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Accelerated Development and Access to Innovative Medicines for Patients

The Sixth Medicines and Healthcare products Regulatory Agency and UK BioIndustry Association Joint Conference

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Executive summary

The wave of innovative medicines coming through the system holds the promise of great benefits for patients, but poses challenges for Europe's hard-pressed healthcare systems – and for regulators and health technology assessment bodies, which are being asked to oversee innovative products, in particular advanced therapies such as T-cell immunotherapies, gene therapies and tissue and cell-based treatments.

While the system adjusts to accommodate innovative products and novel, reformatted development programmes, companies are facing rising costs and challenging market conditions. In recognition that the old way of doing things risks failing patients and undermining the commercial potential of innovative products – many of which rest on publicly-funded academic research – a number of schemes and initiatives are in train with the aim of accelerating patient access.

The Medicines and Healthcare products Regulatory Agency (MHRA) and the UK BioIndustry Association (BIA) brought together experts from across the sector to assess the state of play, discuss how the various schemes have performed, and how the National Health Service (NHS) might respond to current innovation challenges.

The MHRA is the UK medicines and medical devices regulator, responsible for the safety, quality and efficacy of medicines available in the UK. Proportionate regulation and advice and support to life sciences companies can make the UK an attractive place to do business whilst ensuring public health protection. The BIA is the UK trade association for innovative bioscience enterprises which are responsible for biotechnology-derived medicines currently in clinical development in the UK and are at the forefront of innovative scientific developments targeting areas of unmet medical need. It has an interest not only in regulation but in research and development, funding and financing for the sector, and NHS uptake and adoption.

This report summarises the presentations and perspectives from senior experts and leading speakers from the MHRA, the European Medicines Agency (EMA), the life science industry, National Institute for Health and Care Excellence (NICE), NHS England, academia, research charities, patient organisations and investment firms. The conference programme and key points raised by delegates during the panel discussions are found in the Appendices. Slides are available to download via the conference website.

Introduction

A wave of new and innovative medicines emerging from academic labs and coming through corporate pipelines holds the promise of great patient benefit. In some instances there will be therapies for diseases where before there was no approved drug, in other cases there is the prospect of long-term health improvements or even a complete cure.

Products such as targeted cancer drugs, T-cell-based cancer immunotherapies, and cell and gene therapies, embody both significant health benefits and commercial opportunities for UK life sciences.

However, the products are different in kind from the small molecules that went before, presenting challenges around how they are regulated, assessed and commissioned for use in the National Health Service (NHS).

It is an exciting time in the sector, with an "explosion of science" generating a range of new medicines, calling for new approaches to bring safe and effective innovative products to patients, said **Dr Ian Hudson, Chief Executive of the Medicines and Healthcare products Regulatory Agency (MHRA)**, welcoming delegates.

The MHRA at a UK level and in concert with the European Medicines Agency (EMA) is working to accelerate access. Specific initiatives include the establishment of the Innovation Office at MHRA to strengthen advice, the MHRA's role in setting up and implementing the Early Access to Medicines Scheme (EAMS) and participation in the comprehensive Accelerated Access Review, chaired by Sir Hugh Taylor.

At an EMA level, a number of regulatory tools are being brought to bear in the Adaptive Pathways pilot and the PRIME (Priority Medicines) scheme.

"I appreciate the collaboration with the BIA on initiatives to support innovation," said Dr Hudson. The key focus must be to improve safe and timely access to new medicines and to support innovation.

Many of the innovative products coming through the system start life in biotech SMEs, making it important that small companies understand the regulatory requirements.

At the same time, the many novel constructs and new mechanisms of action, present challenges to a regulatory system that developed on the back of small molecules, noted **Alan Morrison, Chairman, BIA Regulatory Affairs Advisory Committee and Vice President, International Regulatory Affairs, MSD.**

The regulatory system "now has to embrace innovative modalities" while SMEs need information from the regulators and feedback from people in the industry who have put their products through the various accelerated access schemes, Mr Morrison said.

Innovation and accelerated access in the UK – Where we are today?

The Accelerated Access Review has been underway since March 2015, staging a public consultation that attracted over 600 responses. An interim review published in October 2015 set out five propositions to speed up access and set the stage for a second phase of engagement.

The final report is due to be published later in 2016, However, **Sir Hugh Taylor, Independent Chair of the Accelerated Access Review** discussed some of the key conclusions, telling delegates a "fantastic range of inputs" indicates there is broad agreement on what needs to be done and that many of the elements that will feed into the proposed reforms are in place.

The final report will propose the establishment of a managed accelerated pathway for a limited number of the most promising products, under which end-to-end plans will be created during clinical development for how to take these products through regulatory approvals, health technology assessment and uptake at scale in the NHS.

It is thought this will require the system as a whole – and in concert – to focus on products that are most needed and will have the greatest impact.

Sir Hugh said the skills and expertise of MHRA and NICE, and the high quality research infrastructure, could be combined with regulatory flexibility offered by conditional approvals, allowing for commercial access before the final health technology appraisals of selected products.

There will also be work to devise new payment models for products, which while expensive, have significant, long-lasting effects.

In parallel with the accelerated pathway for the select few, Sir Hugh said the system needs to become more receptive to smaller advancements. The aim should be, "to make the health environment generally more innovation friendly, in particular for medtech and digital health products, where it should be easier to bring in [technologies] and get products diffused."

There is real potential for the NHS to use technology-driven innovation to support better care and change patient pathways.

The two central themes of managed accelerated pathways and making the NHS as whole more innovation friendly, will be underpinned by three pillars. The first is to encourage partnerships between the stakeholders along the access chain. "I really think there is a need to strengthen collaboration at a national level," said Sir Hugh. "You can have lots of friendly conversations, but that does not necessarily translate to action."

Secondly, there must be specific incentives and support for clinicians to adopt the accelerated access agenda. Sir Hugh, who has front line experience in his post as Chairman of Guys' and St Thomas' NHS Foundation Trust, warned that the financial situation and focus on core indicators will make it hard to get innovation on the agenda.

"A key piece of evidence we heard time and time again, is that the factor preventing innovation uptake is not the cost per se, but the change management associated with delivery," Sir Hugh said.

Third, and very importantly, the patient voice must be allowed to inform the agenda. Patients are the "end users" and should be able to say what outcomes are relevant to them, take part in shaping trials and be involved in deciding what products go through the accelerated access scheme.

"In the end, it will be patient pull that makes the difference; this has been missing in the system," said Sir Hugh.

Despite barriers that must be overcome, in particular for the NHS, in dealing with the Accelerated Access Review, Sir Hugh said he is optimistic there will be a win:win:win outcome. "Patients will get earlier access, the NHS will work smarter and deliver care more productively; innovators can unlock value through new, more flexible innovation adoption models."

Professor Sir John Bell, Chair of the Accelerated Access Review's Expert Advisory Group, suggested an important starting point in supporting the NHS to manage the breaking wave of innovation is to learn from the benefits innovation has delivered in the past. Antibiotics and vaccines for example, have vastly reduced the impact of infections and infectious diseases; the past 30 years has seen a 75 percent reduction in the incidence of cardiovascular disease as a result of new pharmaceuticals and public health interventions; there has been a 50 percent reduction in mortality from breast cancer, and reductions in mortality in other cancers.

More recently, anti-TNF alpha monoclonal antibodies have revolutionised the treatment of rheumatoid arthritis, ending the need for hospital care, while anti-psychotics have allowed residential care to be phased out.

"To sustain innovation in the NHS we are going to have to identify, pull through and adopt [the best innovations] at scale," Sir John said.

Responses to the Accelerated Access Review consultation indicate there is broad agreement on the root cause of the difficulties the NHS faces and how to address this issue.

To reach the point where a drug is ready for use in the NHS, developers have to scale a series of high mountains along the development, regulatory approval and health technology assessment pathway. "They then reach the desert, where the route to adoption is unclear; it should be easier," said Sir John. "The NHS may be cash-strapped", but the fact is it cannot improve its financial stability without deploying innovation to redraw care pathways and deliver more care at home and at the primary level.

True innovation is not embodied in "gizmos", it has to change the system, improve care at the same or lower cost, in the way that anti-TNF alpha biologics have transformed the rheumatoid arthritis pathway.

It will be crucial to get patients involved, to identify breakthrough products, manage the swathe of innovation coming through, work on pricing and reimbursement and ensure adoption of the best innovations at scale.

European perspective: Results of survey on early access schemes / compassionate use of new medicines

Amongst the existing tools and schemes for accelerating access to innovative medicines for patients with high unmet medical need is the European system of Compassionate Use, under which drugs can be made available outside a clinical trial, but before the product is licensed and available in a market.

One regulation (based on Article 5 of Directive 2001/83/EC) allows a company to supply a drug if it receives a bona fide unsolicited request from a patient or doctor. A second regulation (Article 83 of Regulation (EC) 726/2004) enables Member States to make a request for an opinion from the EMA's Committee for Medicines for Human Use (CHMP) on using a drug for a cohort of patients before approval.

Access is usually granted when it would no longer be possible for a patient to join a phase III trial, but before a product reaches the market in a Member State and is reimbursed.

Kate Beaujeux, Regulatory Affairs Senior Regional Director, Oncology, AstraZeneca said the wave of medical innovation means Compassionate Use, "is suddenly back on the agenda". This has prompted the industry body EFPIA (European Federation of Pharmaceutical Industries and Associations) to carry out a survey of how the Compassionate Use schemes are applied in different Member States.

The aim was to provide inputs for the European Commission Expert Group on Safe and Timely Access to Medicines for Patients (STAMP), which is looking at how to use existing regulatory tools to improve access.

EFPIA asked member companies to send examples of their experience of Compassionate Use to scope the hurdles and concerns about how the programme is operating. "The experience of companies was very similar, regardless of country or drug," Mrs Beaujeux said. "One of the most complicated things to do is setting up a compassionate use programme – there is a lot of nuance."

Compassionate Use is approached differently in different Member States, making for a very complex system from the point of view of companies, with varying requirements in terms of the information they are required to provide and of the timelines. Based on the survey EFPIA has made suggestions to STAMP on measures to improve access and reduce disparities between Member States.

Among the proposals discussed with STAMP was the need for more education for patients, so they have greater understanding of Compassionate Use. In addition, there should be an equal chance for patients to get access to new, innovative medicines regardless of where they are in the EU. Aligning national approaches would make access more equitable whilst cutting the administrative burden of setting up Compassionate Use programmes.

EFPIA also suggested the Compassionate Use should be applied to new indications of authorised medicines, in preference to the current system of "off label" use.

It is notable that an Article 83 opinion has only been requested by Member States five times in 12 years. "None of those are in oncology, which given what is happening in the field is surprising," said Mrs Beaujeux. She recommended a study is carried out to find out what the barriers are here, and there should be consideration of whether patient groups and industry can trigger Article 83 requests.

Another proposal discussed with STAMP, said Mrs Beaujeux, was the potential in linking up Compassionate Use to other tools, so that, for example, PRIME designation or the use of Adaptive Pathways could trigger the rapporteur Member State to request an article 83 opinion.

Review of the UK Early Access to Medicines Scheme

The Early Access to Medicines Scheme: Two years on

The UK EAMS was established two years ago with the aim of giving patients with life threatening or seriously debilitating conditions access to medicines that do not yet have a marketing authorisation, when there is a clear unmet clinical need.

The scheme has succeeded in doing this, said **Dr Daniel O'Connor, Expert Medical Assessor, Licensing Division, MHRA,** setting the scene with a brief history of EAMS – from 2008 when the Ministerial Industry Strategy Group (MISG) recommended an early access scheme, through to its launch in April 2014, and the first EAMS scientific opinion in March 2015 – to understand where it might go in the future.

The MISG recommended that the scheme could allow access to drugs one year earlier than the formal approval and market launch. EAMS does not substitute for clinical trials. While primarily aimed at products that have completed Phase III trials, it can be applied after Phase II trials.

"You need evidence of the benefit – risk according to the four EAMS criteria," Dr O'Connor said. These are unmet need, the promise of significant benefits, that the potential adverse events are outweighed by the benefits, and the availability of GMP standard product.

The first step, of securing a **Promising Innovative Medicine** (PIM) designation, involves an early review of the criteria by the MHRA, giving a company reassurance that the clinical development is on track. Sponsors also get access to contacts in the NHS and UK health technology assessment bodies, enabling early discussions on appraisals and patient access issues.

Between 2014 and 2016, the MHRA received 22 applications and has granted 16 PIMs. Most applications have been in oncology, but there have also been applications for products in other areas including in cardiovascular disease, dermatology and anti-infectives areas. EAMS scientific opinion status has been awarded to eight indications.

The EAMS Government Industry Stakeholder Taskforce was set up to inform further development of EAMS and address any issues. There has also been an independent review, which made a number of recommendations to improve the operation of EAMS. In addition, the Accelerated Access Review is considering how EAMS might be strengthened.

"EAMS does give access to patients with high unmet medical need before license," said Dr O'Connor. "It should continue to evolve."

Industry experience: Case study – Keytruda granted the first positive EAMS scientific opinion

When the MHRA announced EAMS in 2014, there was an immediate discussion within MSD about the PD-1 inhibitor pembrolizumab being an ideal candidate. "We thought it could fit very well," said **Joanna Maitland Smith, Executive Director, Regulatory Affairs, MSD.**

However, MSD is a large global organisation and the UK arm was not working in a vacuum, with the company in the throes of putting the pembrolizumab portfolio together, resources were stretched. In addition, MSD was setting up a global early access scheme, and it was not clear what EAMS would add to this.

The case was made by MSD UK that there were clear advantages in getting earlier patient access with defined benefit – risk profile; that going through the EAMS process would add credibility and value to pembrolizumab; and that EAMS presented an opportunity to partner with the MHRA, NICE and NHS England, to look end-to-end, and reduce access timelines once the product was approved.

However, it required considerable internal and external discussion before the application for PIM designation was submitted on 22 August 2014. In the meantime the marketing authorisation application for the use of pembrolizumab in melanoma had been submitted to the EMA in June. "With the marketing authorisation application ready, there was concern it would be too late to apply for EAMS," Ms Maitland Smith said. "The MHRA was very encouraging; it was thought the scientific opinion would be enough ahead of the marketing authorisation for it to be worthwhile to patients."

The face-to-face meeting with the MHRA on 25 September required significant preparation and discussions on requirements for getting the product to patients in advance of licensing, including labelling, risk management plan and pharmacovigilance. Once the PIM designation was granted on 10 October there was then significant further work in the UK office before the application for a scientific opinion was filed on 24 October 2014.

The preliminary scientific opinion which came back from the MHRA on 17 December included a formal list of 22 questions. With Christmas intervening it was not possible to meet the deadline for responding before 1 January 2015, and so the 45-day procedure was switched to the 90-day option, with responses due by 16 January.

"There were issues around the consistency [of EAMS] with the EU marketing authorisation procedure; we were answering EMA questions in parallel, but the MHRA was very flexible," Ms Maitland Smith said.

The EAMS scientific opinion was granted on 9 March 2015. "This was longer than expected but meaningful: more than 500 patients got access from March 15 to the grant of marketing authorisation," said Ms Maitland Smith. The ability to interact with NICE, NHS England and the Department of Health in parallel led to accelerated NICE review and faster implementation of NICE guidance. Following NICE's recommendation in September, Keytruda became routinely available from October 2015.

The effort devoted to the melanoma indication translated through to an easier and faster process when MSD applied for EAMS in non-small cell lung cancer. The PIM submission on 11 November 2015 led on to EAMS scientific opinion on 10 March 2016 and the first patient was treated in April. One potential show-stopper – that a companion diagnostic was yet to be approved – was averted when the CE designation came through. "It was a much smoother process," said Ms Maitland Smith.

NICE perspective

NICE has worked with the MHRA, the Office for Life Sciences and NHS England to ensure there is alignment of processes for EAMS products, as **Dr Nick Crabb, Programme Director Scientific Affairs at NICE** described. Whilst most aspects of NICE's technology appraisals (TA) processes are applicable to EAMS medicines, there are some specific arrangement for products with an EAMS scientific opinion.

These include a requirement that all products that meet EAMS criteria to be selected for TA guidance, encouraging companies to take up joint MHRA/NICE scientific advice, offering companies a NICE EAMS meeting to help them prepare for NICE appraisal, expediting assessment to allow draft TA guidance to be issued within one month of the marketing authorisation, and an agreement NHS England will implement NICE guidance on EAMS medicines within 30 days of the final guidance (it is 90 days for other products).

While NICE applies its regular criteria to EAMS appraisals, Dr Crabb said meeting beforehand ensures companies really understand what they have to do. In addition, NHS England involvement means practical arrangements for the EAMS period can be discussed.

Some of the EAMS medicines have gone through to final guidance without the need for public consultation, resulting in faster timelines.

In terms of NICE experience to date, "The key point additional patient access was achieved – indicating success." However, Dr Crabb said, with EAMS periods lasting as little as 21 days and a maximum of four months, time periods have been too short to allow for the collection of evidence. "If companies engaged earlier, there would be more patient benefit and we would get more real world evidence," he said.

To date, most EAMS medicines have been for oncology indications. This means the new Cancer Drug Fund arrangements allowing for all cancer drugs to be appraised by NICE after the CHMP gives a positive opinion, but before the license is granted, are relevant to EAMS. However, said Dr Crabb, "It is hoped eventually EAMS medicines won't need Cancer Drugs Fund support."

NHS England perspective

NHS England's Specialist Services is keen to support EAMS, but said **Malcolm Qualie, Pharmacy Lead**, it is important to understand the context and the financial pressures under which Specialist Services is operating. There is not enough money to fund the drugs that are currently approved for use, making it hard to make room for products that do not have full evidence of the cost benefit.

In addition to this context, there are issues for NHS England in terms of the EAMS timelines – while the announcement of a PIM designation may be a signal that a scientific opinion is coming through, "We can't do anything with that information," Mr Qualie said. It should also be appreciated that although EAMS medicines are supplied free of charge – which is a positive – there are still cost and budgeting implications for the NHS in terms of care, implementation costs and the cost of collecting real world evidence.

In the case of Keytruda, the first EAMS medicine, its manufacturer MSD gave assistance in identifying costs to the NHS, which was helpful.

All patients receiving EAMS medicines must be registered and hospital trusts that do not sign up are not allowed access. In the case of oncology drugs, all patients will be followed up via SACT (Systemic anti-Cancer Therapy Dataset).

Mr Qualie noted that EAMS access periods have been low overall, and for one drug this was not implemented. "The marketing authorisation came early; there was only ten days and it would not have been worth it," he said. For Mr Qualie, this undermines one of the stated objectives of EAMS, which is the collection of real world data.

From the perspective of a Commissioner, early communication from the MHRA on PIM and scientific opinion status; pharma company support in identifying NHS costs; and the joint working with NICE, are beneficial. However, there is a need for better communication on when the marketing authorisation is likely to be granted, to reduce the risk of a clinician offering a patient a therapy that is no longer available. In addition, it should be made clear to providers that a drug is free of charge for the duration of patient treatment.

Overall, said Mr Qualie, "We should embrace EAMS as a way to get products to the marketplace backed by the NHS."

Opening the panel discussion, Steve Bates, Chief Executive Officer of the BioIndustry Association, said EAMS may have taken root but it is "a delicate flower" that may not survive hard frosts. The success to date is not a result of the process per se, but the amount of effort and the commitment of the people involved.

There has been some clever thinking to ensure EAMS works in parallel with developments in accelerated access at a European level. However, it remains a shortcoming that EAMS is not funded, making it difficult for small biotech companies to take part.

Dr Nigel Blackburn, Director, Drug Development, Cancer Research UK, welcomed the fact that EAMS is improving access.

But with the longest EAMS period to date standing at four months, he questioned the extent of the benefits, saying, "Can we make the process simpler? The example of Keytruda shows it is complicated to go through."

Dr O'Connor suggested the short EAMS periods are a reflection of the learning curve of implementing the scheme and noted it is open for companies to apply for PIM designation earlier in development than has been the case to date. **"We are open to looking at Phase II data – you have got to demonstrate a positive benefit against risk rather than to have reached a particular stage of development," Dr O'Connor said**.

Having the confidence to apply earlier may be a function of how much investment has gone into Phase II development, believes Dr Hudson. "Better Phase II data would help the whole decision-making process from a regulatory point of view," he said.

For Professor Sarah Garner, Associate Director, Science Policy and Research, NICE, EAMS should not be judged solely on the length of the EAMS access period, but over a longer timeline. "The question is, does it speed up downstream issues once the marketing authorisation application is in place?" she said.

It is also important to view EAMS in the context of other initiatives to promote early access, said Dr Crabb. "For example, Adaptive Pathways, modification to the Cancer Drugs Fund, and so on, are all helped by EAMS."

Supporting innovation and optimising development pathways

EU early access tools: Overview

The EMA and Europe's national competent authorities for regulation of medicines are devoting considerable effort to improving access to beneficial treatments for the right patient groups.

Balancing benefit and risk, access should be at the earliest appropriate time in a product's life span, and should be sustainable, both for healthcare systems and product developers.

Given this, these efforts by regulators must be placed in the context of the many stakeholders that are involved in bringing about patient access, said **Robert Hemmings, Manager, Licensing Division, MHRA; member of the CHMP and chair of CHMP's Scientific Advice Working Party (SAWP)**, in an overview of early access tools. "A scientific opinion from the CHMP is not equivalent to access," Mr Hemmings said.

Patient access must be balanced against evidence generation. It is important that comprehensive evidence on efficacy and safety is ultimately generated, even if data generated in clinical practice are used to supplement data generated in clinical trials. There is also concern that a focus on speed of patient access risks compromising the development of some promising medicines. "In other words, it is important that you don't go so fast that a medicine fails, which if it had got to Phase III stage would have been passed," said Mr Hemmings.

Supporting innovation to promote patient access and recognising importance of the commercial success of the life sciences sector in Europe is a central plank of the EU Medicines Agencies Network Strategy to 2020. In addition to making better use of existing tools, the agencies are weighing further incentives to promote innovation.

One area of focus is promoting prospective dialogue in the scientific advice process, as is the case with the Adaptive Pathways pilot and the PRIME (Priority Medicines) scheme. A new procedure allowing companies to have joint meetings with EMA and national health technology assessment bodies (HTAs) has recently gone live. "The aim is to generate data for the needs of all stakeholders, to come up with a plan for development that meets the questions to be addressed by the different stakeholders," Mr Hemmings said.

There are issues to be finessed in coming up with joint development programmes, but said Mr Hemmings, "It is positive in terms of engagement and scientific advice, and we continue to work on it."

Another pillar of early access is the conditional marketing authorisation, and again here, it is important to engage in prospective dialogue through the scientific advice process. "Too often we are just presented with an initial development plan from a company. You need to tell me why you want a conditional marketing authorisation – which implies there would not be a comprehensive clinical evidence base, and if so, what is missing?" Mr Hemmings said.

The development plan must therefore also include details of how the missing information will be addressed through post-authorisation data generation. The requirements will vary depending on the specifics of each development programme and the evidence generated in clinical trials, and it might be helpful during scientific advice to outline different scenarios for the emerging evidence that could result in different requirements for post-authorisation evidence generation.

The Accelerated Assessment procedure can reduce time to market access by a number of months and regulators are keen to make more use of this procedure. However, there are additional challenges in developing risk management plans and setting out the post-authorisation plan under a restricted timetable. "In other words you need to get all your ducks in a row to make the accelerated pathway work," said Mr Hemmings.

In addition to optimising its own processes, the EMA wants to understand how they can help other stakeholders to speed up their processes too. Mr Hemmings suggested one way of doing this could be to reflect on the content of European Public Assessment Reports (EPARs). "A lot of man hours go into a regulatory assessment – so the question is, do we capture everything from an assessment in EPARs to make them as useful as possible to people downstream?" he said.

The Adaptive Pathways pilot and the PRIME scheme are described in detail below. However, Mr Hemmings drew the distinctions between PRIME and Adaptive Pathways and EAMS and PRIME.

While PRIME is a regulatory process that aims to provide early and enhanced scientific and regulatory support for promising new medicines that meet the criteria for accelerated assessment, Adaptive Pathways is a concept for multi-stakeholder discussion of evidence generation and iterative decision making that is likely to be targeted towards treatments in areas of high unmet medical need where usual methods for data generation and pathways for regulator, HTA and payer decision making are compromised.

EAMS is a national scheme for the UK which gives patients access to products that do not yet have a marketing authorisation, while PRIME is an initiative from EMA that provides regulatory support for development to get a marketing authorisation.

Regulators' efforts to speed up access are not solely concerned with changing procedures. There are also multiple initiatives including scientific research, for example into the use of modelling and simulation for planning, and perhaps even to replace clinical trials, and increasingly to understand and to manage uncertainty. In addition, EMA is working on extrapolation of evidence from adults to children, and supporting initiatives in the building of patient registries and increasing patient involvement in the regulatory process.

EMA's Adaptive Pathways pilot

Regulators learning

The Adaptive Pathways pilot is testing ways of reformatting clinical development pathways to support early marketing authorisation, reimbursement and access. The intention is that products are trialled in a specific patient sub population where the benefit – risk balance has to be positive, or approved on the basis of reliable early or surrogate endpoints.

Real world data can be utilised to complement randomised clinical trials, and to explore long term outcomes and effectiveness.

The Adaptive Pathways scheme is addressed in particular at therapies that serve an unmet need, but face additional hurdles in terms of patient access. For example, if such products were to be granted conditional marketing authorisation there may be challenges and delays in completing health technology assessments; it may be difficult to gather sufficient evidence because it is not appropriate or possible to run controlled trials; or in the case of cell and gene therapies, the effects of a single treatment are expected to persist over time, requiring long-term follow-up.

"Adaptive Pathways tries to address these issues by bringing in stakeholders early on, to design a smart development programme," said **Francesca Cerreta, Senior Scientific Officer, EMA**. There must be interaction between regulators, HTAs and, where appropriate, payers in selecting products and agreeing the development strategy and plan for real world data collection, with the aim of ensuring the evidence meets all their decision making needs.

Since the pilot started in March 2014 a total of 62 products have been submitted. Of these, 21 were selected for in-depth discussion with the company. Four submissions were from SMEs, six are orphan medicines, five are advanced therapy medicinal products (ATMPs) and five are cancer treatments. From the 21 candidates that made Stage I, 12 products were chosen for Stage II of the process.

There were three criteria for acceptance to the Adaptive Pathways pilot. First, there had to be an iterative development plan, second there must be a plan for in-market data collection, third the input of all stakeholders, and in particular HTAs, is fundamental. "If these criteria are not present, other support schemes are more suitable," Mrs Cerreta said.

One challenge to be addressed as any Adaptive Pathways products reach the market will be to control their prescription. The requirement for all treated patients to be in a registry provides some level of control. Another possibility could be a system of traceability modelled on that used for blood products, Mrs Cerreta suggested.

A variety of proposals for the collection of real world data were made in applications to the Adaptive Pathways pilot, including registries, using data from early access/compassionate use to supplement clinical trial data, and linking drug registries to risk-sharing schemes, such as pay-for-performance or annuity plans. "Real world data collection has to be a prospective plan," said Mrs Cerreta.

Collecting real world data must have minimum impact on clinical practice, and the data collected must be designed to be useful to patients and prescribers, and be communicated to them. The performance measures must be clear cut, for example, sustained virological response or survival rates, and be actionable, in terms of supporting reassessment of the benefit – risk, value and pricing and reimbursement. It is important companies understand that the value could go down as well as up following subsequent data collection.

While the real world data plan addresses the needs of downstream stakeholders, it cannot remove the uncertainty facing payers at the time of making coverage decisions. Given this, a managed entry approach is essential to the Adaptive Pathways paradigm.

Adaptive Pathways is "relevant only to a limited number of products," said Mrs Cerreta. Nevertheless it is needed because it addresses anticipated access issues for certain products by supporting design of a development plan that is more relevant to stakeholders' needs and optimises data acquisition so as not to expose patients to unnecessary studies.

Industry experience of Adaptive Pathways

One of the products going through Adaptive Pathways currently is IMCgp100, Immunocore's lead ImmTAC (Immune Mobilising Monoclonal T-Cell Receptor Against Cancer). In March 2016 it began a Phase I trial in the treatment of uveal melanoma, a rare disease in which tumours form in the tissues of the eye. The rarity of the condition means it is seldom diagnosed until after the tumour has metastasised, and as a result life expectancy following diagnosis can be as little as six months.

"We think [Adaptive Pathways] is the fastest route to get a potentially highly effective treatment to a very small group of patients," said **Dr Eliot Forster, Chief Executive Officer of Immunocore.** "The process is ongoing, and I hope it will continue to be fruitful. I would encourage those who have a medicine or other technology that will make a real difference for patients to join [Adaptive Pathways]."

IMCgp100 has been administered to more than 84 patients in a Phase I/II trial in melanoma. Uveal melanoma comprises approximately 3 percent of all melanomas. Forster said that in examining the Phase I/II clinical data it was noted that two patients with uveal tumours had responded to treatment with IMCgp100. "This is an ultra-rare condition, so the question was how to take this forward," Dr Forster said.

Engagement with the Adaptive Pathways pilot began in early 2015. "The sentiment about getting early access is what drives the conversation, and that's great for us to hear," said Dr Forster. The discussion on smart pathway design was not about procedures. "It was a scientific and drug development discourse – how to get the best data, what is an acceptable side effect profile, how to design the trial."

For Dr Forster the "really cool thing" is that discussions are collegiate. "In my past experience discussions with the regulators have been combative," he said. "There is enough time for a proper discussion and it's been very positive," he said.

As promised, there has been contact with HTA bodies, though there is more work to be done on this front, he said. There are challenges in trying to get an approval and agree reimbursement in parallel. There is a need for innovation in pricing and reimbursement models.

Endpoints mandated by regulators must be relevant to patients. "A joint commitment to patients needs to be threaded throughout: access to technology that saves lives is not currently fast enough," said Dr Forster. He added, "What I do like and has been a very good experience is the pragmatic use of processes already embedded in guidelines and regulations."

NICE perspective

The current evidence strategy for approving drugs is designed for regulation and not to support HTA and payer decisions. There is "an absolute need" to integrate the requirements of the stakeholders downstream of approval in drawing up the product development plan, said **Professor Sarah Garner, Associate Director, Science Policy and Research, NICE.**

"It's okay if the [HTA/payer decision] is a clear yes or no, but if there is decision uncertainty a product gets stuck – NICE can't take it forward," Professor Garner said.

The Adaptive Pathways framework involves no new tools or legislation, it merely rearranges the existing tools. There is however a new catalyst in Safe Harbour meetings which involve all stakeholders in without prejudice discussions of development options. "It's an opportunity to be open about uncertainty and agree how to manage it, to get provisional approvals and then collect confirmatory evidence," said Professor Garner.

She suggested that the Adaptive Pathways approach could be shaped to work at a UK national level. "There's nothing new particularly; you would get to a [NICE recommendation] anyway, but by moving the discussions to the beginning of the process rather than the end you ensure efficiency in the system."

NICE is also piloting UK Safe Harbour discussions for Stage II products in the Adaptive Pathways pilot. The discussions are being hosted by NICE's Office for Market Access, with inputs from MHRA, NHS England, patient organisations, clinicians and researchers. "Involving all stakeholders leads to an early understanding of what the evidence needs are," Professor Garner said. "It can be difficult to get everything on the table early when it is needed to ensure an appropriate development strategy and efficient process; Safe Harbour has taken that restraint away."

The fact that there have been 62 submissions to the Adaptive Pathways pilot implies the interest/need is there. However, applications were of variable quality, mainly because conditional approval is still seen as a "last ditch" regulatory route. It is therefore vital to have robust selection mechanisms.

Adaptive Pathways may not involve any new tools or processes, however, it does require stakeholders to change their culture. It is also resource-intensive, meaning that once the pilot ends there will need to be a fee for service, Professor Garner concluded

In the panel discussion, Dr Joy Duffen of The Cure Parkinson's Trust said Adaptive Pathways fits admirably with certain indications. However, she questioned the sole focus on innovative products, noting several re-purposed drugs coming through the pipeline hold potential benefits for Parkinson's disease patients, but would not be covered by Adaptive Pathways.

Dr Duffen noted there is a need to be aware that different patients have different perspectives. However, most want access to medicines earlier, but only if there has been a regulatory review that presents the risks and benefits.

For **Dr Christian Schneider, Director, National Institute for Biological Standards and Control (NIBSC)**, Adaptive Pathways represents a new culture. As former chair of EMA's Committee for Advanced Therapies, he was aware of the need for better patient access to medicines, especially in rare diseases, where randomised controlled trials are not feasible.

"But if we agree it is a good idea, we have to convince the assessors who look at the dossiers. I was one – they need training in assessing more focussed datasets and have a mindset on early access. The dossiers will be different to those they regularly see," Dr Schneider said. NIBSC will be developing regulatory science in support of earlier access, to complement the work MHRA is doing in this arena.

Dr Forster agreed that multiple convergent technologies are making the process of regulatory oversight more complex. However, the collaborative culture fostered by Adaptive Pathways and the ability to share information in the Safe Harbour discussion means it is possible to get everyone to the same level of understanding. "You gain by sharing very complex science," he said.

The new EMA's PRIME (Priority Medicines) scheme

The goal of EMA's PRIME scheme, launched in March 2016, is to provide early and enhanced scientific and regulatory support to promising new medicines that fulfil the criteria for accelerated assessment. There are no changes to the approval pathway and eligibility for PRIME is according to the existing Accelerated Assessment criteria.

"We are not building a new regulatory framework," said **Dr Jordi Llinares, Head of Product Development Scientific Support Department, EMA**. Rather the aim is to provide enriched support for development, leading to better informed development plans and submission of higher quality marketing authorisation applications. EMA committees will have greater familiarity with, and awareness of, products coming through the system, making for speedier reviews.

In addition, HTAs will be involved in ensuring development strategies deliver evidence required for reimbursement and pricing.

The review of applications for PRIME eligibility will be carried out by the SAWP and be approved by CHMP. Companies are required to demonstrate products have a high public health potential and represent a significant advance on currently available treatments.

Products at proof of concept stage will be assigned a CHMP rapporteur after PRIME eligibility confirmation. The rapporteur will be responsible for chaperoning a product through the EMA system, providing a single interface and opening up access to other EMA committees, if that is appropriate. "The early appointment of a rapporteur has been seen as a key feature of the scheme. I'm really convinced it will be a key feature of a life cycle approach, Mr Llinares said. "Knowledge will be gained throughout development by the network."

PRIME can be applied at different stages of development, with academic groups and SMEs that are most in need of support being able to secure PRIME designation at Phase I, and any sponsor once there is proof of concept.

At the time of the first submission deadline 18 applications had been received, of which 11 were from SMEs. "This was more than we were expecting and covered a wide range of therapeutic indications," said Dr Llinares. Most products were at proof of concept, and included two ATMPs.

By fostering better development strategies to help companies generate high quality data, PRIME will allow patients to benefit from therapies that may significantly improve their quality of life, as early as possible, Dr Llinares said.

The EMA does not currently have a limitation on the number of products that can be eligible for PRIME. The FDA's counterpart scheme, Breakthrough Therapy Designation has 120 submissions per annum. "We can cope with that," Dr Llinares said.

An ongoing dialogue with FDA about accelerated pathways aims to ensure respective schemes line up, to enable companies to progress products with both regulators simultaneously.

Industry experience with FDA's Breakthrough Therapy Designation: Case study – Approval of Blincyto

In common with EMA, the FDA too has a number of schemes that aim to expedite access, including accelerated approval, fast track designation and priority review. The Breakthrough Therapy Designation was added to this list as part of the FDA Safety and Innovation Act 2012.

Products receiving the designation get benefits including eligibility for priority review. In addition, there is intensive guidance on the development plan. "The aim is to expedite development when you have got remarkable clinical efficacy early in development for a product that treats a serious or life-threatening disease," said **Rhian Thomas, Executive Director, Global Regulatory Affairs, Amgen,** describing her experience of piloting the company's Blincyto (blinatumomab) through the Breakthrough Therapy pathway.

The product, for treating relapsed or refractory Philadelphia chromosome negative, B-cell precursor acute lymphoblastic leukaemia (ALL), is a bi-specific CD19-directed, CD3 T-cell engager, monoclonal antibody. It works by recruiting T-cells to destroy leukaemia cells. The basis for the Breakthrough Therapy Designation was a Phase II trial involving 189 heavily pre-treated patients. Of these, 33.3 percent showed a complete remission. "The complete remission rate was higher than all previously approved ALL single agents," Ms Thomas noted.

Breakthrough Therapy Designation is indication-, not drug-specific, and should be requested as soon as data showing significant clinical efficacy is available. The FDA reviews all requests within 60 days.

Breakthrough Therapy Designation involves a product being assigned a project leader within the FDA and allows companies to get timely advice from FDA senior managers and experienced reviewers. "It becomes a very interactive process," said Ms Thomas. "We worked with the FDA to identify data gaps and follow-up commitments. There were multiple interactions – without them it would not have been possible to do the BLA [Biologics License Application] in record time."

Amgen originally applied for Breakthrough Therapy Designation in 2013, but FDA said there was not enough data at that point. A second application in May 2014 secured Breakthrough Therapy Designation on 30 June and the BLA was submitted on 19 September.

With priority review, the FDA granted approval on 3 December 2014, more than five months ahead of the PDUFA (Prescription Drug User Fee Act) date. At 2.5 months, this was the fastest review of any BLA for a biological medicine, Ms Thomas said. The review started within three days of submission, with real time communication to deal with 250 questions. As the first bi-specific T-cell engager (BiTE®) antibody construct to come before the regulator, there was added complexity around manufacturing to be dealt with, and early inspections were arranged.

By comparison, Blincyto went through the standard review process in Europe (Amgen did not request accelerated assessment). The marketing authorisation application went into the EMA the month after the BLA was submitted to the FDA. Conditional approval in Europe was given in November 2015, almost one year after FDA granted approval.

"Breakthrough Therapy Designation is a good thing; there was transparency and collaboration on problem solving, but also sticking to regulatory standards and appropriate benefit – risk," Ms Thomas concluded.

Opening the panel discussion, **Dr Joep Muijrers, Partner, LSP-Life Sciences Partners,** said that many of the innovative products coming up for regulatory approval begin life in the portfolios of venture-funded biotechs. Given this, private investors should have an interest in accelerated access pathways. However, there is a low level of knowledge about these initiatives amongst his peers, Dr Muijrers noted.

This is a significant gap. "For me it's completely obvious having been here today. Of 700 companies we see each year, we invest in 1-2 percent. So there has to be a high unmet need and a clear development pathway," Dr Muijrers said.

Regulators and private investors would have a lot to learn from each other. VCs have significant influence over what products are developed and a good overview of new technologies that are in development. "Most innovative drugs start in SMEs – which are backed by VCs. If only for that reason, we as investors should be aware of what is happening at regulatory agencies, and vice versa," said Dr Muijrers.


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Appendix 1: Conference Programme

09:00 - 9:30	**Registration and networking**
09.30 - 9.45	**Welcome and introduction from the Co-Chairs**
	Dr Ian Hudson Chief Executive, Medicines and Healthcare products Regulatory Agency
	Alan Morrison Chairman, BIA Regulatory Affairs Advisory Committee, and Vice President, International Regulatory Affairs, MSD
09.45 - 10.30	**Innovation and accelerated access in the UK – Where are we today?**
	Sir Hugh Taylor Independent Chair, Accelerated Access Review
	Professor Sir John Bell Chair, Accelerated Access Review's Expert Advisory Group
10:30 - 10:50	**European perspective: Results of survey on early access schemes / compassionate use of new medicines**
	Kate Beaujeux Regulatory Affairs Senior Regional Director, Oncology, AstraZeneca
10:50 - 11:20	**Refreshments and networking**
11:20 - 13:00	**Review of the UK Early Access to Medicines Scheme**
11:20 - 11:40	**The Early Access to Medicines Scheme (EAMS): Two years on**
	Dr Daniel O'Connor Expert Medical Assessor, Licensing Division, Medicines and Healthcare products Regulatory Agency
11:40 -12:00	**Industry experience: Case study – Keytruda granted the first positive EAMS scientific opinion**
	Joanna Maitland Smith Executive Director Regulatory Affairs, MSD
12:00 - 12:20	**NICE perspective**
	Dr Nick Crabb Programme Director, Scientific Affairs, National Institute for Health and Care Excellence
12:20 - 12:40	**NHS England perspective**
	Malcolm Qualie Pharmacy Lead, Specialised Services, NHS England
12:40 - 13:00	**Panel Discussion / Q&A**
	Speakers from this session will be joined by **Steve Bates** Chief Executive Officer, BIA **Dr Nigel Blackburn** Director, Drug Development, Cancer Research UK
13.00 - 14.00	**Lunch and networking**

14:00 - 17:00 **Supporting innovation and optimising development pathways**

14:00 - 14:30 **EU early access tools: Overview**

Robert Hemmings
Manager, Licensing Division, Medicines and Healthcare products Regulatory Agency, Committee for Medicinal Products for Human Use (CHMP) member, and Chair, CHMP's Scientific Advice Working Party, European Medicines Agency

14:30 - 15:50 **EMA's adaptive pathways pilot project**

14:30 - 14:55 **Regulators learning**

Francesca Cerreta
Senior Scientific Officer, European Medicines Agency

14:55 - 15:15 **Industry experience**

Dr Eliot Forster
Chief Executive Officer, Immunocore

15:15 - 15:30 **NICE perspective**

Professor Sarah Garner
Associate Director, Science Policy and Research, National Institute for Health and Care Excellence

15:30 - 15:50 **Panel Discussion / Q&A**

Speakers from this session will be joined by
Dr Joy Duffen
The Cure Parkinson's Trust

Dr Christian Schneider

Director, National Institute for Biological Standards and Control

15:50 - 16:15 **Refreshments and networking**

16:15 - 16:40 **The new EMA's PRIME (Priority Medicines) scheme**

Jordi Llinares
Head of Product Development Scientific Support Department, European Medicines Agency

16:40 - 17:00 **Industry experience with FDA's breakthrough therapy designation: Case study – Approval of Blincyto**

Rhian Thomas
Executive Director, Global Regulatory Affairs, Amgen

17:00 - 17:30 **Panel Discussion / Q&A: What are the benefits of accelerated assessment in the EU?**

Speakers from this session will be joined by
Dr Joep Muijrers
Partner, LSP-Life Sciences Partners, Healthcare Investment

17.30 **Close**

Appendix 2: Panel Discussions – Key Points

A. The Accelerated Access Review

1. If the NHS was perceived to be unreceptive to innovation, this is not because there is a lack of understanding of the value of new technology. Healthcare professionals have many other things vying for their attention, making it hard to get innovation on the agenda. Targets revolve around indicators such as waiting times and number of patients treated, not whether hospitals are using the best products and making the best use of new technologies.
2. To introduce some headroom, it was considered necessary to work with the Academic Health Science Networks to demonstrate value and provide support for structural change that encourages adoption. Chief among these structural issues are the silos of decision makers in Clinical Commissioning Groups, NHS England and primary care. The incentives facing these bodies are not aligned and more could be done to make the whole pathway work.
3. Involvement of patients will be central in advancing the access agenda. Patients should take part in horizon scanning, in suggesting endpoints that are meaningful and ensuring regulators are aware of this. Patients can be powerful drivers for adoption, but they need information about drugs and technologies coming through the system and what NICE has recommended. Patient representatives now sit on hospital boards, NICE and the MHRA promote patient involvement and the EMA has allowed patient testimony to be heard when making decisions on approvals. Structures are being put in place to support patients in giving evidence and there is more effort to include – the necessarily subjective – patient viewpoint into decision-making.

B. Compassionate Use

1. The wave of innovation has put the spotlight on compassionate use and prompted an investigation of how this long-standing mechanism is being applied and how it could be optimised. A pan-European survey of pharmaceutical companies has shown that variations in applying the legislation from one Member State to another are not only leading to unequal access for patients, but also means programmes are bureaucratic and time-consuming for companies to set up. There is no consistent approach on the timing of various inputs, or on reimbursement (or not). In addition to the variation between countries, different companies have different Compassionate Use policies.
2. Compassionate Use programmes could be applied in concert with other access tools such as the EMA's PRIME scheme and the Adaptive Pathways pilot, and should be systematically used as a source of real world evidence.
3. The bureaucratic overheads and the fact the UK Compassionate Use schemes are not reimbursed makes it difficult for small biotech companies with innovative products to set up programmes.

C. Early Access to Medicines Scheme (EAMS)

1. It is now two years since the EAMS came into effect and speakers who have been involved in its design and implementation summarised their experiences and suggested possible changes and refinements.
2. For the MHRA, EAMS can be seen to be successful in providing earlier access for patients. Implementing the scheme required a significant investment in time and resources and following an independent review there are plans for future improvements.

3. The first product to go through the EAMS process was MSD's Keytruda. Although the outcome has been positive – with 500 melanoma patients getting access in advance of the EU granting marketing approval – a lot of work was required to secure the scientific opinion. This overhead comes at a very busy time for companies, when marketing authorisation applications are being prepared.

4. It is important to engage senior corporate leadership to be sure they understand the rationale for EAMS. With documentation in preparation for filing, it is a challenge to ensure consistency and to align the pharmacovigilance requirements and the risk management plans.

5. EAMS is important in allowing MHRA, NICE and NHS England to provide advice and guidance to companies, if not in parallel, then in an interwoven way. Drug developers understand what is expected of them and MHRA, NICE and NHS England have greater understanding of what is coming down the pipeline.

6. There has been some clever thinking to make EAMS work in parallel with regulatory processes at a European level.

7. EAMS is not funded, and in order to access the scheme companies must supply drugs free of charge. This makes it difficult for SMEs to participate and undermines one of the central objectives, which was to make the UK an attractive destination for carrying out clinical research. Other accelerated access schemes, such as those in France, Germany and Japan, offer better incentives for small companies.

8. Although EAMS has succeeded in providing earlier access, the longest EAMS period to date is only four months - some way short of the objective of advancing access by one year. There is provision for companies to apply for EAMS status earlier in development, but having the confidence to do so depends on building up experience in the use of the scheme. If more effort was devoted to Phase II development it would help the whole decision-making process, because the key requirement is to have demonstrated a positive benefit – risk profile, not to have reached a certain stage of development.

9. The success of EAMS should not only be judged in the light of the number of patients who get accelerated access before marketing authorisation, but also in terms of how going through EAMS helps to speed up access once the marketing authorisation is in place. The benefits for companies of parallel engagement, and what it means in term of access once the marketing authorisation is granted, should be more fully explained.

10. With much activity in train to promote early access, it is important to note that EAMS has been shown to support these other initiatives.

D. EU Early Access Tools: Overview

1. The EMA and Europe's national competent authorities for regulation of medicines are devoting considerable effort to improving access, both for patient benefit and to contribute to the commercial success of one of Europe's most important science-based industrial sectors. However, a regulatory approval does not equate to patient access and it is important that the requirements of other stakeholders are factored into the design of pre- and post-authorisation drug development programmes.

2. In working to foster earlier access, regulators are using existing tools and regulations, but reformatting clinical development pathways to allow for efficient marketing authorisations, reimbursement and commissioning. This optimisation is not solely about honing procedures, it involves discussion of the science and of how to get the best data.

3. A key development has been the greater collaboration with Europe's health technology assessment bodies, with companies now able to have joint meetings with HTA bodies and regulators, to discuss their respective requirements. The current evidence strategy does not necessarily support HTA and payer decision-makers and the ambition is that their requirements are integrated into the clinical development plan.

E. Adaptive Pathways pilot

1. Joint meetings of all stakeholders underpin the Adaptive Pathways pilot, which aims to provide a faster route to market for highly effective products, initially for a small patient sub population. The added catalyst here is the Safe Harbour meeting, at which all the development options can be discussed without prejudice, and integrated development plans to support decisions from multiple stakeholders can be smarter.
2. If the tools and regulations are the same, the culture is not: formal discussions are shaped by an informal Safe Harbour exploration. This is valuable because everyone can reach the same level of understanding when dealing with complex products; it is possible to gain time by sharing complex science so that everyone is aware of the potential impact.
3. There will be further issues to be dealt with once an Adaptive Pathways product is on the market. One is collecting real world data, another is controlling prescriptions so only the designated patient population is treated.
4. Patients do want earlier access, but only with proper regulatory oversight, and it is important to stress that while the considerations on benefits and risks might differ in a sub-population with highest unmet medical need, regulatory standards are in no way compromised.
5. The products in the Adaptive Pathways pilot address life-limiting conditions including cancer and critical limb ischaemia. However, there is also huge unmet medical need in long-term chronic conditions, where patients may be living with a disease for decades, and current treatments deal only with symptoms. These products would also fit under the scope of the adaptive pathways pilot providing the case for unmet need has been made.
6. While Adaptive Pathways acknowledges that randomised controlled trials may not always be possible or appropriate, for example to generate data post-authorisation, it will be important to convince assessors that are trained in assessing data from conventional data sources such as randomised controlled trials, that is the case.
7. New regulatory science is required to properly oversee complex therapies, both to assess the products per se and to design smarter trials.
8. The Adaptive Pathways pilot is intended to be end-to-end, that is, to factor in pricing and reimbursement. There is concern from companies that the quid pro quo for faster development will be lower prices, and that the initial price will be reduced once there is real world data and the patient population expands. There is however earlier market access, less upfront investment and the possibility for the price to be increased once the uncertainty has been resolved.
9. For all the harmonisation at a regulatory level, the requirements of national HTAs are different. Although there is some harmonisation in the methodology used, Europe's healthcare systems are all different and the decision-making process will continue to be country specific.
10. Once the pilot is over, there will be work to define how the Adaptive Pathways pilot fits into the overall regulatory jigsaw. In addition, scientific learnings from the pilot can be integrated generally into regulatory work.

F. The New EMA PRIME (Priority Medicines) Scheme

1. The PRIME scheme was launched in March 2016 to provide early and enhanced scientific and regulatory support to new medicines that are expected to deliver significant public health benefits and which meet the criteria for accelerated assessment.
2. The scheme uses existing tools and legislation, but through increased knowledge of the development plan seeks to proactively apply them in an optimised way. There will be more interaction with EMA committees, mediated through the earlier appointment of a CHMP rapporteur, who will take up responsibility for being aware of the product and its development, helping to identify issues that need to be discussed through scientific advice procedures and involving the different EMA Committees if that is appropriate, as soon as PRIME eligibility is confirmed.
3. Currently, two out of three development plans as submitted by companies will not generate sufficient data. This is more likely to be the case for trials sponsored by academic groups and SMEs, and PRIME will give small companies access to all-embracing support from Phase I. Other trial sponsors can apply once there is proof of concept.
4. PRIME is resource-intensive – given this, the EMA will focus the scheme on products that have yet to receive any approval, and not on variations to extend indications or repurposing of medicines.
5. PRIME has many features of FDA Breakthrough Therapy Designation. If it succeeds in accelerating approval to the same extent there will be significant patient benefit: a new type of leukaemia treatment and the first bi-specific monoclonal antibody to come before the regulators was approved one year earlier by the FDA, through the Breakthrough Therapy pathway, than by the EMA through its standard approval route.
6. The EMA is in discussions with the FDA about the various accelerated assessment schemes, in order to generate a mutual understanding of the application of standards.
7. Discussion of the benefits of accelerated assessment focus on patient access. However, accelerated access is also important in encouraging investors to put money into translating Europe's excellent science into new therapies and promoting a vibrant life sciences sector. Venture capital investors are influential in deciding what products SMEs develop. Given this, there should be an effort to ensure they are made aware of the various accelerated access schemes and become more involved as a stakeholder and partner.

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