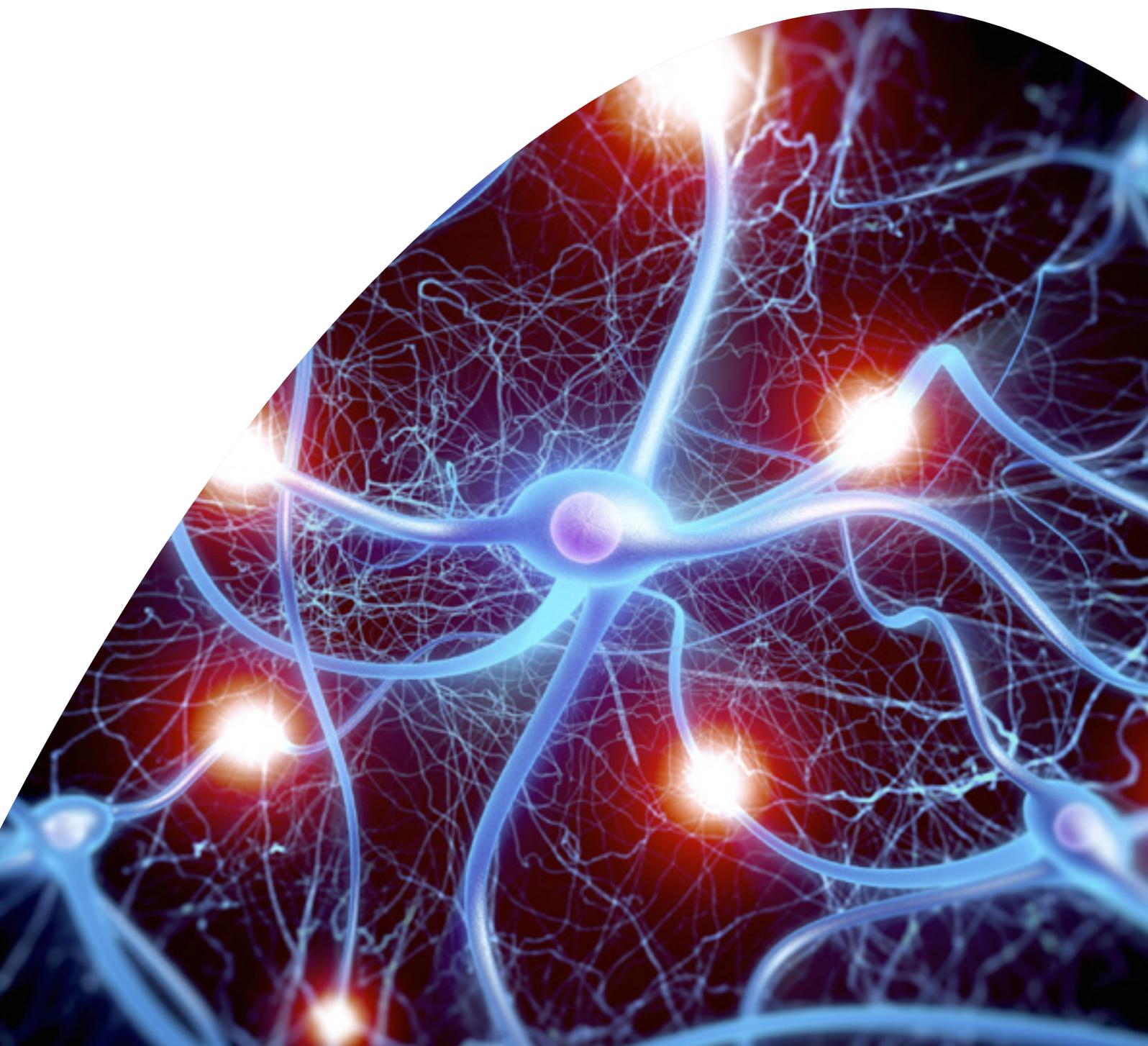




Pinsent Masons

Connectivity in the Life Sciences and Healthcare Sectors

Fast-tracking BioPharma innovation to patients in Europe



Overview

Sweeping changes to the world's healthcare systems are taking place as governments around the world recognise that healthcare costs have to be sustainable. In addition there is a growing call from healthcare professionals and patients with life threatening and debilitating diseases for earlier 'fast-track' access to new medicines. The convergence of technology, drug development and healthcare – using mobile communications infrastructures, digitalised patient information, cloud based systems, improving data analytics, and advances in diagnostic technologies – is making fast-track access to precision and more personalised medicines a real possibility.

There are existing legal mechanisms in Europe and internationally that permit earlier access to both unlicensed and licensed medicines. These earlier access routes include conditional and exceptional circumstances authorisations and accelerated assessment at the EU level, as well as national early access programmes for unlicensed medicines. These schemes however, are seen as failing some patients: the emphasises on the seriousness and rareness 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" may differ amongst stakeholders (e.g. regulatory authority, payer/commissioner, patient and clinician); and, countries may take a different view on available treatment options.

In addition, there are concerns and uncertainties around intellectual property, regulatory data protection, liability and pricing and reimbursement which are currently dissociated from the licensing decision.

Connectivity and a move away from what used to be stand-alone business approaches and interests, including open source approaches to drug discovery, collaborative projects to generate real time data early in the development process and advancements in data analytics are facilitating the development of a more streamlined and flexible regulatory process that will allow patients

access to innovative drugs, and at an earlier stage along the drug development pathway.

In response to these developments and to address some of these concerns, the European Medicines Agency (EMA) recently announced a pilot scheme for its adaptive licensing pathway and the UK has announced a new Early Access to Medicines Scheme (EAMS). There is also a proposal to more clearly define clinicians' liability for prescribing unlicensed medicines.

In this paper we discuss why there is a need for change as well as some of the drivers facilitating the change in approach to regulation. We review the existing legal and regulatory framework for earlier access and the recent changes using Europe as an example and consider the advantages, opportunities and challenges for companies developing early market access solutions as part of their drug development programmes and highlight some important unresolved issues which may influence strategic decisions.

"Breaking an old business model is always going to require leaders to follow their instinct. There will always be persuasive reasons not to take a risk. But if you only do what worked in the past, you will wake up one day and find that you've been passed by"

Clayton Christensen

Introduction

The full development process for an innovative medicinal product can take up to 12 to 15 years and a typical financial investment of over £1 billion¹. Companies can make these large investments only when they have enough certainty about topics like regulatory predictability, market size and market access.

With increasing requests from healthcare professionals and patients globally for access to new innovative drugs that are still in clinical development or awaiting approval, pharmaceutical and biotechnology stakeholders may not be prepared just to sit back and wait until launch. Sweeping changes to the world's healthcare systems are taking place as governments around the world recognise that healthcare costs have to be sustainable. This is playing out in several ways, from legislative efforts to reform healthcare in many major markets including moves to more outcomes-based pricing agreements. Consequently, responsible and sustainable early market access solutions are increasingly required to give a drug the right start.

Connectivity heralds a new era of technological and business convergence involving, amongst others, medicine manufacturers, research organisations, payers, clinicians, patients, data analytics organisations, mobile network operators and insurance providers. The business interests and activities of these differing parties are converging and overlapping in an increasingly connected world with the patient at centre stage. Earlier access has two dimensions: firstly the timing of any regulatory approval, and secondly identifying the proportion of patients who might appropriately benefit from access to a new medicine.

¹ Paul S et al. How to improve R&D productivity: the pharmaceutical industry's grand challenge. Nature Reviews Drug Discovery. 9 March 2013; 12(3): 203-214 (2013). <http://www.nature.com/nrd/journal/v9/n3/pdf/nrd3078.pdf>



Benefits and commercial opportunities of early access schemes

Earlier access programmes both licensed and unlicensed provide clear benefits for the three key main stakeholders – patients, clinicians and innovative drug companies:

- For patients, these programmes can sometimes mean the difference between life and death and earlier access can offer them a new treatment option when all other existing therapies have failed.
- For clinicians, these programmes provide them with an opportunity to give their seriously ill patients new innovative treatments when all existing treatments have failed. They can also gain experience with a new treatment and better understand its potential before it becomes more widely available.
- For companies, earlier access schemes allow them to give access to new treatments before the completion of the full clinical trials programme necessary for a marketing authorisation. Data collected from these schemes can assist in better profiling the product, facilitate fast-track approval and a Health Technology Assessment (HTA).

Evaluation of the opportunities and risks of earlier market access

There are numerous legal, regulatory and logistical challenges (some discussed below) across different countries which need to be considered when developing early access management solutions and specialist expertise and advice is needed to minimise the risks and maximise the commercial opportunities.

The possible regulatory solutions should not be considered in a vacuum. The strategic considerations influencing early market access will vary between drugs and should be looked at on a case-by-case basis and may well vary between disease areas. For example, diseases with genetic properties may have country specific issues with better responders in one population than another and the risk profile will vary from, for example, new drugs to extensions of already approved drugs.

What to do?

- **Plan early:** this will allow time for early consultation with regulatory and HTA authorities and development of information for physicians, patients and pharmacists regarding risks (both known and unknown), dosing, administration and restrictions. More importantly, the clinical criteria for patient participation have to be established sensibly and ethically (also to ensure that enrolment in any ongoing clinical trials is not compromised). This is very much product specific
- **Connect with regulatory and HTA bodies early in the process:** there is a growing promotion of early dialogue and engagement by regulators to assist companies to meet regulators' needs. Opportunities for engagement between companies and agencies include: early scientific advice – EMA/ Medicines and Health Care Products Regulatory Authority (MHRA); early scientific advice – HTA (e.g. NICE); and parallel scientific advice. It is hoped that enabling all stakeholders to consult on the benefits and value of a drug early in development could dramatically improve the drug development process
- **Ensure that there are appropriate resources in place to deliver on commitments around data capture and ongoing clinical trials:** failure to deliver on commitments could have regulatory and reputational consequences
- **Assess what strategic alliances and models of collaboration will facilitate earlier market access for patients**
- **Consider if a patient partnership agreement is appropriate:** this could be a possible means of managing liability risks
- **Consider your IP and regulatory priorities as part of the overall strategy:** carefully consider the impact of early approval or licensing on patent and data and market exclusivities
- **Consider the impact of the possible extra scrutiny by the regulatory authorities:** EU mandatory risk management plans are likely to assume greater significance in the move to earlier access
- **Consider the likely attitudes of HTA's and payers.**

Earlier access – drivers for change

The business climate for pharma companies has changed dramatically in recent years. Patent expiries, declining research and development productivity, pipelines of more high-risk molecules with smaller potential markets and squeezed margins caused by government imposed price cuts and changing incentives are pushing companies to adopt more sustainable business models. Mergers to build scale will not improve returns on their own. Pharmaceutical companies need new business models to restore healthy financial results.

Unsustainable business models and a changing concept of value

Market pressures, in particular a new concept of value are pushing drug companies to reassess their drug development models. There may be commercial advantages for companies who can offer healthcare solutions along the whole disease management pathway and provide novel approaches to healthcare delivery. “Beyond the pill” strategies can encompass several disease management solutions such as disease and therapy awareness, diagnosis, improving access to medications, adherence improvement strategies, self help strategies and general patient support. Measuring patient outcomes is already playing a more central role in reimbursement decisions and an access scheme based on real life patient outcomes could perhaps play a role in getting innovative drugs to patients earlier.

Developing regulatory framework

The speed of decision-making (both regulatory and funding) affects how quickly patients can access products. Balancing early market access to new drugs with the need for benefit/risk data is a mounting dilemma. Since thalidomide, medicines regulators have been progressively increasing the requirements for product authorisation in an effort to promote safety and 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 does not take account of the fact that many patients with serious life threatening conditions are less risk averse than regulators.

Patient pressure

The public, patients and their carers are driving demand for earlier access to innovative drugs. In response to patient and public pressure, significant steps, primarily in response to the HIV/AIDS crisis in the 80's and early 90's, were made towards making experimental drugs intended to treat life-threatening diseases more widely available to severely ill patients, as well as towards speeding up the review and approval of the applications for these products. This pressure continues today. In the UK Empower² campaigns to put patients at the heart of medical innovation and encourages the UK government to lead on the development of more adaptive pathways for clinical research and medical innovation.

Advances in science and technology

Advances in a wide range of fields from genomics to medical imaging to regenerative medicine, along with increased computational power and the advent of mobile and wireless capability are allowing patients to be treated and monitored more precisely and effectively and in ways that better meet their individual needs. 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 particular illnesses (e.g. cancers) are likely to respond to. There are practical challenges in building the clinical evidence base necessary for approval under current regulatory mechanisms where patient populations are very small. The current regulatory and HTA processes and policies need to evolve in response to, and in anticipation of, scientific developments that will be critical for the development of a stratified and more personalised approach to precision medicines.

An open source approach to drug discovery

The concept of open source drug discovery (the 'Open Innovation' paradigm³) borrows two principle aspects from open source computing (i.e., collaboration and open access) and applies them to pharmaceutical innovation. There already exist a number of open source pre-competition ventures: the Innovative Medicines Initiative⁴ (IMI) in Europe; Open Source Drug Discovery (OSDD) in India⁵; and the Centre for Therapeutic Target Validation and the Structural Genomics Consortium⁶, both in the UK. Open source drug discovery offers opportunities to speed up the development of better and safer medicines for patients and to 'smart lead' optimisation strategies⁷.

² <http://www.accesstomedicine.co.uk/>

³ Chesbrough, Henry William (1 March 2003). Open Innovation: The new imperative for creating and profiting from technology. Boston: Harvard Business School Press. ISBN 978-1578518371

⁴ <http://www.imi.europa.eu/>

⁵ <http://www.osdd.net/>

⁶ <http://www.thescg.org/>

⁷ Recent trends in collaborative open source drug discovery – <http://benthamsience.com/open/toprocj/articles/V002/I30TOPROCJ.pdf>



Transparency policies

Patient data can provide great insight for health research and improve the quality of diagnosis, treatments and other interventions. Developing global transparency policies is intended to facilitate wider access to clinical data making data mining possible. The starting point of the proposed EMA policy⁸, due to be adopted in June 2014, is to make data available unless there are good, quantifiable, and real reasons not too. It is recognised that there is a need to balance the benefits of openness with legal and commercial requirements to protect patient and commercial confidentiality and safety and the EMA continues to consult with stakeholders. In the UK, Patients4Data is a campaign about the power of patient data to save lives.

Data mining

Data mining offers the potential to transform drug development from an opportunistic approach to a scientifically robust and logical process of finding new and useful precision treatments in well defined and selected populations. It has the potential to reduce uncertainty, facilitate more targeted drug discovery and make personalised medicines and earlier access to medicines a reality.

New collaboration models and partnerships

Life sciences and healthcare companies are increasingly entering alliances with companies from other sectors such as TMT. The integration of medicine, science, technology, engineering and data analytics has the potential to develop and deploy new cross-functional multi-disciplinary wireless and connected health solutions to reduce inefficiencies, improve outcomes and reduce the cost of care.

⁸ http://www.ema.europa.eu/ema/index.jsp?curl=pages/special_topics/general/general_content_000555.jsp

The legal and regulatory hurdles

Prescribing practices

Clinicians have a pivotal role in access for patients. The final decision to prescribe a medicine rests with the clinician. The decision is often the result of a number of factors – cost may be part of the consideration.

Clinicians may also need to act as advocates for patients to obtain access and funding for a treatment including perhaps supporting an individual funding request or access under a compassionate use programme (CUP). Clinicians also have a role in access through recruiting patients for clinical trials.

Clinicians may be reluctant to depart from the existing best practice in treatment of a disease due to the risk of being sued for negligence. Under the existing law in the UK a healthcare professional takes full responsibility for prescribing an unlicensed medicine. The General Medical Council published its latest guidance on prescribing, including prescribing unlicensed medicines, in 2013⁹. The UK government is currently considering proposed new legislation, the Medical Innovation Bill (commonly referred to as the Saatchi Bill) that would allow doctors to “depart from the existing range of accepted medical treatments for a condition” without having to fear that their actions could be deemed negligent, as long as their decision to do so is a responsible one as defined in the legislation. The purpose of the Bill is to clarify what is negligent and dangerous practice by clinicians and what is careful and responsible innovation. The Bill will effectively introduce a statutory defence of innovation to medical negligence claims.

The current lack of a co-ordinated approach to evidence gathering

Evidence gathering during drug development is geared primarily towards getting regulatory approval. However, much the same evidence, with additional components (economic modelling), is considered by HTA and commissioning bodies. There is an increasing need for biotech and pharmaceutical companies to provide HTA, agencies and other healthcare decision makers with additional information on the health outcomes delivered by a medicine in the real world to establish the potential benefits and true value of a medicine. A shared interest in the evidence base between regulators and payers has led to a range of work to explore how each can meet their own responsibilities with mutual benefits to both. The Salford Lung Study is an example of an ongoing real world study in the UK to access the benefits of a drug before it has been licensed.

Case study – Salford lung project

The Salford Lung Study* is an example of new real world study and is the first attempt to carry out a pragmatic randomised clinical trial prior to registration of a new treatment. It represents a unique collaboration between the biotech and pharmaceutical industry, academia, medical informatics and healthcare providers. Importantly, joint scientific advice was requested and obtained from the MHRA and NICE before the project commenced. It is utilising a linked database system including Salford’s e-Health records infrastructure – a clinical information system providing a single, integrated electronic patient record across both primary and secondary care – and real-time and other integrated data collected from a variety of sources. The electronic health records facilitate concurrent safety monitoring and data collection without direct patient contact for large randomised study populations. The study is exploring the real world benefits of a GlaxoSmithKline late stage investigational respiratory medicine (novel once-daily investigational treatment vilanterol/fluticasone furoate in a new dry-powder inhaler (DPI), Ellipta) before it has been licensed alongside currently available treatments, as thousands of patients manage their chronic obstructive pulmonary disease (COPD) and asthma day to day. Evidence generated from the study will complement GSK’s clinical trial programme assessing the medicine’s safety, efficacy and quality.

* <http://thorax.bmj.com/content/early/2014/03/06/thoraxjnl-2014-205259.full>

Safety, liability and insurance concerns

There is something of a paradox between patient pressures for safe medicines on the one hand and the demand for access to promising drugs that are still in development on the other¹⁰. Earlier access schemes and the move to a more stratified approach to medicines development raise a number of potentially interesting issues under the current legal framework on liability for medicinal products particularly around knowledge of risk and the concept of consent. Safety is an issue with fast-track access and the granting of earlier access and approvals on the basis of limited data sets is arguably more uncertain and risky.

However, one study, carried out to investigate whether procedures of earlier approval in Europe compromise the safety of new drugs, found that despite the fact that these approval mechanisms are based on limited clinical datasets, no special safety issues were found to be associated with using these pathways¹¹. In addition, with the increased use of genomic data and particularly biomarkers to identify good responders early in the process it could be argued that in some circumstances the risks and uncertainties are no greater.

In establishing liability under defect based product liability law and under negligence principles much depends on the extent to which it can be shown that the patient was willing to accept a greater

⁹ http://www.gmc-uk.org/guidance/ethical_guidance/14316.asp

¹⁰ [Adaptive Licensing: Taking the Next Step in the Evolution of Drug Approval](#) H-G Eichler K Oye et al, *Clinical Pharmacology & Therapeutics* (2012); 91 3, 426–437. doi:10.1038/clpt.2011.345.

¹¹ *Clin Pharmacol Ther.* 2010 Dec;88(6):848-53. doi: 10.1038/clpt.2010.207. Epub 2010 Oct 20.

risk, including the risk of the unknown. Therefore as more drugs are released to patients earlier in the development process careful consideration will need to be given to the mode and content of the communication of risk and benefit and the ability of the patient to understand any warnings.

There has been some discussion about prohibiting product liability suits in some adaptive earlier licensing scenarios but it is difficult to see how this could be achieved without new legislation and with provision for some alternative remedy for individuals affected such as an adequate compensation scheme. A recent paper¹² has also explored some possible alternatives to fault based or defect based legal liability as a source of compensation after treatment with medicinal products.

One possible additional challenge for companies is that clinicians, no doubt with good intentions, may withhold information such as data on other drugs their patient is taking to get a patient earlier access. This could mean that this patient is a poor responder, or worse, suffers side effects that are not related to the drug itself but due to an interaction with the other drug. As well as the reputational risks there may also be regulatory risks – such data may negatively impact a future licensing decision and HTA. The move to wider patient e-health records may reduce this risk.

Eroding regulatory data protection

Under EU legislation newly authorised medicinal products may benefit from an eight-year period of data protection and a 10-year period of marketing protection. The period of data and market exclusivity commences from the date of the granting of the marketing authorisation. The market exclusivity periods may be extended in certain limited circumstances. There is no specific guidance as far as we are aware on when the period of data and market exclusivity starts for authorisations granted under EU procedures for earlier approval but it is arguable that it commences on the grant of the earlier conditional approval and not on full approval. Earlier approvals, such as conditional authorisations, commonly focus on a narrowly defined indication with few patients. For commercial viability research generally continues into broader and less urgent indications. During that period of further research the regulatory data protection period is gradually being eroded.

SPC term calculation

As interpreted by recent case law, a conditional marketing authorisation is considered to start the timer for SPC protection¹³. The date of the conditional marketing authorisation is the point from which the possible five year supplementary extension to the patent term is to be calculated. As the decision stands, it can have commercial implications, which should be part of any decision to pursue the conditional or other licensed early access route. The full commercial value of a product subject to an earlier

conditional marketing authorisation may only be realised when the additional clinical tests required are complete and the licensed use is extended to a broader population perhaps.

Data privacy and data security

Electronic data provides a significant opportunity for health research and the potential to significantly improve medicines development and the understanding of how medicines are used by patients to facilitate early access (see the discussion of the Salford Lung projects use of e-Health records) but there are challenges not least patient concerns about privacy and commercialisation of their data. Recently, in the UK it was concluded that GP records should be linked to hospital databases to better understand responses to treatments. NHS England therefore commissioned the 'care.data' programme to address these gaps promising more rounded information available to citizens, patients, clinicians, researchers and the people that plan health and care services. However, in February this year a combination of possibly inadequate communication of the benefits and widely held confidentiality concerns caused a six-month delay in the rollout of this programme. NHS England says that it intends to allay such concerns by installing confidentiality safeguards (including a code of practice as required under the 2012 Health and Social Care Act), offering support for GPs specifically around how patients can opt out and explaining the benefits more effectively.

Pricing, reimbursement, uptake and diffusion

Early access is not simply a matter of licensing but is also an issue of pricing and reimbursement, uptake and diffusion. A critical factor in any early licensing programme will be the response and attitude of payers to a product that has gone this route.

In March 2010 there was a proposal in the UK for joint scientific advice from the MHRA and NICE. Only one joint advice has taken place to date.

The different approaches of HTA agencies across Europe can be challenging. Recovery of costs under compassionate use programs (CUPs) needs to be considered on a product-by-product basis. Member states in Europe have different policies so it is difficult to generalise, for example in Spain it is possible to get a fully funded CUP while in the UK and Ireland most CUPs are funded at cost. Often the same evidence can secure a yes from one HTA and a no from another or a more restrictive recommendation.

Any future adaptive licensing (AL) programme will be valueless if payment schemes are not conceived in which perhaps the lower evidentiary standards required for AL are reflected in the price whilst the uncertainties are resolved. It is therefore vital that companies' regulatory and HTA agencies agree a flexible approach to the pricing and reimbursement of such products.

¹² Adaptive licensing and the law: a new model for compensation? Jeremy Stuart Smith (unpublished).

¹³ C-617/12 Astra Zeneca Iressa.

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.

The 2014 pharmaceutical price regulation scheme (PPRS) stated that companies may request value based appraisal of their new medicines (with such requests not 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 NICE¹⁴. 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.

In the UK a number of disconnections exist between a positive HTA and funding for a product, which can result in a positive recommendation at a national level but limited or variable access at the local level and there is a recognised need throughout the NHS to improve implementation of NICE guidance and guidelines.

The 2011 review 'Innovation Health and Wealth' introduced a NICE Compliance Regime to improve uptake and ensure funding and resources for medicines and treatments recommended by NICE through its HTA work programme.

The recent *Rose* case¹⁵ as it stands seems to impose obligations on commissioning bodies to comply with NICE guidance (even where it is not a legal obligation) unless there are exceptional circumstances. Patient and carer pressure is becoming effective in creating a demand for better adoption and diffusion of innovation in the NHS but there is still room for improvement. The innovation pipeline project (ABHI, ABPI and NHS Confederation) aims to increase adoption and diffusion of proven technologies in areas of high clinical need to deliver quality patient outcomes and efficiencies working with NHS England¹⁶.

Specialist funds do exist in the UK to fund medicines – for example the cancer fund. The cancer fund pays for cancer products that have not been recommended by NICE or have yet to be given NICE guidance. Patient groups are calling for ring-fenced funds to be available in other disease areas but this seems unlikely. In the UK

it is also possible to make an individual funding request (IFR) to either the local clinical commissioning group, or directly through NHS England. This may result in a decision on funding to provide access under exceptional circumstances, either locally, or if there are several IFRs, then a national commissioning policy may be developed by NHS England, to be applied consistently in certain circumstances. However, the ability to demonstrate exceptionality is difficult as it is the disease that is exceptional not an individual patient within a small group of patients (see the *Rose* case).

Challenging unfavourable decisions

Decisions of public bodies such as regulators may in certain limited circumstances be challenged. NHS England is responsible for commissioning prescribed specialised services across England and variations in access are sometimes justified as different areas have different health needs. However, under the NHS Constitution a patient has a legal right to 'drugs and treatments that have been recommended by NICE for use in the NHS, if a doctor says they are clinically appropriate for them'. Additionally, patients have the right to expect local decisions on funding of other drugs and treatments to be made rationally following a proper consideration of the evidence. This was recently tested in the *Rose* case where Rose's arguments in support of a judicial review of the clinical commissioning group's (CCG) decision refusing funding for her treatment were dismissed. However in this case the Judge did find the CCG policy to refuse funding where there was positive (although not obligatory) guidance from NICE was illegal and in breach of its obligation in public law to consider the guidance and follow it unless there were exceptional circumstances which justified departure – mere disagreement with the policy was not sufficient. Whilst it is sometimes seen as difficult to bring a challenge based on the common law judicial review ground of irrationality there is a potential for legal argument based on the right to life in Article 2 of the European Convention of Human Rights which imposes a duty on the State to take reasonable measures to protect life.

¹⁴ https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/282523/Pharmaceutical_Price_Regulation.pdf

¹⁵ R (Elisabeth Rose) v NHS Thanet Clinical Commissioning Group <http://www.bailii.org/ew/cases/EWHC/Admin/2014/1182.html>

¹⁶ <http://www.england.nhs.uk/wp-content/uploads/2014/02/adopt-diff.pdf>





Existing framework for pre authorisation access to medicines

Medicines – with a few exceptions – require a marketing authorisation before they are placed on the market. However, the requirement for a licence creates an ethical dilemma in specific cases where a product under development has been shown to have a positive effect but has not yet obtained a marketing authorisation.

Clinical trials

European legislation¹⁷ distinguishes between early access and clinical trials. Clinical trials are performed to allow data on the safety and efficacy of the relevant medicinal product to be collected as part of the regulatory assessment of a new drug. Commonly participation in clinical trials would be as a patient in a Phase II or III study. However, some Phase I studies involve enrolling patients with a serious or terminal disease without treatment options (principally cancer). This is valuable information; however the data do not typically demonstrate how medicines perform in a normal clinical setting. This can make it difficult for decision makers to determine accurately a medicine's possible value and this may subsequently restrict patient access. Clinical use outside the restrictive environment of trials may be the only way to achieve a full understanding of the safety and efficiency profile of a new drug.

The participants in clinical trials (especially Phase I studies) are protected through the regulatory requirements needed for any clinical trial (e.g., ethical review, informed consent, insurance). In addition, trial participants who benefit from a new drug as part of a clinical trial programme are required to have access to that drug after the trial has finished¹⁸.

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 – which recognises that every patient's cancer is unique and adopts a more personalised approach, targeting particular genetic abnormalities in each patient's tumour¹⁹.

¹⁷ Regulation 726/2004/EC.

¹⁸ Declaration of Helsinki.

¹⁹ <http://www.cancerresearchuk.org/about-us/cancer-news/press-release/revolutionary-clinical-trial-aims-to-advance-lung-cancer-treatment-thanks-to-cancer-research-uk-and>

Compassionate use programmes (CUPs)

Some patients with critical or life-threatening illnesses do not qualify for clinical trials – perhaps they are too sick or another ongoing or previous medical treatment disqualifies them from the study. If no alternative treatments exist, patients might be deprived of potentially life-prolonging medication. Regulatory bodies worldwide have created mechanisms for granting such patients access to medicines not currently licensed in their country. These mechanisms fall under the titles of Named Patient Programmes (NPPs) outside the US and Expanded Access Programmes (EAPs) in the US. They are also often referred to as early access, managed access, named patient supply, and compassionate use programme. For simplicity, we will use the term compassionate use programme (CUP) in this paper. These regulatory programmes are put in place on a country-by-country basis and can vary significantly across markets.

Under the current European legislation²⁰, compassionate use is only permissible if clinical investigators are actively studying the new treatment in well-controlled studies, or all studies have been recently completed or closed to recruitment²¹. There must be evidence that the drug is likely to be effective in the patient(s) to be treated and the drug must not expose patients to unreasonable risks.

The European legislation provides a CUP framework for products eligible for centralised marketing authorisation²², and at the same time serves as a point of reference for national legislation on products headed for national authorisation. However, national authorities might take divergent views on CUPs, not least on the unavailability of treatment options. In such a case, the Committee for Medicinal Products for Human Use (CHMP) might have to resolve the issue by delivering an opinion²³.

CUPs²⁴ can be divided into the following two major types:

- **Cohort compassionate use programmes (Coh-CUPs)**²⁵: the clinician or the company requests a CUP authorisation for a group of patients or a hospital site. The approval is then granted for a defined group of patients, for a limited time
- **Named patient compassionate use programmes (NP-CUPs)**²⁶: the clinician requests a CUP authorisation for a single identified patient. The approval is then granted for this single patient for a limited time.

Cohort compassionate use programmes

The EU legislation²⁷ sets a broad framework for CUPs but implementation remains the competence of a member state.

Accordingly, although the CHMP may give an opinion on use, the conditions of distribution and the patients targeted, this option is complementary to national laws and the CUP approval remains national. However, member states are required to notify the EMA of any permitted compassionate use. The legislation is silent on whether or not the patient may be charged for the product.

Named patient compassionate use programmes

Under EU legislation member states may provide an exemption, from the need for a licence, for medicinal products supplied at the request of a clinician for a named patient under his direct care. In the case of these named patient CUPs, the clinician responsible for the treatment will contact the manufacturer directly. While manufacturers do record what they supply, there is no central register of the group of patients that are being treated in this way²⁸.

National variants of compassionate use programmes

Given the flexibility permitted at EU level it may be useful to consider some national variants of CUPs. EURORDIS (Rare Diseases Europe) has a very useful resource describing the main characteristics of CUPs in different EU member states – the type of CUP, procedure and review times for seven member states²⁹.

Off-label use and the hospital exemption

For completeness it is worth mentioning off label use and the hospital exemption for certain advanced therapy medicinal products (ATMP).

Off-label use: A clinician may prescribe for an 'off-label' use a licensed medicinal product for an indication, or to a patient for which the product is not specifically licensed. This should be distinguished from a CUP where the medicinal product is not licensed as a treatment for any disease or that indication at the time it is prescribed.

Hospital exemption for certain ATMP: The Advanced Therapy Regulation³⁰ includes a hospital exemption (HE)³¹ as a way to offer individual patients a treatment with a customised, innovative and safe product, particularly when a disease occurs so rarely that the regular development and validation of the required therapy is not feasible. The HE provides for the implementation of national procedures and control measures to regulate the manufacturing and use of certain restrictively defined non-routinely produced ATMPs outside the scope of the AT regulation³².

²⁰ http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000293.jsp

²¹ Article 83 (1) of Regulation (EC) No 726/2004.

²² Article 83 (1) of Regulation (EC) No 726/2004.

²³ http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000293.jsp

²⁴ EMA guidance on compassionate use.

²⁵ Article 83 of Regulation (EC) No 726/2004.

²⁶ Article 5 of Directive 2001/83/EC.

²⁷ Recital 33 of Regulation (EC) No 726/2004; Article 83(1)/(2) of 726/2004.

²⁸ As stated in Directive 2001/83/EC.

²⁹ <http://www.eurordis.org/content/main-characteristics-cups-different-eu-member-states>

³⁰ European Regulation 1394/2007.

³¹ Article 28 of the European Regulation 1394/2007.

³² ATMP Regulation, pre-amble 6).



Existing framework for early authorisation access to medicines

Several fast-track licensing schemes exist in the EU³³ to support patient access to innovative breakthrough therapies as quickly as possible. These include the EMA conditional authorisation (CA) and authorisation under exceptional circumstances (EC) and accelerated assessment of products. In Europe, CA and EC procedures do not shorten the approval procedure itself but reduce the time it takes for a medicinal product to reach the market – a way of fast-tracking a medicine to patients. The treatments being considered under either of the CA or EC schemes may also qualify for the accelerated procedure³⁴.

Conditional approvals

CA was introduced in Europe under the centralised procedure by Regulation (EC) 726/2004³⁵ and is underpinned by a guideline that sets out the criteria for demonstrating a positive risk/benefit balance³⁶. The categories of products eligible for a CA are restrictively defined³⁷. Where a drug in development promises significant health benefits, but full safety or efficacy testing has not been completed and it is considered desirable to meet unmet medical needs³⁸ and in the interest of public health, it is possible to obtain a marketing authorisation – a CA – with this less complete data.

³³ Regulation (EC) 726/2004 of the European Parliament and of the Council of 31 March 2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency.

³⁴ Regulation (EC) 726/2004 of the European Parliament and of the Council of 31 March 2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency.

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³⁶ Regulation (EC) 726/2004 of the European Parliament and of the Council of 31 March 2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency.

³⁷ Products falling under Article 2 of Regulation 507/2006.

³⁸ 'Unmet medical need' is defined as a condition for which there exists no satisfactory method of diagnosis, prevention or treatment authorised in the EU. Even if such a method exists, then the medicinal product concerned will be of major therapeutic advantage to those affected.

Approval under exceptional circumstances

Authorisations under exceptional circumstances (EC)³⁹ are granted where an applicant can demonstrate it is not possible (for example due to patient population size) to provide comprehensive data on the efficacy and safety of the medicines under normal conditions of use. The EC authorisation may be granted subject to certain specific obligations such as an identified programme of studies within a time period specified by the competent authority, the results of which will form the basis of a reassessment of the benefit/risk profile and appropriate warnings in the package leaflet. The fulfilment of any specific procedures/obligations imposed as part of the EC marketing authorisation is aimed at the provision of information on the safe and effective use of the product and will normally not be sufficient to provide comprehensive data on the efficacy and safety under normal conditions of use – a full dossier required to get a 'full approval'. In the rare cases where the applicant is able to complete a full dossier and no specific procedures/obligations remain, a "normal" marketing authorisation could be granted. A guideline on the granting of an EC authorisation is available⁴⁰.

Accelerated approval

An applicant for a marketing authorisation, may request an accelerated assessment procedure, for a medicine that is of major interest from the point of view of public health and in particular from the view point of therapeutic innovation⁴¹. The procedure is set out in a guideline⁴². There is no single definition of what constitutes major public health interest. This needs to be justified by applicants on a case-by-case basis. Arguments to support the claim could include evidence that the medicinal product introduces new methods of therapy or improves on existing methods.

Some limitations of the existing earlier access schemes

Pre-authorisation

- **Patchwork of national regulations:** A company, who sets up a CUP in Europe, has to comply with a patchwork of national regulations.
- **Lack of information on CUPs:** One major shortcoming of the European legislation on CUPs, is the lack of specific provisions governing the information on CUPs that may be made available to patients.
- **Lack of a coordinated approach to sharing data:** Currently under most CUPs there is no obligation to set up registries for data collection (although there is under the new UK Early Access to Medicines Scheme (EAMS)). Facilitating more coordinated collection and sharing of the information and data developed as a result of these CUPs could provide information that could support decision-making in each individual country.
- **Responsibility and liability for CUPs:** In the UK at least, under the existing law, a healthcare professional takes full responsibility for prescribing a medicine under a CUP to his patient.

Early authorisation

- **Emphasis on seriousness and rareness of disease could be limiting access:** Drugs for some diseases; non-serious chronic conditions, or serious but slowly progressing conditions, may not qualify for a CA, EC or accelerated approval even where available therapy is considered by many stakeholders to be inadequate. In addition the interpretation of "seriously debilitating" and "need for immediate benefit" may differ amongst stakeholders (e.g. regulatory authority, payer/commissioner, patient and clinician).
- **Underutilisation of CAs:** This may be due to low awareness of the availability of this regulatory route in the EU, concerns about patient willingness to participate in ongoing clinical trials and broader commercial concerns around patent and data exclusivity.

³⁹ Article 14(8) of Regulation (EC) 726/2004.

⁴⁰ http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2009/10/WC500004883.pdf

⁴¹ Article 14(9) of Regulation (EC) No 726/2004.

⁴² http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2009/10/WC500004136.pdf



What's changing?

UK – Early Access to Medicines Scheme (EAMS)

The UK Government launched an Early Access to Medicines scheme on 7 April. The scientific aspects of the scheme will be managed by the MHRA who has published guidance on how the scheme will operate⁴³. The scheme will coexist alongside the existing early access

When launching the EAMS scheme the UK government said

"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."

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. The scheme is unfunded.

There will be three stages to the scheme:

- **'Promising Innovative Medicine' Designation**

This is thought to be modelled on the Food and Drug Administration's (FDA) 'Breakthrough Designation' in the US. This status is intended as a clear indication that a product may be a possible candidate for the EAMS based on, for example, early clinical data from Phase II studies. The designation will be issued after a MHRA designation scientific meeting but the MHRA will not be responsible for publishing details of the particular drug awarded the PIM designation. Products eligible for designation include not only new chemical entities (NCEs), but also the re-purposing of established medicines provided that they target life threatening or seriously debilitating conditions with no satisfactory treatment options.

- **An 'Early Access to Medicines' scientific opinion**

This will be issued by the MHRA and is designed to support the prescriber in making a decision with a patient on using the medicine when it is still unlicensed or used off-label. The MHRA will issue an opinion on the quality, safety and efficacy of the data provided in support of the application if sufficiently compelling, with a positive benefit: risk balance. The MHRA and NICE will also make available joint parallel scientific advice meetings for clinical development programmes. The trigger for a scientific opinion does not necessarily have to be the submission of a dossier for a marketing authorisation application, but can be the availability of a sufficiently compelling case based on the total data and evidence collected to date. Information will be published on the MHRA website and prescribers may also be informed through stakeholder engagement. It is anticipated that opinions will be reviewed on a yearly basis. The scheme is unfunded

⁴³ <http://www.mhra.gov.uk/NewsCentre/Pressreleases/CON404193>

so it is expected that companies will receive no payment for patients having access to medicines under this scheme. As the scheme is unfunded many companies may prefer to continue to use NP-CUPs which in general are refunded at cost. One advantage to using this scheme over NP-CUP is data gathering, although this can be achieved under a CUP if processes are put in place.

• **Licensing and rapid commissioning**

The EAMS scheme can be distinguished from existing CUP schemes as it is intended to facilitate licensing by the EMA and rapid commissioning by the NICE. Once licensed (possibly a CA under the adaptive licensing pathway discussed below) medicines developed through the EAMS will be appraised by NICE for routine use on the basis of the evidence collected in the earlier stages of the scheme. The scheme anticipates that medicines under the EAMS will get a fast-track NICE appraisal but currently there is no procedure for this, and under the current system NICE cannot issue guidance on unlicensed medicines unless directed by the Secretary of State. In addition medicines in the scheme, once licensed, will be commissioned by NHS England. However, currently there is no allocated fund to pay for these medicines.

UK's Early Access to Medicines Scheme (EAMS)

Some unresolved issues:

- Will there be a requirement to file an MA within a particular time frame as there is with CUPs?
- Will NICE initially give a preliminary opinion on an EAMS to encourage uptake?
- How will the fast-track NICE assessment and commissioning under the EAMS work? Will it be a fast-track adaptive HTA with a new assessment as more data becomes available?
- How will the significant data gathering obligations work in practice?
- Where will the data registries be held and who will own the data and will third parties have access to the data?
- If the clinical development programme is not completed within the time frame agreed (or at all) or an authorisation is refused will the PIM designation be removed?
- What role will ethics committees have – will they want to be included in the decision process?
- How will commissioning of PIM designated medicines work during the evaluation process and will commissioning be restricted to specialist centres?

Europe – EMA adaptive licensing pathways

In another recent development, drugs companies have been invited to submit applications to participate in a new adaptive licensing (AL) pilot project being run by the EMA⁴⁴.

AL is a more flexible pathway for the approval of innovative medicines to treat life threatening conditions⁴⁵. A staggered approach to market access is envisaged, in which a product is allowed earlier market access but under carefully controlled conditions, and its authorisation – 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.

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.

"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,"

"The approach seeks to maximise the positive impact of new medicines on public health by balancing timely access for patients with the need to provide adequate evolving information on their benefits and risks."

Hans-Georg Eichler, the EMA's senior medical officer

A framework to guide discussions of individual pilot studies has been published⁴⁶. Ongoing medicine development programmes submitted by companies should be experimental medicines in the early stage of clinical development, i.e., prior to the initiation of confirmatory studies, to enable actionable input from relevant stakeholders. The EMA intends to include as many programmes as necessary in this pilot phase in order to gather sufficient knowledge and experience, address a range of technical and scientific questions and further refine how the adaptive licensing pathway should be designed for different types of products and indications. A comprehensive development and licensing plan would be agreed in advance by the applicant, regulators and health technology assessment bodies for each product.

⁴⁴ http://www.ema.europa.eu/docs/en_GB/document_library/Other/2014/03/WC500163409.pdf

⁴⁵ <http://www.nature.com/clpt/journal/v95/n2/full/clpt2013177a.html#bib17>

⁴⁶ <http://www.nature.com/clpt/journal/v95/n2/full/clpt2013177a.html#bib17>

The European pharmacovigilance legislation adopted in December 2010 provides an important new legal basis to impose requirements for post-authorisation safety studies on pharmaceutical companies when needed and is the legal foundation of the new AL pathway⁴⁷. In addition, a new integrated Efficacy-to-Efficient (E2E) clinical trial model has been proposed⁴⁸. It is suggested that if proposed E2E trials were to be embedded in the adaptive approach to drug licensing sponsors may be able to secure market access for drugs potentially reinforced by payers that provide benefit for subgroups of patients but do not pass the usual 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' trial⁴⁹.

As the AL project progresses, it is envisaged that the European Commission will examine the legal and policy aspects of adaptive licensing in collaboration with the EU Member States and by consultation with relevant stakeholders.

Europe's adaptive licensing pathways

Some unresolved issues:

- Although it was originally anticipated that this would cover a wider group of medicines than a CA it is questionable whether this is possible if AL is going to fall within existing legal framework?
- There is a provision for safe harbour under the pilot but it is unclear at the moment how this will work as the rules of engagement are still under development
- What adjustments or changes in intellectual property rights may be needed to secure access to data needed for evaluation of effectiveness?
- Who can compel the generation of and analysis of this data?
- Who should own data on safety, efficacy, and effectiveness of drugs in use?
- Will AL be linked to an adaptive HTA?
- What happens to patients already using the particular medicine if the AL it is not renewed for reasons other than safety?
- What mechanism is there to prevent companies withdrawing drugs approved under an AL pathway?

⁴⁷ <http://www.nature.com/clpt/journal/v94/n3/full/clpt201395a.html>

⁴⁸ <http://www.nature.com/clpt/journal/v95/n2/full/clpt2013177a.html>

⁴⁹ <http://www.cancerresearchuk.org/about-us/cancer-news/press-release/revolutionary-clinical-trial-aims-to-advance-lung-cancer-treatment-thanks-to-cancer-research-uk-and>

Conclusions

Funding and commissioning of new innovative medicines remains a concern, but there are opportunities for companies to help shape the new earlier access pathways to patients in Europe.

- Although the EAMS and the AL pilot are important developments companies need to take a global view. Industry no doubt would prefer funded earlier access schemes such as the scheme operating in Japan for regenerative medicines. The lack of funding under the UK's new EAMS may make it unattractive compared to other earlier access routes. It will be important to get clarity around the proposed rapid HTA and commissioning at stage 3 of the EAMS so that it is clear at the outset what the commercial advantages are for companies (and their investors) considering this route. It is vital that the regulatory and HTA agencies agree an approach to the pricing and reimbursement of products using early access routes so that they reach patients. A possible solution may be managed entry agreements or risk sharing agreements under which a manufacturer and a payer or provider establish specific conditions for reimbursement of a medicine.
- Although the EAMS and AL are separate schemes work is needed to establish how these new European earlier access routes to patients will work together and whether there are possible advantages for companies engaging with both.
- Good data and early engagement with HTA and commissioning bodies is and will remain critical.
- There is an opportunity for companies with appropriate therapies in the pipeline to shape these new earlier access pathways. Manufacturers will need to engage with all stakeholders including governments, regulatory authorities, HTA and commissioning bodies, clinicians and patients on the issues to ensure the correct messages get through.
- These new regulatory approval pathways are untested so there is uncertainty. The patent and regulatory position is complex and expert advice is recommended.

How we can help?

The current market creates both opportunities and challenges for companies in the life sciences and healthcare sectors. We are committed to leveraging our knowledge of the law to create a business tool to provide you with strategic advice and support. We will work with you to identify and capitalise on new opportunities, defend and open up markets and diversify so you achieve your commercial objectives.

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