Early Access to Medicines Scheme

On 28 April 2014, the Association of the British Pharmaceutical Industry (ABPI) and the BioIndustry Association (BIA) jointly organised a stakeholder event in London to publicise the Medicines and Healthcare products Regulatory Agency (MHRA) Early Access to Medicines Scheme (EAMS). This allowed interested parties the opportunity to understand and discuss the practicalities of implementing the scheme. The event was organised to ensure pharmaceutical and biotech companies, as well as patient groups, medical research charities and clinical researchers, could appreciate how the guiding principles of EAMS were formulated and how the scheme could benefit them.

Executive summary

EAMS is recognised by all parties as having many benefits in providing access to unlicensed, promising treatments to patients who have life threatening or rare disease indications. However, while the initial framework for applying for EAMS is now in place, issues affecting the uptake and implementation of the scheme continue to be the subject of much discussion.

EAMS is a three-step voluntary evaluation process consisting of Step I, the Promising Innovative Medicine [PIM] designation; Step II, the Scientific Opinion and Step III, Commissioning in the NHS. Applicants can only apply for an EAMS Scientific Opinion for therapies with Phase III data (Phase II data in exceptional circumstances). The event participants discussed why providing this type of data is going to be impractical for many therapies to treat rare disease indications. There was a suggestion from medical research charities and industry that for these types of disease, robust Phase II data should be an accepted standard for submission in a Scientific Opinion application.

The question of funding for applying and running the scheme, as well as providing therapies free of charge, was also raised several times by industry experts. They stated that the PIM designation was affordable, while applying for Scientific Opinion would require very careful review as to its cost effectiveness, especially for many SMEs. Payment models, similar to those utilised in Japan for expensive to manufacture cell therapy treatments, were mooted as one possible solution. Another avenue discussed to resolve this issue would be to have government funding available for

EAMS application, and to review UK Government funded reimbursement models based on the success of the therapy in EAMS. The availability of UK Government funding for EAMS is supported by both the ABPI and the BIA as a way forward and they are calling for a one year on joint review of the scheme to appraise its first year and potentially review its functioning, including funding options.

Industry experts and medical research charity representatives highlighted that in Step III EAMS commissioning by NHS England, the process for National Institute for Health and Care Excellence (NICE) evaluation and timelines for commissioning require greater clarity to allow companies to fully evaluate the utility of EAMS. NHS England's view was that these issues would be resolved during the coming year when the first treatments have been through EAMS. The MHRA also encouraged industry to engage with the scheme and provide feedback on their experiences so that EAMS would provide the intended patient benefit.

To maximise the potential of EAMS, the ABPI and the BIA continue to call for central government reimbursement, as well as greater clarity on the commissioning process, to ensure both patients and industry benefit from the development of these ground breaking therapies.

Background

On 7 April 2014, the MHRA launched the Early Access to Medicines Scheme (EAMS) with the aim of providing patients in the UK who have life threatening or seriously debilitating conditions access to medicines that do not yet have marketing authorisation and which address an unmet medical need. The scheme could potentially allow patients access to medicines up to one year earlier than at present.

The EAMS is a culmination of over five years work which began with a proposal developed in 2008 by the MISG (Ministerial Industry Strategy Group) consisting of Government, biotech and pharmaceutical industry experts. The MISG led discussions with all interested stakeholders, and one of the key commitments in the 2011 Strategy for UK Life Sciences[1] was to have the MHRA bring forward consultation on EAMS.

The MHRA and the Department of Heath (DH) then launched a joint public consultation in 2012 to explore when a medicine could be entered into EAMS, patient treatment and surveillance, how the scheme would be funded and what benefits such a scheme would offer the UK economy.

In 2013, a report was published from an Expert Group on Innovation in the Regulation of Healthcare[2] (set up in June 2012) in which the ABPI and the BIA were represented. The report found that EAMS did not offer a step (similar to one found in the FDA's "Breakthrough Therapies Designation"[3]) which sends positive early signals to investors about promising new drugs. Therefore, an additional stage of EAMS to introduce a new Promising Innovative Medicine (PIM) designation was proposed and is now included in the scheme.

Steve Bates, CEO of the BIA summarised the benefits of the scheme for patients and the UK as a whole, stating: "EAMS will enable UK-based patients to access much needed innovative therapies sooner. The data arising from their use of these experimental therapies will also contribute to increased understanding of the disease, how the drug works and how the NHS can operate most effectively to deliver on their needs."

Bates added: "By being a country where there is a speedy and effective way to develop medicines and the new types of data needed for adoption, this scheme can help ensure the UK continues to be the 'go to location' where companies from around the globe want to develop and bring to market their innovative therapies."

EAMS in practice

EAMS is a three-step voluntary evaluation process and is aimed at allowing access to therapies that have completed Phase III trials, but may be applied to those that have completed Phase II trials in exceptional circumstances. If data is really outstanding and there is a significant unmet medical need, the MHRA will be flexible and assess Phase II data but companies have to provide solid data to demonstrate risk versus benefit of the therapy. In Step I, the PIM designation, the MHRA will approve or decline this after reviewing the PIM application (which includes non-clinical and clinical data on the therapy) at an MHRA scientific meeting. The PIM designation can be based on Phase I/II data. A PIM designation requires the applicant to pay a fee of £4,027 and the MHRA will not make positive or negative PIM designations publically available.

When a positive PIM designation is obtained, applicants can then proceed to Step II, the EAMS Scientific Opinion, where the MHRA aims to be both fast and flexible and complete its opinion in 75 to 90 days. This Scientific Opinion will describe the benefits and risks of the medicine and will support the clinician and patient to make a treatment decision on using the medicine before its licence is approved. The Scientific Opinion is based on information submitted to the MHRA by the applicant, and positive opinions will be made publically available in a Public Assessment Report (PAR) on the MHRA's website. The fee for assessment of the Scientific Opinion application is £29,000.

The PIM and Scientific Opinion application documents can be accessed via the MHRA website.[4]

Step III is commissioning of the drug by NHS England. NHS England envisages that the commissioning process will run in parallel with positive PIM designation and Scientific Opinion. It will not require ethics committees approval (as they have not requested involvement in commissioning) and will rely on information of potentially useful treatments being

flagged and sent to the relevant Clinical Reference Group (CRG) of which there are 75 across five programmes of care in the NHS. The CRG will assess those therapies for commissioning that have been assigned a PIM designation and/or positive Scientific Opinion by the MHRA. It will then put in place a steering group to include industry representation, and potentially NICE representatives, to discuss outcome measures; cost effectiveness of the treatment; identify how many and which centres could evaluate the treatment and the need for developing additional diagnostic tests. Information on promising treatments for EAMS commissioning will then be sent to the Clinical Priorities Advisory Group (CPAG) for recommendation and then to NHS England Board for final sign off. NHS England has not yet set a timeline for EAMS drug commissioning and it is currently unclear at what stage NICE will be involved in the commissioning process.

The expectation from the MHRA is that between five and 10 drugs will go through the scheme each year.

The UK Government perspective

According to **Lord Howe**, Parliamentary Under-Secretary of State for Quality, DH, the UK Government has supported the creation of EAMS, which also has cross-party support, as a central tenet of allowing life science innovation to thrive in the UK.

Although the granting of a PIM designation will not be made publically available, the UK Government believes it will be in a company's interest to make this information available because it will signal to investors that a therapy is on the 'right track' with the regulators.

Stage II, EAMS Scientific Opinion, is of value to industry because it allows regulators early access to clinical and non-clinical data to assess. **George Freeman**, MP, states: "An early 'no' or a 'no, not like that but like this' from the MHRA and NICE is very valuable information to a drug company." This input can help to steer the clinical strategy of new therapies, as well as assess pricing, and allow the company to adjust the value proposition accordingly. He went on to say: "The scheme needs to lay out landing lights for a different model of drug development and procurement."

Stage III, commissioning of the therapy, will also benefit industry because it will encourage collaborative working with the NHS and access to patient populations and expert clinicians. Freeman concludes: "EAMS will help companies with good data to access specific patients that need their new treatments and to determine which of their treatments have real clinical value."

The regulatory perspective

The MHRA introduced EAMS and is responsible for the Step I and II scientific aspects of the scheme. The main aim of EAMS from the MHRA viewpoint is to provide patients who have life threatening or seriously debilitating conditions access to medicines that do not yet have a marketing authorisation when there is a clear unmet medical need. The benefit of entering EAMS for an R&D company is that they will receive constructive advice and guidance on the application of their treatment. Since there isn't any limit on the number of products a company can enter into EAMS (provided they fulfil the EAMS's criteria) and negative opinions of either the PIM or the Scientific Opinion are not published, this provides companies with another avenue to interact with regulators, the NHS and NICE at an earlier stage in the clinical development of their product. The MHRA advised companies to only apply for each PIM and Scientific Opinion step as and when they have the available data to fulfil the criteria for that step, rather than applying and having to halt the process to await additional trial data.

Dr Daniel O'Connor, Expert Medical Assessor at the MHRA states: "Since launch we have had 63 downloads of the PIM application and 28 downloads of the Scientific Opinion application. Additionally, we have scheduled meetings with life science companies to discuss the scheme so there appears to be early interest. However, there is still a lot to learn and we would encourage applicants to fill in our electronic survey on their experience of EAMS as we all want it to be a successful process."

The clinical perspective

Malcolm Qualie of NHS England described how the NHS views EAMS as being able to provide new opportunities for patients to access innovative medicines, as well as the potential to improve the care and experience of patients where existing treatments are ineffective. It could also offer an alternative avenue for patients to enter clinical trials for drugs that are not being routinely evaluated in clinical trials in the UK. EAMS provides further opportunities for NHS England to work in partnership with industry to improve patient outcome and could be particularly useful in treating cancer and rare diseases. The medicines given priority for use will be those where there are no viable treatment options and where the drug is between 18 months to two years from obtaining a licence.

NHS England sees EAMS as providing a risk/benefit partnership with industry. It will contribute specialist professionals and advice in the form of its CRGs and trust personnel, support standard diagnostic testing with the treatment and also treat adverse events.

Currently, it is not clear how many NHS centres will take part in EAMS as Mr Qualie states: "We can't have a scattergun approach where every single clinician has access to innovative medicines that have positive Scientific Opinion." According to Mr Qualie the number of centres involved in EAMS for particular treatments will depend on the patient population for that indication and the therapies will be used in specialist centres geographically spread across the UK. It is envisaged that the Drugs and Therapeutics Committees will not intervene to prevent prescribing of therapies in EAMS as they would support this scheme.

The benefits of EAMS to the pharmaceutical and biotech industry are a consistent approach to measuring the value of medicines within the NHS, as well as the provision of a controlled environment to deliver treatments in specialist centres, where clinicians will monitor and report any serious adverse events in a timely manner. In return, pharmaceutical and biotech partners will need to provide the therapy free of charge up to the point of licence and fund any new diagnostic tests required to evaluate treatment. Mr Qualie concludes: "EAMS will allow drugs to be tested in a 'real world' setting by clinicians who understand the disease and the issues around it. This will help produce data which will support both a licence application and NICE assessment, as well as provide information on patient cohorts to steer companies to apply for a licence in indications where their drug will be most effective."

The patient perspective

From the patient perspective, EAMS 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, EAMS is supported by many patient groups and medical research charities and viewed as a method of partnering with industry to assist in funding promising treatments.

Nigel Blackburn of Cancer Research UK states: "Time is of the essence for many cancer patients, particularly those with more advanced disease. It can mean the difference between life and death. Therefore, this scheme, which has at its heart the potential to bring promising new medicines to patients faster, is to be warmly welcomed. The scheme should also make it more attractive for life sciences companies to conduct their development activities in the UK, which we believe will bring a multitude of benefits to the UK population."

NICE also supports EAMS because according to **Meindert Boysen** of NICE, it can help to collect data that could be useful for appraisal at an earlier stage. This includes the efficacy and safety of a promising medicine, as well as gaining a better understanding of the burden of disease which the medicine is aimed at addressing. He expressed the need for companies to share with NICE the fact that a medicine has received a PIM as a matter of course. Boysen also called for companies and other interested parties in the EAMS to engage with NICE early on in the process through obtaining joint scientific advice with the MHRA, and by supporting involvement of NICE to provide data on current treatment options and to establish what kind of data has to be collected as part of the EAMS and Commissioning through Evaluation system. NICE are keen to discuss how other information produced by NICE, such as the Evidence Summary of Off-Label or Unlicensed Medicines, could be of use in communicating an EAMS opinion to doctors, patients and the wider NHS.

NICE is, however, concerned that EAMS Scientific Opinion will be focusing on therapies in Phase III trials. This was echoed by medical research charities as their representatives pointed out that with some of the rare diseases the Phase II data is the defining dataset, as it is impractical to recruit a large enough cohort of patients with many rare diseases for a Phase III trial.

The other issue raised by the medical research charities is the lack of clarity around the commissioning stage of EAMS. One delegate commented: "We don't want to shift the bottleneck in access to innovative medicines from the regulatory stage only to have it stall at the commissioning stage."

The industry perspective

The pharmaceutical industry views EAMS as a potential method for evaluating drugs in small populations and gaining access to patients in the UK. It envisages that EAMS will be most applicable for therapies being developed in the oncology or rare disease spaces.

For SMEs in the biotech and pharmaceutical industry, EAMS is seen as validation that they are actively engaging with regulators. While smaller biotechs welcome EAMS as a step in the right direction, for many the major stumbling block is funding associated with applying and having their therapies evaluated as part of the scheme.

The PIM designation is viewed positively as a relatively inexpensive method of obtaining validation for a therapy. However, at Stage II the Scientific Opinion is more costly and many SMEs will review whether it is more cost effective to continue with the usual route to drug approval without applying for the EAMS Scientific Opinion.

Additionally, since the cost of providing the treatment will reside with the company during the duration of EAMS and perhaps beyond, rather than being reimbursed, SMEs developing cell therapies or biological medicines which have high manufacturing costs will find this challenging. **Michael Hunt** of ReNeuron states: "With EAMS, the MHRA has eased the pathway to drug approval in one sense but at the later stage clinical development has perhaps presented a challenging decision to be made on the part of SMEs. We support the view of the ABPI and the BIA that EAMS should

be funded by government. In the field of cell therapy in particular, Japan is introducing an early access scheme that is likely to be reimbursed as early as Phase II. With an unfunded scheme, many biotechs will apply for PIM designation because this provides a validation tool, but how many will progress to a Scientific Opinion stage which they have to fund themselves and has a significant cost remains to be seen."

Mercia Page of MSD UK adds: "When making decisions about applying for EAMS the fees and internal resources, including drug costs, will need to be taken into consideration".

There was some uncertainty around how this scheme sits alongside the European Medicines Agency (EMA)'s adaptive licensing scheme[5] and how straightforward the pathway of commissioning therapies would be within the NHS. The MHRA view is that EAMS and adaptive licensing are not competing schemes and companies are encouraged to apply to both provided their drugs fulfil each scheme's criteria. The ABPI also stressed the importance of raising EU level awareness of EAMS and, if appropriate, of finding ways for EAMS to be incorporated into adaptive licensing discussions.

Future challenges

The EAMS event identified several challenges in the scheme. Funding is one issue that has to be overcome and attendees discussed the possibility of different funding models in the future which could reimburse life science companies according to the efficacy of the treatment in EAMS were discussed. One possible avenue suggested by industry for cell therapies, which have high manufacturing costs, is to look at implementing a system similar to the Japanese Pharmaceutical Affairs Law for regenerative medicine products, which allows the Japanese government to give conditional approval to products if their safety is confirmed in clinical trials, as may occur on completion of Phase II, at which point the patient then pays towards their treatment. Until the issue of funding for EAMS is resolved, many believe that EAMS will only be accessible to larger pharmaceutical companies as Stage II and III will be prohibitive in terms of cost, time and staff resources for SMEs to pursue.

Access to data was highlighted as another issue with many saying that there needs to be flexibility with EAMS so that therapeutics with solid Phase II data can also enter the scheme. Many believe that for rare disease indications, Phase II data should be the accepted standard rather than the exception for the Scientific Opinion.

The timeline and framework for Stage III, commissioning the therapy within the NHS, has to be formalised in more detail. Currently, it is not clear how many centres will take part in EAMS, how the process pathway for gaining commission approval will work and at what stage NICE will be involved in the commissioning. NHS England believes the framework and timelines for the commissioning pathway will be governed by the type of therapy and disease indications which gain an initial positive Scientific Opinion. It states that the commissioning process will be more established in the coming years when therapies have been through EAMS.

Dr Bina Rawal, Director of Medical, Innovation and Research at the ABPI summarised: "EAMS is an end-to-end process covering promising new therapies from early stage development to their access within the NHS. It is extremely important and commendable that key bodies such as the MHRA, DH, NHS England and NICE have worked together, engaging stakeholders such as patient groups, academia and industry along the way to make this a reality. EAMS has so far been received positively by industry and patient groups in the UK but issues of funding, data clarity and commissioning of the therapy must be addressed. Therefore, we need to commit to reviewing the EAMS in one or two years time to ensure that early access to innovative medicines does become a smooth and successful process."

1 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

2 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

3 Fact Sheet: Breakthrough Therapies http://www.fda.gov/regulatoryinformation/legislation/federalfooddrugandcosmeticactfdcact/significantamendmentstothefdcact/fdasia/ucm329491.htm

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

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 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 per cent 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