Great oaks from little acorns

This month should see the publication of new European guidelines on early access programmes, helping innovative pharma companies offer more treatments to patients prior to marketing approval. Alain Gilbert, Mark Larkin, Vanessa Coudre and Xavier Paoli explain how big things can come from small beginnings with an EAP

Developers of drugs for indications that are either rare or have no existing treatments are turning to early access programmes as a means of getting drugs to European patients before their market launch. These programmes provide developers with a range of benefits which can include revenues, market information and post-launch sales, but they also give patients a vital lifeline. New European legislation, scheduled for publication later this month, will make such programmes much easier to implement, bringing treatments to patients more quickly.

Early access programmes (EAPs) – known as expanded access programmes in the US – allow access to innovative medicines before marketing approval has been granted, for patients suffering from rare and/or severe life-threatening diseases with no satisfactory treatment. With up to 30 million people potentially affected in Europe, rare diseases have been identified as a priority area by the EU. Based on the US model, where a legal framework for orphan drugs has been in place since 1983, European orphan legislation was established by the European Medicines Agency (EMEA) in April 2000. The regulation has been extremely successful since its inception, with around 450 applications submitted, of which more than 260 drugs have been granted orphan drug status, and 22 have received marketing approval.

It would be wrong to think of these treatments as simply small or niche products. Both Novartis' Gleevec (indicated for chronic myeloid leukaemia and malignant gastro-intestinal stromal tumours) and Actelion's Tracleer (for pulmonary arterial hypertension, or PAH) were granted orphan drug status and were available via EAPs in Europe before their subsequent hugely successful launches.

Furthermore, EAPs for Gilead's Truvada (for HIV-1 infection in adults) and Sanofi-Aventis' Eloxatine (for metastatic colorectal cancer), with more than five million and one million new cases respectively diagnosed yearly world-wide, illustrate that these programmes are not only designed for rare diseases but for severe life-threatening conditions affecting large populations. Strong lobbying has ensured HIV and oncology are two key areas for EAPs.

The successful EAPs of Tracleer and Eloxatine demonstrate that these programmes are invaluable components of pre-launch activity that can contribute to a successful subsequent launch, whether or not the drug has orphan status. Both drugs have peak sales in excess of US$1 billion but neither was initially predicted to become such blockbusters. Eloxatine's post-launch success was based on strong market penetration achieved through a pre-launch EAP which, since the drug was paid-for rather than free-of-charge, was itself very profitable. Sanofi-Aventis' Eloxatine is today a cornerstone of chemotherapy, prescribed to 44% of new colorectal cancer patients worldwide.

What's in the mix

So what are the key components of a European EAP programme? Typically, EAPs are provided for products in phase III clinical trials, although developers should begin planning in phase II, and last for around 12 months. The drugs involved have usually been granted orphan drug status or are treatments for HIV or cancer. In most countries, prescribing physicians, often supported by patients' associations, act as unofficial advocates for an EAP and also hold the legal responsibility. A new product's therapeutic benefit means that key opinion leaders also play a major role, often in discussions with regulatory agencies. Although developers can run programmes themselves, most companies – especially from North America – choose external specialists to run their EAP for them.

Beyond these generalisations, EAPs are governed by European Commission (EC) legislation aimed at improving access to innovative drugs for desperately ill patients, which defines 'compassionate use' as "making a medicinal product available to a group of patients with chronically or seriously debilitating disease or whose disease is considered to be life-threatening, and who cannot be treated satisfactorily by an authorised medicinal product. The medicinal product concerned must either be the subject of an application for a marketing authorisation…or must be undergoing clinical trials".

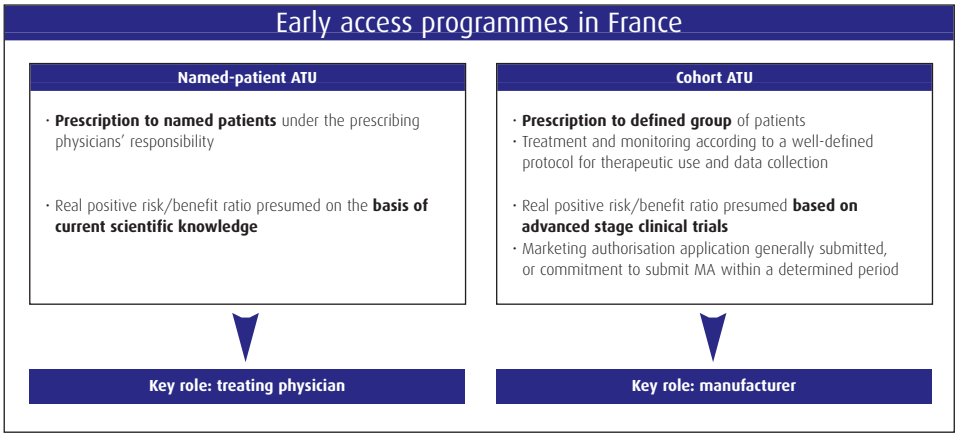

Figure 1: France has two different EAP models, known as ATUs (authorisations of temporary use) – the named patient programme and the cohort programme.

EAP regulations in the main five European pharmaceutical markets

Country	Name of the procedure	Health authorities	Applicant	Validity	Liability	Importation authorisation	Timelines for EAP
France	ATU	Afssaps	Physicians; license holder	1 year	Physicians or license holder	Required	n/r
Germany	Compassionate use	BfArM	Physicians	n/r	Physicians	Required	n/r
UK	Supply of unlicensed relevant medicinal products	MHRA	Physicians; dentists	n/r	Physicians	Required	28 days
Italy	Uso therapeutico di medicinale sottoposto a sperimentazione clinica (Therapeutic use of medicines under clinical trials)	ISS	Physicians	n/r	Physicians	Ethics committee approval to be presented for importation	n/r
Spain	Uso compassivo (Compassionate use)	AEMPS	Physicians	n/r	Physicians	Required	n/r

n/r = not regulated

Figure 2: Legislation on EAP application procedures currently varies significantly from country to country in the EU.

This regulation does not, however, provide any practical guidelines about EAP approval processes. Each national agency is therefore responsible for programme authorisations in its own territory, so an EAP could, for example, be accepted in France but refused in Italy. Furthermore, national specificities including medical practices, flexibility of legal frameworks, and health insurance systems all introduce additional variability into EAP procedures. As a consequence, an approved EAP programme is likely to vary greatly from country to country in terms of such key factors as the complexity of application processes, the liability for drug administration, and the modality of payment. Additionally, developers' own product and corporate strategies are key drivers of programme structure, so that success at the European level is dependent on detailed EAP design and planning on a national basis.

Actelion's early access programme for Tracleer raised awareness of the need to diagnose and treat PAH

Of the five major European pharmaceutical markets, France is a pioneer and reference in EAP procedures, and has the best-defined legal framework in Europe. Since 1994, over 400 drugs have been subject of applications for authorisations of temporary use (ATUs) – the French version of an EAP. France is unique in Europe in allowing two different types of EAP programme: named-patient and cohort (see Figure 1). Cohort programmes require significant involvement in, and legal responsibility for, the EAP by the license holder. By contrast, treating physicians play a greater role in named-patient EAPs. These differences mean that cohort programmes are far more complex than named-patient programmes, principally because of the extensive supporting documentation required – roughly comparable to a marketing authorisation (MA) – which is evaluated by the MA committee. Consequently, named-patient ATUs are far more numerous in France than cohort programmes.

The UK has the next most detailed legislation, where EAP regulation is limited to a clearly defined importation process for an unlicensed drug. Compared with the French and British frameworks (see Figure 2), legislation in Spain and Italy is relatively light, while Germany does not yet have clear EAP legislation and is currently awaiting the new EMEA guidelines. In the meantime, many important aspects of EAPs – such as duration of validity, pricing and reimbursement and timelines for EAP approval – are not explicitly covered by existing regulation. However, in reality these issues are crucial for regulators, and common practices have emerged.

Payment and reimbursement

Although legislation provides only limited EAP guidelines, national regulatory authority approval is nonetheless required for all aspects of a programme. In this 'grey' area of regulatory practice, key opinion leaders play a vital role in liaising with the agencies. Unfortunately, many developers (especially North American firms) with potential EAP products have often not yet developed relationships with European key opinion leaders. Yet without this kind of support, approval can be slow or it can stall, even for treatments that could prove successful if the correct approach had been followed.

An EAP characteristic of keen interest to both developers and patients is payment and reimbursement. Drugs are considered on a case-by-case basis and sometimes even on a patient-by-patient basis, depending on the country. The degree of centralisation of healthcare systems, the availability of funds (which could come from government, insurance, patient advocacy groups or patients) and the existence of precedent programmes all contribute to the final modality. Within a given programme, a treatment can be provided on either a paid-for or free-of-charge basis, depending on where the patient lives. In purely financial terms for the developer, therefore, an EAP could be loss-making, neutral, or profit-making. Irrespective of payment modality, however, longer term benefits of EAPs should make all types potentially attractive to developers.

Raising prescriber awareness

Experienced pharma and biotech EAP practitioners believe these programmes are an invaluable component of pre-launch activity, with many potential benefits. First, EAPs are seen as a good means of testing the product in 'real life', convincing prescribers and patients of product efficacy before launch. If the drug is eligible for an EAP, convinced prescribers will try and recruit a strong corpus of patients during pre-launch. Actelion's EAP for Tracleer, for instance, raised awareness about the need to diagnose and treat PAH among both PAH-aware and PAH-naïve physicians. Thus, whether a drug is charged for or not, market penetration is maximised pre-launch which, when converted to post-launch usage, favours a successful launch. In practice, a good rule of thumb is that first-year market penetration with an EAP is equivalent to second-year market penetration of a regular launch (see Figure 3).

Even when EAPs are loss-making or neutral in standalone financial terms, long-term benefits make them an attractive choice for developers. In fact, patient recruitment is

generally faster for not-for-profit EAPs, so if these patients keep using the drug post-launch, a not-for-profit scenario could provide the most benefit to developers.

The harmonisation effort

High-profile success stories such as Gleevec and Tracleer have raised the profiles of EAPs, yet many companies, especially in North America, remain unaware of the possibilities offered by European EAP programmes. Even among the informed minority, many wrongly assume an EAP would either be too complicated or too costly to consider.

The EMEA initiative to harmonise European EAP application procedures and to improve access to medicines designed for severe and/or rare diseases should make EAP implementation easier. With the new guidelines due out this month, the regulatory framework should produce a semi-centralised procedure, with the European regulatory agency playing a consultative role. Application processes will be initiated in one member state, and the application dossier transferred to the EMEA through the national agency. The European regulator will then be in charge of scientific and medical evaluation, and its consultative decision will be sent to each national agency in Europe. EAPs are still likely to require a country-by-country approval process, but the final decision will be based only on pharmacoeconomics' considerations.

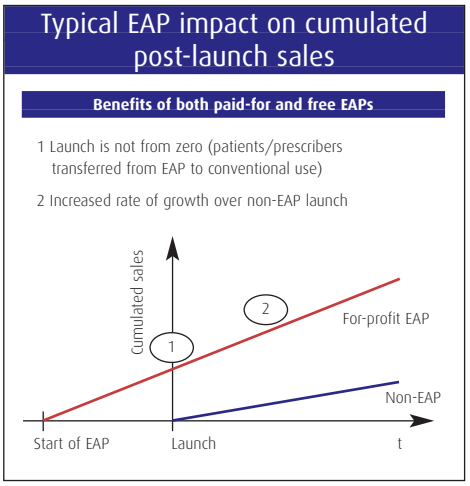

Figure 3: EAPs can convince prescribers and patients of a drug's efficacy before launch.

It would be difficult for national agencies to refuse an EAP if the EMEA gives a positive decision, as medical needs take precedence over financial considerations. But approval of the new guidelines is not the final step in the process – subsequent adoption into national legislations will be required before any impact is felt in practice. It is impossible to predict how quickly national governments will incorporate this legislation into national law, or whether any resistance is likely from national regulatory agencies. These uncertainties notwithstanding, the new guidelines should facilitate EAP implementation in Europe, and with it improve and accelerate access to innovative drugs – good news for both innovative pharma and patients.

Bionest Partners is a strategy consultancy and corporate boutique specialising in the healthcare sector. Alain Gilbert is managing partner, Mark Larkin is practice leader and Vanessa Coudre and Xavier Paoli are consultants in Bionest's dedicated Early Access Programmes unit, located in Paris, France.