs, sales and Net Present Value

Stem cells:Layout 1 26/6/09 13:34 Page 13

Table 1: Industry average (top 10 pharma) Phase III launch success rates for small molecules and biologics[8]

PHASE III LAUNCH SUCCESS RATE	OVERALL AVERAGE SUCCESS RATE (N=162)	BIOLOGICS AVERAGE SUCCESS RATE (N=35)	SMALL MOLECULES SUCCESS RATE (N=127)
Top 10 pharma	59%	74%	54%

the number of patients which can be treated. Companies entering this new area may therefore have to consider setting up specialist centres or entering into collaborations with centres of medical excellence to maximise the ability to make stem cell therapy available to sufficient patients to make the product commercially viable.

A further difference to traditional drugs is the patentability of stem cell therapy. Despite warnings from experts about potential dangers for patients who engage in 'medical tourism', unregulated stem cell therapy is ongoing and may undermine patent protection of branded stem cell treatments[9]. Patents on stem cell production, processing or delivery rather than the cells themselves, may be the only protection available and may increase the risk of 'generic' competition by companies which may be able to cost effectively develop rival production processes and exploit the experience of their first-to-market competitors.

Regulatory authorities in the USA[10] and EU[11] are developing policies for the approval of stem cell therapies with suggestions that requirements for safety monitoring may be different to traditional drugs. For example, lifetime follow-up of patients to monitor cancer risks after stem cell therapy may be required. The need to be able to track stem cells after administration may require

Stem cells:Layout 1 26/6/09 13:34 Page 14

References

1 Datamonitor. Pharmaceutical companies must adapt to changing market dynamics. Expert View. April 2008.
2 Bernstein Research. Eight thoughts on biosimilars. December 2008.
3 MedTRACK database. April 2009.
4 Pathways to biosimilars. (http://frwebgate.access.gpo.gov/cgi-bin/getdoc.cgi?dbname=111_cong_bills&docid=f:h1548ih.txt.pdf).
5 Waxman, H. Promoting Innovation and Access to Life-Saving Medicine Act. (http://frwebgate.access.gpo.gov/cgi-bin/getdoc.cgi?dbname=111_cong_bills&docid=f:h1548ih.txt.pdf).
6 Teva and Lonza Announce Strategic Partnership to Become a Leading Global Provider of Biosimilars. (http://www.tevapharm.com/pr/2009/pr_818.asp). January 2009.
7 Young, R. Stem cell commercialization 2005-2018; RRY publications LLC; February 2009.
8 Cence analysis of MedTRACK data for period between 1999 and 2009; April 2009; unpublished.
9 Barclay, E. Stem-cell experts raise concerns about medical tourism. Lancet 2009;373:883-884.
10 Federal Drug Administration. Guidance for Industry: Somatic cell therapy for cardiac disease. March 2009.
11 European Medicines Evaluation Agency. Guideline on human cell-based medicinal products 2007.

sophisticated biomarkers that can be used in clinical development and for post-marketing safety monitoring. The potentially high costs of establishing long-term safety may mean that specialist stem cell companies will be forced to partner with large pharmaceutical companies to manage potentially extensive post-marketing patient safety programmes and these costs may need to be included in commercial evaluations. In addition, current EU regulatory thinking on stem cell therapy appears to be more advanced than in the USA: if this leads to different regional approval requirements, the impact on sales potential needs to be included in forecasts, uncertainty analyses and opportunity valuations.

Political issues related to stem cells may be different to traditional drugs. Price and affordability have typically been key political issues surrounding new highly priced small molecule and biologic drugs. However, in some quarters there is fundamental philosophical opposition to the use of embryonic stem cells which may prove a new risk to trial programmes and to commercial success. Opposition could lead to geographical restrictions on sites for production and administration which may limit the available patient population to those who are willing to or can afford to travel to countries where the treatment is available. Additionally, it is clear that, as with traditional drugs, affordability will be important for both payers and patients. As bodies such as NICE in the UK have no experience of assessing stem cell therapies, it is unclear if they will be subject to the same cost-effectiveness thresholds as other drugs, or if the barrier will be lowered for diseases with high unmet needs in what could be small and well-defined patient populations. In either case, understanding health economic factors specific to stem cell therapy is essential.

Despite the other issues that need to be understood, stem cell therapies may offer the industry a unique chance to redefine its sales and marketing model. In specialised settings in diseases with very high unmet needs, the industry could develop close relationships with select specialist physicians and their patients, creating a fundamentally different communications environment. This could reduce the need for large sales forces and traditional promotional activities, significantly reducing sales costs and raising the attractiveness of developing treatments for small specialised indications.

The potential for stem cells to provide new medicines is an exciting prospect in the near future. The willingness of pharmaceutical companies to invest in the area will depend on their ability to accurately predict the commercial value of the opportunity. Therefore, how the pharmaceutical industry conducts its opportunity evaluations may have a significant impact on the progress of stem cell therapies into mainstream clinical practice. Investment in the first generation of stem cell therapies will require a leap of faith for both technical and commercial reasons, and may only appeal to companies who are prepared to accept high financial risk for uncertain rewards. DDW

Su Webber *is a co-founder and director of Cence Consulting which specialises in evaluating the commercial opportunity of pharmaceutical and biotechnology products. She has a background in global pharmaceutical product strategy and marketing gained in leading pharmaceutical companies where she led teams that worked across products in all stages of development.*

Mark Williams *is the lead pharmaceutical business analyst at Cence Consulting. He has extensive experience in forecasting and market analysis gained in a top 10 pharmaceutical company. Mark trained as a chemist and had hands-on experience of the drug discovery process before moving into market research and business analysis.*

Andrew Millest *is the medical affairs analyst at Cence Consulting. He is a pharmacologist and chartered biologist with further qualifications in pharmacovigilance and epidemiology. He had extensive academic and industry drug discovery experience before moving into medical affairs where he specialised in competitive intelligence and analysis.*