

MAKING EARLY ACCESS REAL

getting treatments to patients with no other option

For patients who have no other option to treat their condition, early access to drugs in clinical development can be critical. As a trained physician, there is an intrinsic understanding that early access to investigational or pre-launch drugs can potentially offer life-saving treatment options when no other option is available. The challenge for the pharmaceutical industry is to successfully and ethically manage early access to their drugs.

Patients with unmet medical needs can gain access to drugs in clinical development through ethical and regulated managed access programmes known as Expanded Access Programs (EAP) in the US and Named Patient Programmes (NPPs) in the rest of the world. The growing focus on controlled access to pre-approved therapies is a reflection of patients', physicians' and the industry's increased awareness of the important role that pharmaceutical companies can play in the management of access to their medicines.

The role of managed access programmes

Managed access programmes facilitate access to investigational drugs for individual patients or groups of patients with unmet medical needs. These programmes also allow access, in specific circumstances, to drugs that are approved in other countries but not yet approved in a patient's home country pending ongoing pricing and reimbursement negotiations.

In Europe, NPPs are controlled and restricted access programmes set up by pharmaceutical and biotechnology companies under which physicians

and pharmacists can gain access to investigational therapies on a 'named' patient basis. At the same time, they also offer physicians the opportunity to utilise new medicines and stay at the forefront of medical advances. For pharmaceutical and biotechnology companies, NPPs can help address demand and build a network of physicians and knowledge about who, where, and in which patient populations the drug can be used effectively. There are limitations on data that can be collected during an NPP such as efficacy data.

This understanding of the impact of a new drug can enable more informed strategic decisions and feed into pre-launch plans that can be shared within a company and may indeed help influence future marketing and reimbursement strategy.

Facilitating access in a range of scenarios and different markets

There are several EU Directives that apply to managed access programmes. They provide a set of rules under which patients can receive investigational or pre-launch drugs:

By Dr Rav Seeruthun



- The Directive 2001/83/EC states that an unlicensed drug may be made available in response to a *bona fide* unsolicited order by a healthcare professional for use by their individual patient in their direct personal responsibility.
- The EU Directive 726/2004 outlines the type of patient who can be considered for these programmes based on compassionate use grounds. According to the Directive, unlicensed drugs can only be made available on compassionate grounds to patients with a chronically or seriously debilitating disease or whose disease is considered to be life-threatening and who cannot be treated satisfactorily with an authorised medicinal product.

The latter regulation also underlines that managed access programmes may not interfere with or replace clinical trials, ie patients should always be considered for inclusion into a clinical trial first.

In addition to this general framework laid down on a European level, the 27 member states of the European Union – all of whom nominally come under the jurisdiction of the European Medicines Agency (EMA) – each have their own nationalised regulations regarding the import of investigational or pre-launch medications for NPPs. National programmes differ widely from one member state to another due to differences in national medical practices, resources available, funding of the product, hospital structures and national insurance systems. The terminology also differs, but broadly

speaking, access is created via named patient programmes.

Implementing managed access programmes

Putting into place a managed access programme can often be a complicated process (see Figure 1).

My experience has involved implementing three NPPs, including one for a drug with orphan status from the EMA and the US Food & Drug Administration (FDA) for Lennox Gastaut Syndrome. The programme was implemented both on a pan-European and domestic level during reimbursement discussions in a number of the EU27 member states.

Orphan drugs do provide an interesting challenge to many companies. To be designated an orphan drug in the EU, the condition treated needs to occur in less than five per 10,000 patients in the European Union. This differs from the United States where less than 200,000 patients need to have been diagnosed with the condition.

As these conditions are rare the numbers of patients included in the pre-licence trials are often limited. The orphan drug legislation creates an incentive for pharmaceutical companies to develop drugs that due to the rareness of the conditions may have limited marketing gain. Often these conditions such as Lennox-Gastaut Syndrome are catastrophic in their nature. Therefore an early access programme is an ethical approach to supplying orphan

drugs both while awaiting a marketing authorisation, or as is becoming more common, awaiting a pricing and reimbursement negotiation.

Planning for a managed access programme should be considered as early as possible from Phase II trials onwards. This allows time for preparation of standard operating procedures, consultation with regulatory authorities for approval of the programme, agreeing the label and development of information for physicians and pharmacists regarding dosing, administration and restrictions.

An important factor when implementing a programme is clear delineation of which patients will be included. While all programmes must specify access/inclusion criteria, this decision can be particularly challenging with some disease areas, for example oncology. In some cases, the mechanism of action of the drug may extend to more than one type of cancer. This may lead to requests for access from patients suffering from a form of cancer not currently being evaluated in trials. For this reason, companies must proactively establish criteria to ensure proper selection of patients for inclusion in the programme.

Successful development and implementation of these programmes requires the involvement and co-ordination of many disciplines across in-house teams including medical affairs, pharmaceutical development, regulatory and supply chain. A cross-functional team is necessary for ensuring that the clinical criteria for patient participation are established, physician educational materials are defined, the supply of drug is adequate to support the programme, and enrolment in any ongoing clinical trials will not be compromised.

Managed access programmes: key considerations

Regulations differ widely among EU member states due to differences in national medical practices, resources available, product funding, hospital structures and national insurance systems; one example is whether an authorisation from competent authorities is necessary. This is true in a majority of member states, but in others, a simple notification or an import certificate is sufficient. There are also other differences that sponsoring companies should be mindful of:

Who pays?

While patients, hospitals and/or national insurance systems bear the costs in the majority of member states, the company is expected to provide nominal compassionate-use products free of charge in a few member states such as Austria, Greece and Spain.

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Therapeutics

One should consider that if the drug is charged for then this price can be used as a benchmark for pricing and reimbursement committees.

Ultimately, the choice to offer early access – or not – is left up to the drug developer. Existing regulations do not force companies to offer access to drugs prior to approval or launch. When considering this option, however, companies must undertake a thorough evaluation of important questions such as when to offer access and for which patients.

Ensuring supply and vetting healthcare professionals

Companies must ensure that there is adequate supply of the drug to complete registration studies and support the access programme in parallel. Another consideration is the resource needed to establish and run the programme, including processes for handling and vetting requests, the mechanisms to review physicians requesting the drug and procedures to handle adverse event reporting. Another key factor is proper vetting of physicians and pharmacists.

Taking responsibility

Liability risks are an important consideration and in most instances rest upon the treating physician. In Germany, Greece and Sweden, however, liability resides with the company. Both France and the UK distinguish between responsibility for quality aspects; this is the responsibility of the company; and clinical negligence for which the physician is responsible. Importantly, adverse event reporting is mandatory in all member states. The Czech Republic, Denmark, Finland, France, Greece, Latvia, Luxembourg, Malta, the Netherlands and Sweden have national regulations including both named and cohort programmes.

Working in partnership

Implementation and management of an access programme requires significant knowledge, experience and resources. In some cases, pharmaceutical companies often don't have the specific experience in this highly regulated environment or the dedicated resources for these types of programmes, particularly when managing small quantities in a number of different markets. In addition, it is rare for there to be one stakeholder within a company who 'owns' this function.

Partnering with a strategic consultancy is crucial as they can implement these programmes for pharmaceutical companies. When selecting a company to work with, it is essential to verify that they have the expertise, experience, systems and policies in place that will provide absolute peace of mind that the programme is devised and managed effectively

and within local regulatory guidelines. Based on past experience, working with a global specialist consultancy such as Idis, which has more than 20 years' experience within this field, meant that the programmes were robustly implemented taking into consideration national regulatory nuances.

New horizon: embracing the need for managed access

As the pharmaceutical industry is rapidly changing, it is becoming more and more likely that drug developers will find themselves on the receiving end of requests for access to drugs in the pipeline. Publicity generated by the release of updated 'expanded access' regulations by the FDA in 2009 created greater awareness of these programmes. At the same time, the increased transparency of clinical research and accessibility of powerful social media tools have led to a more informed and vocal population of patients.

For companies with drugs in development that may generate early demand, managed access programmes offer a way to meet the needs of patients on a global basis in a regulated; ethical and transparent manner. Managed access programmes provide access for patients who otherwise would not be able to participate in company-sponsored clinical trials and allow sponsors to engage with physicians, providing early, hands-on experience to potentially life-saving medicines.

For patients with life-threatening illnesses, licence approval or commercial launch of an innovative new drug may come too late. In some cases, such as those involving the EU registration and approval process, a drug may not clear reimbursement hurdles in an individual country until well after centralised approval is granted. In geographies where a formal launch is not feasible, a patient may not have any other opportunity to receive the drug other than through such a programme.

In all of these scenarios, managed access programmes provide an effective route to innovative drugs prior to approval or launch, potentially providing patients who have run out of therapeutic options with an important lifeline. **DDW**

Dr Rav Seeruthun is a member of the faculty of pharmaceutical physicians and a General Practitioner. He is currently Head of Clinical Affairs at Napp Pharmaceuticals, and previously was Head of CNS and GI at Eisai Europe where he ran a number of named patient programmes. He trained at St Mary's Hospital Medical School at Imperial College and has a BSc (Hons) in Psychology from University College London.