Adaptive licensing, collaboration and convergence – fast-tracking BioPharma innovation to patients in Europe
Challenges

Balancing access to new drugs particularly in life-threatening circumstances with the need to ensure a positive benefit/risk data so as not to compromise patient safety is an ever-present dilemma. Since thalidomide, and as a result of methodological advances, medicines regulators have been progressively more explicit about the evidence requirements for product authorisation in an effort to ensure safety and demonstrate efficacy. Current regulatory systems are seen by some as a barrier to early patient access to new medicines: medicine regulation is seen as overly concerned with safety and failing to take account of the fact that many patients with serious life threatening conditions are less risk averse than regulators. Yet there is a conundrum as individual patients expect drugs to be ‘safe’ and look for recourse in the event of adverse events.

The current approach to regulation of medicines poses particular challenges in the era of ‘stratified medicines’ which involves looking at smaller groups of patients to try and find ways of predicting which treatments are particularly suitable for which subgroups of patients for example those with specific genetic markers. There are practical challenges in building the clinical evidence base necessary for approval under current regulatory mechanisms where patient populations are very small.

Additional challenges include the historic lack of a co-ordinated approach to evidence gathering by the regulatory and health technology assessment (HTA) bodies, prescribing practices, often dictated by concerns around safety, liability and insurance and eroding regulatory and intellectual property protection.
Fast-tracking drugs to patients – existing legal mechanisms

Medicines – with a few exceptions – require a marketing authorisation before they can be promoted for specific indications. However, there are existing legal mechanisms in Europe and internationally that speed-up access to both unlicensed and licensed medicines.

In Europe, there are a number of regulatory routes that aim to expedite the licensing process in specific circumstances; including conditional and exceptional circumstances market authorisations and accelerated assessment at the EU level, as well as national early access programmes for unlicensed medicines. These schemes are thought to be under utilised. It could be that drug companies are currently not taking advantage of the existing flexibilities in the system or possibly the emphasis on the seriousness and rarity of the disease under current approaches may be too restrictive and exclude drugs for some diseases; the interpretation of “seriously debilitating” and “need for immediate benefit” as specified in the legislation may differ amongst stakeholders (e.g. regulatory authority, patient and clinician); and, countries may take a different view on available treatment options. In addition to the regulatory aspects, companies have to also take account of intellectual property, regulatory data protection, liability and, pricing and reimbursement.

What’s changing?

In order to encourage and support innovation there have been a suite of recent initiatives to facilitate earlier patient access within the current legislative framework without compromising patient safety. The European Medicines Agency (EMA) recently announced a pilot scheme for its adaptive licensing pathway. Additionally, in the UK, the Medicines and Healthcare Products Regulatory Agency (MHRA) announced a new Early Access to Medicines Scheme (EAMS). There is also a legislative proposal in the UK to more clearly define clinicians’ liability for prescribing unlicensed medicines in order to encourage and support innovation.

Europe – EMA adaptive licensing pathways

Drugs companies have been invited to submit applications to participate in a new adaptive licensing (AL) pilot project being run by the EMA.

AL is a flexible pathway for the approval of innovative medicines to treat unmet medical need as defined in the current EU legislation. A staggered approach to market access is envisaged, in which after a multi-stakeholder planning phase in a ‘safe harbour’ a product is allowed earlier market access in a defined group of patients and under carefully controlled conditions; the licensing indications – and its price and reimbursement status – are progressively modified in the light of greater knowledge from wider use. Amidst an environment of continual testing and development, this new staggered approach allows an initially restricted number of patients to benefit from new treatments before being gradually expanded for use by more individuals as more information on the drug is generated particularly around safety.

“With the adaptive licensing pilot project we intend to explore with real medicines in development a progressive licensing approach that would allow timely access for patients to new medicines that address serious conditions with unmet medical needs…”

Hans-Georg Eichler, the EMA’s senior medical officer
It is anticipated that AL will build on existing regulatory processes and extend the use of elements that are already in place, including scientific advice, centralised compassionate use, the conditional marketing authorisation mechanism (for medicines addressing life-threatening conditions), patients’ registries and pharmacovigilance tools that allow collection of real-life data and development of risk management plans. A framework to guide discussions of individual pilot studies has been published and the EMA has advised that 20 companies have applied. The EMA has selected two medicines to be included in the pilot from the applications received so far. These will now be assessed for suitability by the EMA and successful companies will then be invited, with other stakeholders (e.g. payers and patients) to take part in an informal discussion without risk. The formal process will only commence after this stage. The EMA continues to accept applications from interested companies.

The European pharmacovigilance legislation provides an important legal basis to impose requirements for post-authorisation safety studies on pharmaceutical companies when needed and is the legal foundation of the new AL pathway. In addition, a new integrated Efficacy-to-Effectiveness (E2E) clinical trial model has been proposed in which an effectiveness trial would commence seamlessly upon completion of the efficacy trial. This new approach offers the opportunity to improve understanding of how a treatment will work in routine clinical practice. It is suggested that if the proposed E2E trials were to be embedded in the adaptive approach to drug licensing, sponsors may be able to secure market access for drugs that provide benefit for subgroups of patients but do not pass the usual evidentiary thresholds for approval. Interestingly, Cancer Research UK has recently announced a revolutionary adaptive approach to ‘clinical trials’ to advance lung cancer treatment – the ‘National Lung Cancer Matrix’ trial.

It is anticipated that drugs approved under AL will be funded through existing routes. However, any future adaptive licensing (AL) programme will not achieve its aim if companies are not willing to use the flexibilities in the current payment schemes, such as the Pharmaceutical Price Regulation Scheme (PPRS) in the UK discussed below, to ensure that the price reflects the uncertainty that arises as a result of the lower evidentiary standards required for the grant of a conditional license and until the outstanding clinical trial data required to resolve uncertainties has been generated. It is therefore vital that companies’ and HTA agencies agree a flexible approach to the pricing and reimbursement of such products. A possible solution may be managed entry agreements or risk sharing agreements under which a manufacturer and a payer or provider establishes specific conditions for reimbursement of a medicine. This may possibly be a useful stepping-stone towards the development of new pricing and reimbursement models. Risk sharing arrangements can enable faster patient access to drugs that might otherwise be held up in protracted reimbursement negotiations due to uncertainty about the benefits.

In the UK the 2014 PPRS stated that companies may request value based appraisal of their new medicines (with such requests not to be unreasonably refused) and also that the launch price proposed to the Department of Health should be set at a level that is close to their expected value as assessed by the National Institute of Health and Care Excellence (NICE). Through the PPRS negotiations, flexible pricing was introduced in 2009 and reaffirmed in the 2014 scheme. This allows a scheme member to apply for an increase or decrease to a product’s original list price in light of new evidence or a different indication being developed. It may be that this approach is the most logical solution to the evidence base changing through adaptive licensing, in that it may justify a higher price over time and for different indications.
UK – Early Access to Medicines Scheme
The UK Government also launched an Early Access to Medicines (EAMS) scheme on 7 April 2014 for medicines that are in the licensing process but have not yet received a license. The scientific aspects of the scheme will be managed by the MHRA who has published guidance on how the scheme will operate. The proposed scheme is unfunded and will coexist alongside the existing early access and early licensing European framework and is intended to support development and patient access in the UK to medicines being developed for life threatening or seriously debilitating conditions without adequate treatment options. Under the EAMS, drug companies will have the chance to follow a three-stage fast-track process for bringing their products to the market. They will be able to obtain a ‘Promising Innovative Medicine’ (PIM) designation from the MHRA to signify, during the development stage of a new drug, the potential of that product for treating patients with life threatening or seriously debilitating conditions for which there is either no cure or where existing treatments are unsatisfactory. The companies could also obtain a scientific opinion which would allow doctors to prescribe the drug whilst still unlicensed, provided the potential benefits outweigh the risks. In addition, the companies would also be able to be considered for a new licensing and rapid commissioning process being created by NICE and NHS England, ‘commissioning through evaluation’.

“We are streamlining the process so these medicines can be used much earlier – particularly if they have early promise – and that is something which will bring hope to a lot of patients.”
Jeremy Hunt UK Secretary of State for Health – when launching the UK’s Early Access to Medicines Scheme

[Image]
Conclusion

Although funding and commissioning of new innovative medicines is likely to remain a concern, there are opportunities for companies to help shape the new access pathways to patients in Europe.

Cross sector collaborations, convergence of technologies and adaptive approaches to clinical trials, licensing and reimbursement will help in getting new medicines to patients faster and in optimising patient outcomes.

Further consequences of adaptive licensing may well include a re-appreciation of development risk by potential investors and licensees in life sciences technology where they can see earlier marketing potential. In addition to an increased willingness to invest, accelerated licensing may well lead to changes in milestone and royalty structures and in the parties’ respective roles and responsibilities in development agreements and similar collaborations in terms of managing the development process.

A version of this paper will be published in the Pharmaceutical Licensing Group’s Business Development and Licensing Journal.
How can we help?

The life sciences and healthcare teams at Pinsent Masons operate out of hubs in London, Scotland the British Midlands, Paris, Munich, the Gulf and Asia Pacific. We have been actively involved in the sector for many years, working with our clients on a truly diverse range of transactions to demonstrate and develop the breadth of our sector knowledge and experience. Our TMT, IP, Data Protection, Insurance, Commercial, Competition and Corporate teams all have a wealth of experience within the sector and we regularly draw upon the complementary and specialist skills these teams offer.

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