

Cornering the EU Market: the Need for Creative Strategies

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When it comes to the accessibility of the EU pharmaceutical market, it is clear that a number of factors have changed in the past few years. Alain J Gilbert and Mark Larkin at Bionest Partners consider whether this amount to evolution or revolution

Before co founding Bionest in 2003, Alain was European Founding President of Biogen Inc (BGEN). He has held several positions at senior management level such as European founder of IDEXX Labs Inc (IDXX), and President of Medtronic Europe. He started his career in sales and marketing at Abbott's Diagnostic Division where he remained for 17 years, holding key executive positions in the US and Europe.



Mark Larkin has eight years of healthcare consulting and corporate finance experience. Within Bionest, he has worked on over a dozen product launch assignments including opportunity assessments, pricing and reimbursement, sales force sizing and launch plans.

The European Union (EU) is a key pharmaceutical market, representing almost 28 per cent of the total world pharmaceutical market value in 2003 (1). A number of changes over recent years, ranging from EU size and regulatory framework to pricing and reimbursement, suggest that the attractiveness and accessibility of the market may, in theory, have changed. We wanted to assess the practical consequences of these changes by examining all centralised marketing authorisations (MA) granted in the EU over the last five years. Given the factors at play, our hypothesis was that, in theory, a weighted balance towards more streamlined access would be reflected in the numbers of approvals granted. However, results from this analysis were equivocal, arguably reflecting the importance of complexities within the changing dynamics of the EU markets, in particular concerning the post-approval issues faced by companies today.

TOWARDS MORE ACCESSIBLE AND ATTRACTIVE EU MARKETS

One of the biggest changes to accessibility of the EU market was the 1995 introduction of a centralised drug approval procedure, matching the US FDA approval structure more closely. This new system was created to unify the regulatory process and provide EU-wide marketing authorisations for innovative medicinal products and, in so doing, significantly improve market access for developers. Since the implementation of this system, drugs approved by the centralised procedure appear to have approval times comparable to the US (2). Although centralised approval is compulsory for biologicals, AIDS, cancer, diabetes,

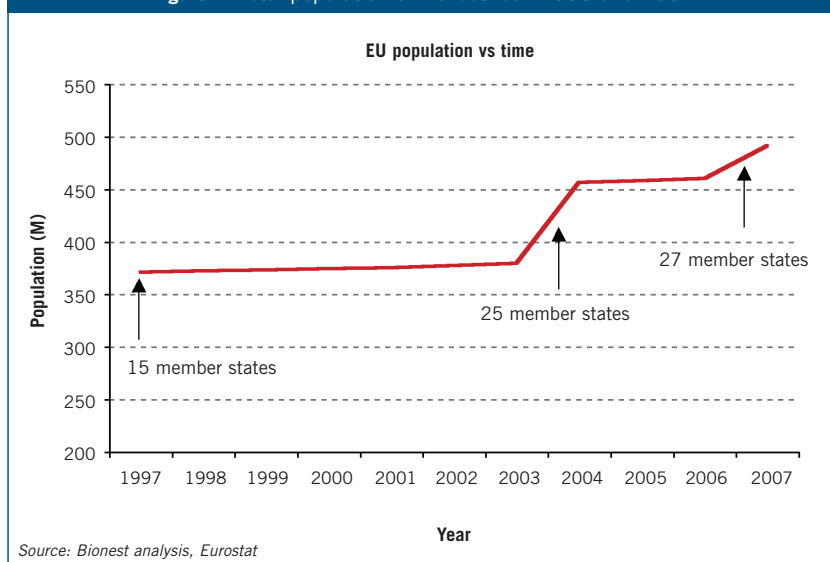
neurodegenerative disease and orphan products, other drugs may still be approved by the decentralised and mutual recognition procedures.

Within the EU, it was hoped that the centralised system would resolve three basic issues: better quality evaluation, faster approval mechanisms and, if possible, lower global costs (2). External to the EU, it was also considered to play an important role in making sure that non-European regulators and companies develop an understanding and trust of the European authorisation procedures. This appears to be succeeding – in June 2007 a new agreement was announced between the EMEA and the FDA to extend their collaboration, already existing in areas such as vaccines, oncology and pharmacogenomics, to also cover paediatric medicines, orphan drugs and risk management plans. The ultimate goals of this collaboration were defined as promoting and protecting public health and reducing regulatory burden and costs, as well as getting medicines to patients as fast as possible. Commission officials stated that this forms part of a significant drive to broaden cooperative activities between Europe and America which includes sharing safety information about drugs.

And why wouldn't such collaborations with the EU be attractive? With the expansion of the EU from 15 to 27 member states since the creation of the centralised procedure, the number of patients potentially covered by one regulatory approval has now increased to over 490 million (see Figure 1, page 18).

In addition to regulatory aspects, also contributing to improved EU market access has been the development of European-wide

Figure 1: Total population of EU between 1995 and 2007



drug distributors, who offer increasingly broad services and geographical footprints. From core logistics services involving warehouse-to-hospital (or pharmacy), these companies now offer other services such as billing, pharmacovigilance and sales representatives. Consequently, developers are now able to outsource a wider range of operational activities, reducing some of the execution risks associated with a product launch.

Thus the continuing geographic expansion and influence of regulatory and distribution factors seems attestation to the phrase 'bigger is better'. However, an equally positive impact is also being observed in the opposite direction, with the shrinking geographical implication resulting in the evolution of mass markets towards specialised markets with the creation of numerous medical 'centres of excellence'. These 'centres of excellence' which have appeared in Europe over the last five years seem to mirror similar institutions in the US, with the nomination of various academic and clinical institutions that serve as hubs for therapeutic advancements, and that provide a benchmark for clinical practice in the surrounding regions. Consequently, companies can develop marketing strategies –

particularly for hospital-based products – which focus on these centres of excellence, because not only are they likely to be the biggest prescribers, but also to influence wider prescribing centres. In short, markets have become more concentrated in supporting the 80/20 rule (80 per cent of prescriptions made by 20 per cent of prescribers). The expected result? Market entry is made more affordable for a broader range of developers.

A FIVE-YEAR SNAPSHOT OF CENTRALISED MARKET APPROVALS

To investigate the real impact of the factors considered to positively influence drug EU market entry, we looked at the number, details and evolution of drugs being approved by the

EU centralised procedure. Unlike the FDA for the US market, no single detailed database exists for all EU marketing authorisations (MA). Therefore, our analyses compiled several data sources including the European Medicines Agency (EMA) Annual Reports, the European Public Assessment Reports (EPAR), pharma projects, developer press releases and websites (3,4). Data were collected for approvals granted between 2003 and 2007 inclusive, and products approved were individually assessed as to whether they represented a new molecular entity (NME) or not (5).

STRONG GROWTH IN PRODUCT APPROVALS

There were a total of 187 centralised marketing authorisation approvals granted by the European Commission during the period 2003-2007, and these approvals were separated according to whether they were for a NME or an orphan drug (see Figure 2). If 2005 is excluded, approval numbers increased with time. When the numbers of equivalent approvals in the US were examined during the same time period, such an increase was not seen, with the FDA approval numbers remaining fairly stable. Although there were consistently more approvals in the US, the most recent data in 2006 also showed the smallest gap between the two regions suggesting that Europe may be catching up. The relatively small number of approvals observed in 2005 may reflect regulatory conservatism consequential to the high-profile safety alerts and authorised medicine withdrawals that marked 2003 and 2004, including the drugs rofecoxib (Vioxx®) and nefazodone (Serzone®).

Similar to the total number of approvals, the number of NMEs approved increased each year. However, the percentage of total approvals that these NMEs represented was seen to decrease from 74 per cent in 2003 to 54 per cent in 2007. Interestingly, the

Figure 2: Number of marketing authorisation approvals between 2003 and 2007

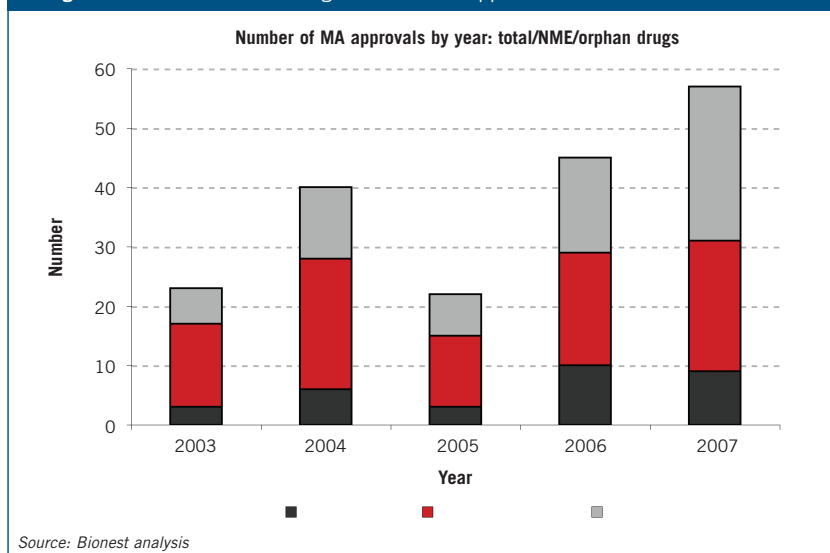
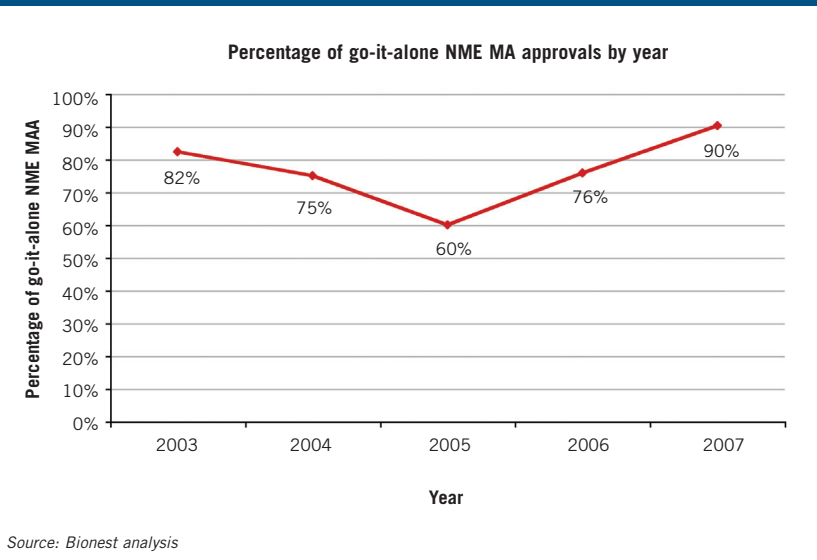


Figure 3: Percentage of MA approvals by year received by 'go-it-alone' companies



market. Recent approvals reflect the oncology pipeline boom of the mid 1990s, which built on scientific and technological improvements of the early 1990s (such as the development of 'omics' technologies and advances in preclinical and toxicity studies), and also the remaining high unmet medical needs of this market. As a result, oncology R&D that represented 18 per cent of the pharmaceutical pipeline in 1995 expanded to reach 25 per cent in 2005.

As with oncology, the increasing weight of metabolism drugs in the pharmaceutical market is not only being felt in the EU. The continuing growth of obesity and diabetes in developed countries as a whole has encouraged significant R&D activity in this

proportion of NMEs for orphan drugs increased significantly each year from 18 per cent in 2003 to 34 per cent in 2006. This would be related to the fact that orphan drug legislation was implemented in Europe only recently, in April 2000. However, in light of the recent agreement between the US and EU to unite their orphan drug designation request forms to make life simpler for pharmaceutical companies, it seems that the proportion of NMEs approved in Europe is likely to grow, responding to one of the main driving factors behind the creation of the centralised EU approval system – to encourage innovation.

ONCOLOGY AND METABOLISM LEAD THE WAY

Overall, the most approvals were in oncology, followed by metabolism, and no significant growth in terms of approval numbers was observed in these areas over the five years assessed. The prominence of oncology is not surprising given the significance of the growth and future direction of this market – a phenomenon by no means restricted to the EU

area, reflected in the increased number of MAs. Approvals for all other indications were relatively constant with no clues to significant areas of growth in the EU resonating at this level.

CAN MORE DEVELOPERS PERSONALLY BRING DRUGS TO MARKET IN THE EU?

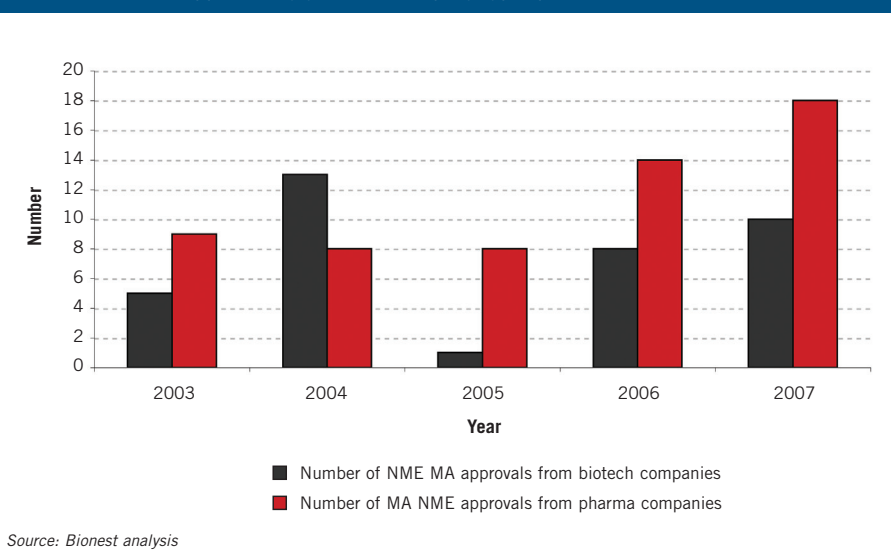
When the data of all centralised EU marketing approvals over the last five years were assessed, companies that were listed as both the originator and the marketing authorisation holder of an approved product were considered to have 'gone-it-alone', as opposed to out-licensing, in bringing the drug to the EU market. The proportion of companies doing this varied between 90 per cent and 60 per cent as illustrated in Figure 3. These 'go-it-alone' companies were divided according to company type, pharma or biotech, and the results of this split are displayed in Figure 4.

Biotech companies, loosely defined as immature drug development companies (likely to have no or little revenues and

which are unprofitable) represented only 39 per cent of these 'go-it-alone' companies overall. This reflects, in our view, conservatism from this key group of drug developers who may not yet be comfortable with the changing dynamics of the EU markets, and a preference to out-licence products rather than commercialise them themselves.

However, overall, with out-licensed products representing the minority of MAs, the 'not invented here' syndrome appears alive and well. Big pharma's internal R&D machines cannot supply sufficient products to supply their expensive marketing infrastructure. This productivity crisis

Figure 4: 'Go-it-alone' companies with NME MA approvals by year and company type (pharma or biotech)



is particularly difficult, as it is felt at many different stages of the value chain – for instance, from early stage research, where molecular targets are increasingly complex, through development, where regulators make approvals increasingly tough following high profile cases such as Vioxx®. The extensive effort put into business development by big pharma underlines one solution: to simply increase the number of product candidates that pass through the big pharma R&D machine. This should serve to increase competition internally so that in-licensed projects compete objectively with their home-grown counterparts for the limited resources to be taken to the next developmental stage. However, vested interests in internal projects, and distrust and/or lack of necessary skills for external projects, mean that the competition is not always objective so that, despite the urgent need for pipeline products, large companies with productivity crises paradoxically still often view in-licensing as a failure.

POSITIVE EU MARKET CHANGES

Whilst the number of approvals in the EU over the last five years was observed to be increasing, a result not to be ignored in light of stable US approval numbers, the results from our MA analysis did not correlate as expected with the significant advancements in EU market accessibility as a consequence of important structural reorganisation over the last ten years. However this itself underlines the fact there are additional complexities to this market that cannot be ignored.

AT WHAT PRICE?

Recent developments in European pricing and reimbursement (P&R) are an important factor in EU market attractiveness and accessibility. Innovative new P&R mechanisms are being developed against a backdrop of increasing limits on spending by European national health providers. For instance, in response to NICE's refusal of UK reimbursement for Velcade in the treatment of multiple myeloma, J&J proposed that the NHS pay for a patient's treatment only when it has been proven to work as defined by specific clinical criteria. In Germany, health insurers estimated that the budgetary impact of Novartis' Lucentis for the treatment of age-related macular degeneration (AMD) could cost up to €700 million per annum. In response to this, Novartis offered to reimburse statutory health insurers for any Lucentis costs exceeding €315 million a year. Both these cases underline the point that, even if access to markets is becoming easier in the EU, this advantage may be tempered by P&R hurdles, although creative solutions may nonetheless be possible. Time will tell how successful these solutions are for developers, but one thing seems sure: if EU P&R strategy is not optimised, the potential impact on product success is huge.

INCREASING DEMANDS OF RISK MANAGEMENT

Introduced in November 2005, risk management plans (RMPs) are a pivotal factor in EU efforts to augment confidence in the

safety of new drugs. However, this proactive surveillance is proving a challenge not only for EU official and regulators in terms of organisation, but also for companies who have to consider the implications of this legislation carefully in terms of their approach to the development, implementation and monitoring of these programmes. Repercussions are also being felt in the time and resources required to bring a drug to the European market. The marketing authorisation for Accomplia® in 2006 was granted, together with the obligatory RMP which included rigorous post-approval monitoring and communication with patients, healthcare professionals and the appropriate national health authorities, illustrating the difficulty added by the diversity of requirements for each EU country in addition to EU regulations.

RMPs have been reason for some concern by companies in relation to potential allegations of product liability, and there is an ongoing need for understanding of this regulatory hurdle, with the EMEA finding just three out of 12 RMPs submitted as part of authorisation procedures to be of acceptable quality.

THE NEED FOR A SPECIFIC EU STRATEGY, NOT EXTRAPOLATION

With 27 countries and more than 490 million people, the EU pharmaceutical market is sophisticated but also rapidly evolving, given the changes that should make it a far more accessible market. Whether the changes we have discussed are the key drivers of accessibility remains open to debate, but from our snapshot of centralised approvals, it is clear that more drugs are being launched. However, we believe that the impacts of the positive drivers are not yet maximised. Uncertainties around pricing and reimbursement and suboptimal performance of in-licensed products are slowing momentum. However, these are normal teething problems that can be resolved by development of bespoke product strategies that leverage a thorough understanding of EU markets and regulatory framework, and should not deter companies from entering this enormous market with its potentially significant rewards. ♦

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