Adaptive Licensing

On 2 June 2014, the Association of the British Pharmaceutical Industry (ABPI), the BioIndustry Association (BIA) and the Centre for the Advancement of Sustainable Medical Innovation (CASMI) jointly organised a stakeholder event in London to publicise the EMA's Adaptive Licensing pilot project. This workshop allowed pharmaceutical and biotech companies, as well as patient groups, to understand better which medicines (the EMA terms 'live assets') would be appropriate to put forward for the Adaptive Licensing pilot and to appreciate how the pilot would work in practice. In some cases this could be complementary to the MHRA's Early Access to Medicines Scheme (EAMS).

Executive summary

The Adaptive Licensing pilot is welcomed by all parties as having the potential to provide timely access to licensed, promising medicines to a well defined patient population to address life threatening or rare disease indications where there is a clear unmet need. The initial framework for applying to the pilot is now in place and is open for applications until further notice. Issues affecting the implementation and resourcing of the pilot were the subject of constructive discussions at the event.

The Adaptive Licensing pilot is a voluntary evaluation process consisting of an initial application from the biotech or pharmaceutical company of their ongoing medicine development programme using the EMA's adaptive licensing framework document. The pilot is open to candidates in the early stages of development. Early stage would normally mean prior to initiation of confirmatory studies (i.e. during or prior to Phase II), although this would be considered on a case-by-case basis. If the medicine is assessed by the EMA as suitable, then this is followed by a meeting in a safe harbour environment in which all relevant stakeholders will discuss the asset. This meeting will include the EMA, the sponsor company, health technology assessment (HTA) bodies, organisations issuing clinical treatment guidelines and patient organisations. This safe harbour meeting is confidential and does not result in binding commitments.

All participants at the event welcomed the safe harbour meeting as many believed it offered an environment to work in a more collaborative manner if all parties were willing to be more open in sharing their thoughts on all aspects of the development and commercialisation pathways for the

medicine. However in order for this pilot to work, the need for trust was repeatedly emphasised.

The question of whether the EMA, Medicines and Healthcare products Regulatory Agency (MHRA) and National Institute for Health and Care Excellence (NICE) could handle the potential additional workload of the Adaptive Licensing pilot was asked and the EMA and UK Health Minister confirmed that the agencies are adequately resourced. Additional concerns raised by industry representatives included how adaptive licensing pricing would fit in a global product development strategy, and models of reimbursement were mooted that include higher pricing structures for therapies that are most effective in specific patient populations on the one hand, whilst also considering that HTAs may accept a lower price for uncertainties. Delegates agreed that pricing and reimbursement will be fundamental to the success of the pilot, and going forward marketing communications will have to adapt to reflect products that are approved through adaptive pathways.

The EMA discussed how the Adaptive Licensing pilot is designed to allow the acceptance of greater uncertainty, not increased risk, and in principle assessing a therapy in a smaller population as part of an adaptive pathway should allow greater control and monitoring of side effects. The EMA argued that when a medicine is authorised under the current 'magic moment' scenario of licensing then it is being prescribed and used widely in a 'real world' environment where close monitoring is more difficult to achieve so adverse events, especially in patients with multiple chronic conditions become more difficult to attribute.

To ensure successful evaluation of the Adaptive Licensing pilot, the ABPI, the BIA and CASMI all called for UK based companies to engage and champion the project by submitting suitable live assets to the pilot project so that both patients and industry could potentially benefit from the development of these innovative medicines.

Background

On 19 March 2014, the EMA launched the Adaptive Licensing pilot project with the aim of providing patients in the EU, who have life threatening or seriously debilitating conditions, timely access to new medicines which address unmet medical needs. The pilot project could potentially allow patients access to medicines that they would otherwise only be treated within the context of a clinical trial.

The adaptive licensing approach, sometimes known as 'staggered approval' or 'progressive licensing', is the culmination of seven years' work which stems from feasibility studies with the EMA and the Massachusetts Institute of Technology's Center for Biomedical Innovation (CBI).[1]

The UK government has supported the introduction of an Adaptive Licensing pilot since 2011 as mentioned in its 2011 Strategy for UK Life Sciences[2]. The introduction of an Adaptive Licensing pilot was reiterated as one of the key recommendations in a 2013 report published from an Expert Group on Innovation in the Regulation of Healthcare[3] (set up in June 2012) on which the ABPI and the BIA were represented.

The Adaptive Licensing pilot will allow biotech and pharma companies to propose experimental biological or small molecule drugs, 'live assets', to become part of a planned process using the existing regulatory framework, starting with early authorisation of a medicine in a restricted patient population. This will then be followed by iterative phases of evidence gathering and adaptations of the marketing authorisation to expand access to the medicine to broader patient populations.

The EMA is currently encouraging interested companies to submit suitable live assets to gather sufficient knowledge and experience and further refine how the adaptive licensing pathway should be designed.

Steve Bates, CEO of the BIA, summarised the benefits of the pilot project for patients and the UK as a whole, stating:

"The BIA and the ABPI have championed innovation for many years and by encouraging engagement with the main players in government, regulatory agencies, and the NHS we can bring the vision of promising new therapies to life. Adaptive licensing has the potential to allow patients in Europe and beyond access to much needed medicines sooner and this pilot project as the first step is to be welcomed. We would encourage UK pharma and biotechs to submit suitable drug candidates to the Adaptive Licensing pilot so that we can help speed the delivery of innovative therapies to patients."

The Adaptive Licensing pilot in practice

The Adaptive Licensing pilot is a voluntary evaluation process consisting of an initial application from biotech or pharma companies of their ongoing medicine development programmes using the EMA's adaptive licensing framework document. The experimental medicines submitted should be in the early stages of development, generally Phase II or earlier, and be used to treat serious or life-threatening conditions for which there is a clear unmet medical need.

If the medicine is assessed by the EMA as suitable, then this is followed by a meeting, (scheduled within two months of receipt of the pilot framework documents) in a safe harbour environment. The meeting will include stakeholders who have a role in determining patient access, such as the EMA, the company, health technology assessment (HTA) bodies, organisations issuing clinical treatment guidelines and patient organisations.

This safe harbour meeting is confidential and without commitment so will allow free discussion of aspects such as risk-benefit, ethical concerns, options for development pathways, assessment, licensing, reimbursement, commissioning and monitoring during initial utilisation.

Companies that are submitting suitable medicines for the EMA's Adaptive Licensing pilot can also apply (provided it meets the criteria) to the MHRA's Early Access to Medicine Scheme (EAMS)[4] as the two pathways are complementary.

The Adaptive Licensing pilot builds on existing EU regulatory processes, including scientific advice, centralised compassionate use, the conditional marketing authorisation, marketing authorisation under exceptional circumstances, patients' registries and pharmacovigilance tools that allow collection of real-world data and development of risk management plans.

The EMA intends to include as many programmes as necessary in the Adaptive Licensing pilot phase in order to gather sufficient knowledge and experience to 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.

The Adaptive Licensing pilot framework application document can be accessed via the EMA website.[5]

The UK Government perspective

According to **Lord Howe**, Parliamentary Under-Secretary of State for Quality, Department of Health (DH), the UK government has supported the creation of the EMA's Adaptive Licensing pilot and believes that alongside the MHRA's early access scheme these will allow patients in the UK to access innovative medicines in a more timely manner. Lord Howe commented: "EAMS and the Adaptive Licensing pilot are good examples of the UK having a strong voice on the development of innovative medicines in Europe."

Lord Howe continued: "In the UK we have a golden opportunity to seize how we think about science and regulation. Regulation is not a noose but a safety mechanism to release medicines in a safe way. EAMS and the Adaptive Licensing pilot could ensure the NHS can prepare for rapid uptake and commissioning of these new innovative medicines. In making both these schemes a reality, there has been great interaction from UK based pharma and biotech companies, and I would appeal for companies to put forward suitable candidates for the Adaptive Licensing pilot to make this a success for patients, business and the UK as a whole."

The regulatory perspective

The EMA introduced the Adaptive Licensing pilot and is responsible for the scientific and technical assessment aspects of the pilot. The main aim of the pilot from the EMA viewpoint is to address the access versus evidence conundrum by allowing patients timely access to innovative medicines to treat life-threatening conditions with unmet medical needs in a carefully controlled and monitored manner.

Dr Hans-Georg Eichler, of the EMA stated: "As regulators we have been good at relying on randomised controlled trial data and expert opinion but have not been good at utilising controlled study data without randomisation or cohort studies. By adaptive licensing of drugs in small patient populations we can see how drugs work in a 'real world' situation. This will allow the number of patients treated to grow slowly and we can monitor the safety of the drug more closely. With the current 'magic moment' model of licensing the patient population using the drug grows very rapidly and monitoring is less controlled, which in some cases makes it difficult to determine the significance of adverse events, especially those with a high background incidence."

The Adaptive Licensing pilot will provide an avenue for companies to submit medicines to treat small defined patient populations with life-threatening or seriously debilitating conditions when there is a clear unmet medical need.

According to Dr Eichler, the EMA envisages that the live assets submitted will be during or prior to Phase II trials and will be treatments that have the promise to address an unmet need. He states: "We don't believe the Adaptive Licensing pilot offers the right licensing route for 'me too drugs' or treatments for toe fungus."

Companies can apply for the Adaptive Licensing pilot as well as the MHRA's EAMS. **Dr Daniel O'Connor**, of the MHRA explained: "The MHRA was actively involved in designing the Adaptive Licensing pilot, which means we have a comprehensive understanding of the process and the scientific expertise to help steer companies successfully through it. We can advise on when companies should be submitting their products for the Adaptive Licensing pilot or for EAMS, and in some cases companies could be submitting to both as these are not competing schemes."

The benefit of entering the Adaptive Licensing pilot for the industry is that it will receive constructive advice and guidance on their experimental medicine in a safe harbour environment. This provides companies with a less formal avenue to interact with regulators and other interested stakeholders. Dr Eichler commented; "The safe harbour meetings will be a 'coalition of the willing' involving regulators, payers, HTA bodies and patient representatives. It will obviously be impossible to get all 28 HTAs for Europe to attend so it may be a selection of countries that attend. The meeting might take the form of a cup of coffee and a chat and not progress further. However, we know that some will progress to scientific advice and to the granting of a marketing authorisation."

Dr Sarah Garner of NICE added: "The safe harbour meeting is changing the nature of the dialogue with the EMA as it now allows a more iterative question and answer session to determine what is the best pathway to support this drug through licensing".

The Adaptive Licensing pilot has been well received and the EMA reported that 14 companies have completed the Adaptive Licensing pilot framework documents (at time of going to print this had increased to 20 applications, two of which are now being taken forward). Dr Eichler concluded: "The pilot is still open so we are inviting companies to consider submitting an asset and we will continue with the pilot until we have enough experience and evidence of its effectiveness for patients."

The HTA perspective

NICE also supports the Adaptive Licensing pilot because according to Dr Garner of NICE it can help to collect data that could be useful for appraisal of the benefit/risk at an earlier stage. Dr Garner states: "Risks in drug use are inherent, but now they can be properly managed with a staggered entry to market which should mean we have less market withdrawals. With the Adaptive Licensing pilot we will get real world evidence and are moving to a new paradigm where care and research are coalescing."

Dr Garner emphasised that NICE has been championing adaptive licensing and that their doors are open, and they are looking forward to free flowing open dialogue between all stakeholders in the safe harbour environment instead of more rigid Q&As. She also highlighted that PPRS has been set up to allow flexibility around pricing, and expressed surprise that not more companies had taken advantage of joint NICE, MHRA scientific advice meetings.

Dr Garner also made comparisons with the Commissioning through Evaluation process which is currently being developed with a focus on medtech products.

Dr Eichler confirmed that the UK, Netherlands, France, Germany, Sweden, Italy and one or two others are expected to be the most active HTAs with regards to adaptive licensing. He said that he forsees payers as full partners in the same discussions, and said that it would be up to the company to decide which payers to invite to these discussions, and that EMA would be willing to support companies with little experience, in order to suggest payers to invite, and broker that.

Research and clinical support in the UK

Dr Tony Soteriou of the Department of Health described how the UK is well placed for supporting adaptive licensing. He stated that the National Institute for Health Research (NIHR) provides opportunities for researchers, universities and the NHS to work in partnership with industry to develop new treatments to improve patient outcomes. He cited the NIHR Rare Diseases Translational Research Collaboration (RD-TRC), with its focus on deep phenotyping, together with the availability of genomic abnormality information, as an ideal opportunity for testing compounds which could utilise the adaptive licensing pathway.

Dr Soteriou stated: "NIHR units and centres can provide expertise and access to patients on a flexible basis, including on a paid for service model or shared risk and reward model. The shared rewards could include access for researchers to investigational compounds or downstream revenue sharing via royalty payments.

According to Dr Soteriou, medicines going through the adaptive licensing pathway could be trialed at a later stage via the NIHR Clinical Research Network across England.

Dr Soteriou explained: "We have recruited more than 630,000 patients to NIHR Clinical Research Network Portfolio studies in 2012 to 2013 so the UK has wide patient reach and demonstrates that the NHS could participate in adaptive licensing of innovative medicines."

The industry perspective

The industry views the Adaptive Licensing pilot positively and envisages that adaptive licensing will be most applicable for therapies being developed in the oncology, rare disease or anti-infectives spaces.

For SMEs in the biotech industry, the Adaptive Licensing pilot is a particularly welcome development. **Chris Sharpe** of cell therapy company, Cell Medica, explained: "Adaptive licensing is an ideal SME strategy as SMEs often don't have the revenues to spend on large trials so may target an unmet critical need niche. Adaptive licensing will sit well with us as individualised cellular therapies allow a unique level of post-marketing control through direct interaction with physicians."

For the larger company with global development plans, adaptive licensing can present challenges in terms of global pricing strategy. **Dr Gillen** of Celgene stated: "Global pharma don't think in single country terms for drug launch and different regulators and HTAs will accept different levels of uncertainty across different countries in the EU. This could lead to different pricing." Dr Gillen also noted that it will be difficult to explain the uncertainties of the pilot to US headquartered companies.

Alan Morrison, of Amgen added that the industry believed that alignment of HTAs across Europe was difficult. He stated "There are 28 member states and alignment is still an area of concern when developing drugs for the European market." Dr Gillen suggested that to achieve return on investment using adaptive licensing might require taking a more flexible approach and asking HTAs if they would increase the prices if a sub-group of, for example, cancer patients responded particularly well to a product. Dr Garner of NICE confirmed that on a couple of occasions companies have increased prices after a NICE assessment.

The industry also raised concerns about whether the EMA, the MHRA and NICE would have the capacity to cope with all these extra resource requests that EAMS and the Adaptive Licensing pilot would cause. Dr Eichler explained why he believed this would not be an issue by saying, "It is difficult to predict the workload but I believe that using an adaptive licensing approach we can manage our workload better because a more staggered drug licensing approach will reduce the bottleneck at the later stages of conventional licensing." The Minister also confirmed that the MHRA are "geared up to respond, and resourced to respond, and are well equipped to do it."

The patient perspective

From the patient perspective, the Adaptive Licensing pilot could help move towards precision medicines to treat the rarest conditions where patients are willing to take higher risks with experimental drugs and there are no viable treatment options. Therefore, the pilot is supported by patient groups and viewed as a potential mechanism for development stage therapies to become medicinal products more readily.

Nick Meade, of Genetic Alliance UK stated: "In 2013 there were around 1000 drug candidates available for treating rare genetic diseases but only 95 had marketing authorisation by October 2013. It will be a large hurdle to smooth out that approval ratio. In the UK, the NHS is making the vast majority of payer decisions so it makes sense here to bring in the NHS Clinical Reference Groups as early as possible to ensure drugs undergoing adaptive licensing get to those patients in most need."

Meade added: "For adaptive licensing to work, patients need to be central and have to be properly informed and should be involved in how adaptive licensing studies are designed."

Future challenges

The event identified several challenges in the approach. Reimbursement is one issue that has to be overcome in the future, and funding models which reimburse life science companies according to the efficacy of the treatment in niche indications were discussed. Industry called for a flexible approach to pricing of therapies approved through adaptive pathways.

Resources from the regulatory perspective were highlighted as another potential roadblock with many saying that the new Adaptive Licensing pilot and EAMS needs to be sufficiently resourced to ensure that applications are assessed and meetings are scheduled in a timely fashion for the schemes to achieve their aims.

Building trust was seen as vital to the success of the pilot and that industry needs to adapt to this new way of working. The workshop was seen a step in the right direction with Dr Garner finishing by saying that "at least we are now being open and honest about underlying problems."

Professor Richard Barker, Director of CASMI, commented: "We are now determined not only that effective adaptive development pilots are launched but also that the UK plays a major role in proving out the concept - as called for by the Prime Minister in his December 2012 life sciences speech. There are significant challenges in the trial design, informatics, reimbursement, ethics and public and patient communications which will be vital to success, and to which CASMI's academic fellows are contributing. We are also working with UK trade bodies and other stakeholders, such as MHRA, NICE and the NHS, to explore the potential in the UK."

Dr Bina Rawal, the ABPI's Research, Medical and Innovation Director, summarised: "We welcome the EMA's Adaptive Licensing pilot which has rapidly built a 'coalition of the willing' with regulators and biopharmaceutical companies coming together to have open dialogue with a wide range of stakeholders, many of whom have not been able to engage in this way at such an early stage of development of a new medicine. This will bring forward the development of much needed medicines, such as novel antibiotics and medicines for dementias and rare diseases, which will ultimately benefit us all."

[1] Adaptive Licensing: Taking the Next Step in the Evolution of Drug Approval http://www.nature.com/clpt/journal/v91/n3/full/clpt2011345a.html

[2] Strategy for UK Life Sciences https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/32457/11-1429-strategy-for-uk-life-sciences.pdf

[3] Report of the Expert Group on innovation in the regulation of healthcare http://www.mhra.gov.uk/home/groups/pl-a/documents/websiteresources/con336728.pdf

[4] Early Access to Medicines Scheme (EAMS) http://www.mhra.gov.uk/Howweregulate/Innovation/EarlyaccesstomedicinesschemeEAMS/index.htm

[5] Adaptive licensing http://www.ema.europa.eu/ema/index.jsp?curl=pages/special_topics/general/general_content_000571.jsp&mid=WC0b01ac0580665b62
http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000601.jsp&mid=WC0b01ac05807d58ce
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About the Association of the British Pharmaceutical Industry

The ABPI represents innovative research-based biopharmaceutical companies, large, medium and small, leading an exciting new era of biosciences in the UK.

Our industry, a major contributor to the economy of the UK, brings life-saving and life-enhancing medicines to patients. Our members supply 90% of all medicines used by the NHS, and are researching and developing over two-thirds of the current medicines pipeline, ensuring that the UK remains at the forefront of helping patients prevent and overcome diseases.

The ABPI is recognised by government as the industry body negotiating on behalf of the branded pharmaceutical industry, for statutory consultation requirements including the pricing scheme for medicines in the UK.

For further information, please go to www.abpi.org.uk or follow us @ABPI_UK

About the BioIndustry Association

Founded 25 years ago at the infancy of biotechnology, the BioIndustry Association (BIA) is the trade association for innovative enterprises involved in UK bioscience. Members include emerging and more established bioscience companies; pharmaceutical companies; academic, research and philanthropic organisations; and service providers to the bioscience sector. The BIA represents the interests of its members to a broad section of stakeholders, from government and regulators to patient groups and the media. Our goal is to secure the UK's position as a global hub and as the best location for innovative research and commercialisation, enabling our world-leading research base to deliver healthcare solutions that can truly make a difference to people's lives.

For further information, please go to www.bioindustry.org; follow us @BIA_UK or join our LinkedIn community

About the Centre for the Advancement of Sustainable Medical Innovation

CASMI is the Centre for the Advancement of Sustainable Medical Innovation, a partnership between Oxford University and UCL, created to develop new models for medical innovation. The centre aims to address the issues that have led to current failures in the translation of basic bioscience into affordable and widely adopted new treatments.

By bringing together a broad range of academic disciplines and other stakeholders, including patient groups, industry, regulators, policy-makers and clinicians, CASMI will tackle the problem at a systemic level, designing socially and economically sustainable solutions that are acceptable to all.

For further information, please go to www.casmi.org.uk or follow us @CASMIorg