Pharma
Marketletter

Global pharmaceutical, generics and biotech industry news

September 29, 2008

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Early access programs in Europe: a regulatory tool with pre-marketing impact

Early Access Programs are country-specific regulatory tools that allow a drug to be available on the market before its official launch, providing that it fulfils specific criteria. Despite potential significant advantages of these programs, many pharma/biotech companies remain unaware of the possibilities available in Europe. In addition, even amongst the informed minority, many assume - wrongly - that an EAP will be too risky, too complicated or too costly to consider. Alain Gilbert, Vanessa Caignault and Murielle Foist of Bionest Partners explain why European EAPs are worth considering by pharma/biotech companies.

They cite the cases of Actelion's Tracleer (bosentan) for pulmonary arterial hypertension (also granted orphan drug status) and Sanofi-Aventis' Eloxatine (oxaliplatin), for use in metastatic colorectal cancer, which were available in Europe *via* EAPs prior to their official launches.

Neither of these drugs, now firmly established as cornerstone therapies in their respective target conditions, were initially predicted to be the blockbusters they are today. The Tracleer EAP raised awareness of the need to diagnose and treat the disease early among a growing number of non-PAH experts. Eloxatine's success was based on strong market penetration achieved by its EAP, which resulted in very profitable returns once on the market. These successful EAPs demonstrate that such programs can be invaluable components of pre-launch activity.

Key components of a European EAP

European regulations require that drugs are granted marketing approval before being made available in the community. Unauthorized drugs may be available through clinical trials. However, in order to facilitate the availability of new treatments in development, European countries have implemented national EAPs. The name of these EAPs varies by country and is otherwise known as compassionate use or treatment Investigational New Drug in the USA. EAPs make drugs available either on a named patient basis or to cohorts of patients, governed by country-specific legislation.

To be eligible for an EAP, the new drug must fulfil several criteria. Firstly, regulation states that the treatment is available to "*patients with a chronically or seriously debilitating disease, or a life threatening disease, and who cannot be treated satisfactorily by an authorized medicinal product*." These programs are not only designed for rare diseases but also for severe conditions affecting large populations. Typical examples are cancer, HIV/AIDS, neurodegenerative disorders and auto-immune diseases. "*Patients who cannot be treated satisfactorily*" means those who are left without treatment options, or those whose disease does not respond to or relapses with available treatments, and/or those for whom current therapy is contraindicated or inadequate.

The drug must either be the subject of an application for marketing authorization or must be undergoing clinical trials. Typically, EAPs involve products in Phase III (although planning should begin during Phase II). Sufficient safety and efficacy information are required to demonstrate a positive benefit/risk ratio and permit use of the drug in a minimally controlled out-patient setting. Although safety data may be collected during EAPs, these programs are not substitutes for clinical trials. Therefore, patients should always be considered for inclusion in clinical trials before being offered a drug through an EAP.

EAP regulations are country-specific

Out of the five major European pharma/biotech markets, France can be considered as a pioneer and reference in terms of EAP procedures, having the most well-defined legal framework which was first created in 1994. In the UK, EAP regulation is limited to a clearly defined importation process for unlicensed drugs. In Spain and Italy, EAP regulation is relatively underdeveloped and in Germany legislation is currently being implemented. Many important aspects of EAPs - such as program duration, pricing and reimbursement - are not explicitly covered by existing regulation. In practice, however, these issues are crucial for regulators, and common practices have emerged.

Looking at France, the most frequent scenario that results in a named-patient EAP is a physician who is aware of a new drug in development and wants to use it as a "last chance" treatment for patients. In this case, the physician will be the EAP applicant and will hold legal responsibility for the program, report any adverse events and keep track of patient information. The drugmaker will provide the supply and submit product information to the relevant health authority prior to circulation as well as a pharmacovigilance report. In contrast, the application for a Cohort EAP is done by a drug firm and it holds the legal responsibility. The applicant company is also required to provide detailed protocols and guidelines describing the drug's therapeutic use, ensure compliance with protocol, perform information collection including adverse events and carry out pharmacovigilance procedures. The physician's role in the Cohort EAP model is limited to prescribing the drug in compliance with protocol.

Since July 2007, European countries can access European Medicines Agency (EMEA) recommendations related to Cohort EAP applications. But it remains the case that EAPs are co-ordinated and implemented by the spe

cific country, under the relevant national law if it exists, with the EMEA recommendations serving as guidelines.

Barriers seen to outweigh advantages

Success stories such as Tracleer and Eloxatine have raised the profiles of EAPs, yet many companies - especially in North America - remain unaware of the possibilities offered by European EAP programs. Pharmacovigilance teams sometimes fear potential safety issues that could be reported during an EAP, especially if the drug is misused by a physician having requested the agent under a named-patient EAP (whereby there is no protocol).

From a regulatory point of view, potential adverse safety results could be considered to endanger the marketing approval of the drug. In addition, regulatory teams in companies sometimes have minimal knowledge and/or experience of EAPs and the country-specific nature of the programs. EAPs are also assumed to require a significant administrative workload in terms of paperwork, *etc*. Marketing and commercial teams often do not see how they could benefit from an EAP due to the perception that this is purely a regulatory tool. This is compounded by the fact that promotion of EAPs is prohibited. Last but not least, very few pharma/biotech companies are aware that it is possible to charge for EAP drugs in several European countries. In this case, the key issue is to set the right price, which is close to the price at launch.

...challenging programs to manage

Unlike standard clinical trials, the number of patients and sites involved in EAPs are unpredictable (particularly in named-patient EAPs), which makes assessment of adequate drug production and supply difficult.

In addition, pharma/biotech firms with no drugs on the European market, especially American ones, will not yet have developed any distribution channels in Europe. Finally, EAPs must be managed on a country-by-country basis, which is challenging for companies with limited knowledge of the European markets. In this context, is an EAP worth considering? The answer is definitely YES. Despite all the issues raised, no barriers are insurmountable. All activities related to EAP management can be outsourced to a third party. In Europe, fully integrated service providers offer an efficient and cost-effective approach to managing global EAPs. These third parties are aware of local variability within the programs and work within the boundaries of local regulations.

Drugmakers based in Europe, potentially having affiliates in different countries and a distribution partner, have the capabilities to fully manage EAPs and some do this. As much as possible, companies do try to keep control of all strategic activities that are easy to manage and have high added-value (*ie*, customer management, health authority relations and information collection). These activities can be shared between two to three partly-dedicated employees (*eg*, medical/clinical, regulatory affairs, product manager/commercial support). However, companies should outsource time- and resource-consuming activities such as drug supply (handled by pre-wholesalers and wholesalers for instance). For named-patient EAPs, drug supply can be managed internally. In the case of Cohort EAPs, which are more complex to handle, drug companies tend to outsource protocol-related activities (*eg*, patient inclusion, paperwork) to the companies that may already be managing the product's clinical trial (*eg*, contract research organizations).

According to a product manager of a European pharma/biotech company, "*keeping control of relationships with our customers is key, as well as managing data reporting and processing in order to better understand our clients' needs and gain their loyalty pre-launch. We take advantage of EAPs as a pre-marketing tool*."

EAPs offer real marketing rewards

EAPs are a good means of testing the product in "real life" and convincing prescribers and patients of product efficacy before launch. One advantage is that "real life" data are obtained, reflecting a more clinically and ethnically diverse population than often encountered in clinical trials. This information gained pre-launch can also shape post-launch marketing messages. "Early Adopters" or brand advocates can be identified as a wider group of physicians gain experience with the drug, and physician loyalty may be developed. Furthermore, key opinion leaders often play a major role in discussions with regulatory agencies.

Equally with respect to patients, as well as providing them with access to a potentially life saving medicine, there is the opportunity for feedback, the development of patient loyalty and building relationship with patient advocacy groups and associations.

There is the potential for early revenues in countries where EAPs can be designed as "for-profit" programs, but whether or not a drug is made available free of charge, market penetration can be maximized pre-launch through an EAP, which can then translate to a successful launch and increased post-approval usage. In practice, a good rule of thumb is that first-year market penetration after employing an EAP strategy is equivalent to the second year market penetration of a regular launch.

Even when EAPs run at a loss or neutral returns in standalone financial terms, long-term benefits make them an attractive choice for companies. In fact, patient recruitment is generally faster for not-for-profit EAPs, so if these patients keep using the drug when it is sold post-launch, a not-for-profit scenario could in fact provide the most benefit to pharma/biotech firms.

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