

The Seventh Joint BIA/MHRA Conference

Innovation in Life Sciences in a Changing and
Dynamic Environment



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Introduction



It is a priority of the Medicines and Healthcare products Agency (MHRA) to support innovation across industry, SMEs, academia and healthcare, providing help to develop novel medicines, devices and manufacturing processes, through mechanisms such as the Early Access to Medicines Scheme and the MHRA Innovation Office, said **Dr Ian Hudson, Chief Executive of the Medicines and Healthcare products Regulatory Agency (MHRA)**, opening the conference.

With Brexit negotiations underway, a new Life Sciences Industrial Strategy in preparation and the government's response to the Accelerated Access Review pending, "We certainly are in a dynamic and changing environment," Dr Hudson said. "The number of delegates reinforces the need to collaborate for public health."



It is important not to lose sight of innovation when navigating this dynamic and changing environment, said **Alan Morrison, Chairman of the BioIndustry Association's (BIA) Regulatory Affairs Advisory Committee and Vice President, Regulatory Affairs International, MSD**. Better understanding of human genetics and biology means the industry is now "in a better place", with an increase in very innovative products, such as treatments for rare diseases and cancer immunotherapies. "Innovation is at the fore," Mr Morrison said.

Beyond the medicines themselves, the industry now faces the further challenge of developing biomarkers, companion diagnostics, sophisticated devices for administering drugs, and digital health apps to assist with self-care and generate real world evidence of the effectiveness of novel therapies.

The need for such innovation is a dynamic driving the industry, Mr Morrison said, welcoming delegates.



Accelerated Access Review recommendations and the Life Sciences Industrial Strategy

Opening Keynote Address

Whilst it is facing a series of pressures, there is a lot of which to be proud in how the National Health Service (NHS) is performing, most recently being ranked the best, safest and most affordable in a Commonwealth Fund Analysis of eleven national healthcare systems.



This is both “a reflection of the fundamental design strengths” and “a call to action for the further improvements we need to make,” said **Simon Stevens, Chief Executive of NHS England.**

Alongside its three key duties to care for patients, to provide equity of access, and do a good job for the taxpayers, the NHS is a supporter of British life sciences and recognises the contribution the sector makes to the health of the nation and the health of the economy, Mr Stevens said.

Despite its fundamental strength, the NHS faces three paradoxes that call for changes to how it operates.

First, as a nation we are getting healthier. There have been some “staggering” improvements in the past 15 years, such as the fall in deaths from heart disease and stroke, and the fall in lung cancer mortality. But despite better health, an ageing population and constrained budget growth mean the pressures on the NHS are as intense as they ever have been.

Second, the quality of care has never been better, but because the NHS is more transparent about the gaps and shortfalls, it may not feel like it.

Third, while public satisfaction with the NHS is currently higher, there is concern about its future.

There is an “underlying consensus” of how healthcare needs to change to address these paradoxes. “The fragmentation of the healthcare delivery chain is no longer appropriate to dealing with long-term conditions,” said Mr Stevens.

The NHS Five Year Forward View, launched in October 2014, sets out measures for integrating services and taking advantage of the opportunities that science and technology offer.

Innovation, including new medicines, has a role to play here, but first it is necessary to square the circle between funding pressure and paying for innovation, Mr Stevens told delegates, noting the seven percent increase in annual drugs spending which is two to three times greater than the growth in other areas of NHS spending. “That may be fine if we are getting value, but we need the [budget] headroom to be able to invest,” he said.

Amongst other measures, the NHS will use new freedoms it got from April 2017 to negotiate directly with companies.

As one example, Mr Stevens cited the “first of a kind” managed access agreement with Alexion Pharmaceuticals, broadening access to asofotase alfa (Strensiq) for treating the rare inherited bone condition, hypophosphatasia, which affects 1 per 6,370 of the population. The agreement addresses the lack of certainty about the health value of Strensiq by allowing a five-year period to gather real world evidence on how much patients benefit, before longer-term commissioning decisions are taken.

The patient’s role in promoting access

This example, and agreements for therapies for other rare diseases, underlines the growing influence of medical research charities and the voluntary sector in promoting access. “Groups associated with a particular condition have got a strong shared interest in new treatments getting approved. In specialised commissioning, there have been a number of cases of a charity being involved,” Mr Stevens noted.

It is also the case that where there is a large patient population, the use of an innovative medicine – no matter how effective – may need to be phased in to avoid busting the budget. One case in point are nucleoside analog drugs, which in effect are a cure for Hepatitis C infection. However, Mr Stevens said, there would have had to be “billions of cuts elsewhere” if everyone got access at once.

Under the phased introduction 10 percent of the infected population have been treated in the past year, resulting in an 11 percent fall in mortality and 50 percent fewer Hepatitis C-related liver transplants. “This is a big return in a short time,” said Mr Stevens. In the real world, phased introduction of anti-Hepatitis C drugs, has made sense.

NHS England has made arrangements for access to other innovative medicines and is also spending on other forms of innovation, such as microprocessor-controlled knee prostheses and tooth-in-eye surgery for cataract repairs.

Whilst appreciating that how the NHS deploys its purchasing power impacts the life science industry, these examples show “the NHS is putting its money where its mouth is”, and that from an industry perspective there are ways to make room for innovation, Mr Stevens said. Further headroom could come from devolving budgets to the regions, a move which is giving greater flexibility on where to invest and providing a tool to break down silos and promote integration.

The industry has argued that the rate of return on its investment is already subject to control via the Pharmaceutical Price Regulation Scheme. Under this voluntary agreement the industry has agreed to a cap on NHS expenditure on branded medicines over five years. The industry has made payments of £1.87 billion since the scheme came into effect in January 2014.

However, Mr Stevens said while it is right to have an overall framework, there is still a need to strike individual agreements.

Driving uptake

Access does not equal uptake, and in common with most other countries, there are geographical variations in prescribing and use of medicines in England. There is now a targeted programme to drive the uptake of treatments that are known to be effective. For example, in November 2016, NHS England said it would provide central funding for mobile electrocardiogram devices for identifying atrial fibrillation. The move is based on evidence that early detection of the frequently undiagnosed condition can help prevent strokes.

Another route to accelerating uptake of innovation is through the Academic Health Science Networks. Since they were set up in 2013, the networks have promoted the adoption of more than 200 innovations.

Uptake of innovation can be affected by the requirement to reshape care pathways. Mr Stevens said there is an onus on the industry and the NHS to make innovation simple to operationalise. “We need high-impact opportunities that can be scaled up. That’s the practical challenge for all of us,” he concluded.



Panel discussion and Q&A – Taking medicines through regulatory approval, health technology assessment and faster adoption of innovative healthcare across the NHS for the benefit of patients



There is a balance to be struck in terms of the life sciences sector's contribution to the economy and jobs and the NHS paying for new technologies. The aim must be to sustain the industry and keep the NHS at the cutting edge, **Dr Luisa Stewart, Deputy Director of the Office for Life Sciences**, told delegates.

The government is keen to work collaboratively with the sector in addressing the recommendations of the Accelerated Access Review and in implementing the Life Sciences Industrial Strategy, which is being developed by Sir John Bell in the context of the broader cross-government Industrial Strategy. Once the Life Sciences Industrial Strategy, with its focus on the themes of science, growth, the NHS, collaboration, digital and skills, is published, the industry will be invited to come forward with bids for a sector deal that builds on Sir John's vision.

In terms of the Accelerated Access Review, Dr Stewart said there will be a full response later in the year, when a number of actions will be proposed with the aim of coordinating and speeding up access to cost-effective technologies.



For **Dr Ian Hudson, Chief Executive of MHRA**, the Life Sciences Industrial Strategy and the Accelerated Access Review will set the stage for ever-closer working between the MHRA, the National Institute of Health and Care Excellence (NICE) and NHS England, "smoothing the path for rapid adoption". Areas where it is possible to make a difference include giving patients a greater role and the adoption of novel methodologies, such as new clinical trial designs.



Sir Andrew Dillon, Chief Executive of NICE agreed, saying the Life Sciences Industrial Strategy and the implementation of the Accelerated Access Review, "will unlock some important conversations, aligning ambitions across the life sciences sector, to get new products to patients."

The NHS is investing to stimulate innovation, but there should also be investment to ensure the consistent use of treatments that are known to work. "Innovation is needed to improve uptake and so stimulate new innovation," Sir Andrew said. He suggested that early discussions between companies, NICE and NHS England, to agree what needs to change in care pathways, would help with subsequent implementation.

NICE is ready to take advantage of the platform the Life Sciences Industrial Strategy and the Accelerated Access Review will provide. The whole system needs to be engineered for adoption, Sir Andrew said. There is no point in expediting the process up to NICE approval, only for medicines “to pile up at the front door of the NHS”. In addition, it would be helpful if discussions about price could happen further upstream, with companies being prepared to commit sooner, rather than being bid down at the end.



Greater patient involvement is central to identifying patients’ needs and improving outcomes, said **Hilary Newiss, Chair of National Voices**, an umbrella group representing 160 health and social care charities. From the perspective of patients’ groups the Accelerated Access Review recommendation that patients are centre-stage across the whole pathway will be the key to achieving this. “We regard innovation as a means to deliver better care and better patient-centred care,” Ms Newiss said.

Ms Newiss acted as patient champion in the drawing up of the Accelerated Access Review, making the case for bringing “what matters to patients” into the heart of innovation. The result is a series of ‘I Statements’ that set out patients’ and citizens’ expectations. “We want a commitment to make sure that implementation of the Accelerated Access Review makes the patient voice central,” Ms Newiss said. There must be transparency on the uptake of innovation to make it evident the system is equitable to all citizens, in all medical conditions.

Giving patients good quality information about what is coming down the pipeline is one way to pull forward the adoption of innovation. In addition, Ms Newiss called for investment to support commercialisation of digital technologies.



Jessamy Baird, Sanofi’s Director of Patient Access, said the company is very supportive of the Accelerated Access Review and the Life Sciences Industrial Strategy, and views the UK as a leading location for investment. However, as a global company, Sanofi has to balance the UK’s requirements for value against the need to support investments worldwide. This global context means it is difficult to make early pricing commitments to NICE. “The strategy for commercial entry evolves as the label evolves [...] that’s why we can’t commit earlier than we do,” Ms Baird said.

The products selected for the Early Access to Medicines Scheme have exemplified the need for pathways to be truly end-to-end – including working on uptake – to ensure patients get access to new and effective medicines. Based on this experience, it is hoped that the Accelerated Access Review will remove the current blockages which mean that after NICE has recommended a product it can take up to 9 - 12 months to get it on the formulary. As a result the UK lags in the uptake of new medicines in comparison to European neighbours. “This is a burden for the industry and the NHS,” Ms Baird said.

It should be possible to have early talks about what happens when a medicine ‘lands’, with industry being enabled to participate in discussions about new care pathways. At the same time, NICE could have a greater role in supporting uptake, Ms Baird suggested.

Keynote address – The future of medicines regulation



Lord O'Shaughnessy, Parliamentary Under Secretary of State for Health, opened by thanking the industry, and in particular the BIA, for the work it is doing in helping the government to shape the UK's future relationship with the EU in life sciences.

The government recognises preparations for Brexit start from close regulatory alignment stretching back decades. "There is trust and a spirit of cooperation – and an ongoing close collaboration – between the UK and the EU," Lord O'Shaughnessy told delegates. Brexit now presents a "once in a life time opportunity" to build on the UK's strengths as a scientific and regulatory centre of excellence. However, it would be "panglossian" not to recognise the complexity of the task or the scale of the challenge, Lord O'Shaughnessy said.

Three principles will underpin the government's position in negotiations on the future relationship of the UK with the EU:

- That patients will never be disadvantaged;
- That the UK will continue to play a leading role in public health;
- That the industry must be able to get its products into the UK market as quickly and as simply as possible, with the UK and Europe at the forefront of medical innovation.

No matter what the outcome of the negotiations, the UK "will always be a willing and reliable partner for Europe in patient safety and public health," said Lord O'Shaughnessy.

The position stated by Greg Clark, Business Minister and Jeremy Hunt, Health Minister in their joint letter to the Financial Times on 4 July, that there should continue to be a deep and close working relationship between the UK and the EU in medicines regulation, is "supported across government," Lord O'Shaughnessy said. The EMA and the UK are in a mutually beneficial relationship. Knowledge and innovation are not exclusive to one country and science collaboration needs to be maintained.

In many areas, medicines are based on global requirements, Lord O'Shaughnessy noted. "As part of the vision we will play a leading role in international fora," he said, calling on the industry "to lobby for what success looks like."

However, it is important also to be prepared for alternative scenarios. If it is not possible to secure collaboration with EMA, an independent regulatory system will be set up in the UK. This will be robust and effective, with no additional burdens.

As is the case currently, the UK will negotiate for zero tariffs on medicines as part of a new customs agreement with the EU. At the same time, the UK will pursue new trading relationships globally.

Vision for the future

Sir John Bell is in the process of finalising a Life Sciences Industrial Strategy that will sit within the broader cross-sector Industrial Strategy. Lord O'Shaughnessy said the government looks forward to working with the industry on implementing the strategy, with life sciences identified for priority review.

Turning to the Accelerated Access Review, the government wants its response to be "transformative" said Lord O'Shaughnessy. There are multiple and complex routes to market. "We want the response not to provide another layer, but a new direction." The Accelerated Access Review is "a really important piece of work" and there will be a full response later in the year.

In the meantime, Lord O'Shaughnessy announced a £86 million package of measures as the first step in taking the Accelerated Access Review forward. The funding is split between four areas:

- £39 million of funding to the Academic Health Science Networks, enabling them to assess the benefits of new technologies and support NHS uptake of those that deliver real benefits to patients according to the local need;
- £35 million Digital Health Technology Catalyst for innovators to match-fund the development of digital technologies;
- Up to £6 million over the next 3 years to help SMEs with innovative medicines and devices get the evidence they need by testing in the real world, building on existing opportunities such as the Early Access to Medicine Scheme;
- £6 million Pathway Transformation Fund, which will help NHS organisations integrate new technologies into everyday practice, including addressing practical issues such as training staff how to use new equipment.



Panel discussion and Q&A – Implications of the EU Referendum outcome: Practicalities, challenges and opportunities



Steve Bates, Chief Executive Officer of the BIA, opened the panel discussion by outlining the work the BIA and the Association of the British Pharmaceutical Industry (ABPI) have done to identify what the industry needs post-Brexit and in engaging the government to ensure the options for minimising disruption for the industry and patients were understood.

Much of this effort was carried out in a policy vacuum until Prime Minister Theresa May's Lancaster House speech on 17 January, in which she set out the government's negotiating priorities. But it was the EU/EMA communication to companies to prepare for there being no agreement that was the catalyst for discussions with the government to ensure there was an alternative to this extreme Brexit scenario.

That led on to Greg Clark and Jeremy Hunt's letter to the FT on 4 July, putting the UK's intentions in the public domain. A letter to the FT from the industry agreeing with the government's position followed, and it was then endorsed by the industry in Europe in an open letter to Mr Barnier and Mr Davis. The arguments the industry has been making "are at the core" of the government's position, Mr Bates said.

One aspect the BIA has emphasised is the threat to the UK's position as a natural launch market for new medicines. While the EU represents 24 % of the global market for pharmaceuticals, the UK is 3 %. "We are nested in a big market and that's why people come here," said Mr Bates. Pharmaceutical companies have to launch their products sequentially, and the simple fact is that the UK will be at the back of the queue unless it is as closely aligned as possible with the EU-27.



Andrew Gregory, Deputy Director of the Policy Division, MHRA, echoed the industry's position that there must be a deep and close relationship with the EU. The MHRA appreciates the dilemma facing industry at the current stage of the Brexit process. "You don't know what the future regulatory framework is going to look like, and you need to plan, but you don't know what for," Mr Gregory said.

Over the next few months MHRA will set out principles to guide the industry in a more concrete way, said Mr Gregory. The EU/EMA notices to Marketing Authorisation Holders advising companies to relocate marketing authorisations was predicated on an extreme version of a no deal scenario. "Even if the UK was a third party, there are scenarios in which you wouldn't need to take all the actions [...] so wait a while," Mr Gregory said.

In the event there is no deal, it will be incumbent on MHRA as regulator to make sure there are no gaps and to work to make the UK's smaller market attractive. Elements of this might include applying experience from the Early Access to Medicines Scheme and conditional licensing to expedite approvals, and to examine possibilities of cooperating with other regulators elsewhere. As one exemplar, the regulators in Australia, Canada and Switzerland recently cooperated on the approval of a generic drug.



While the industry is used to dealing with risk and uncertainty, Brexit represents a particular challenge, said **Dr Paul Huckle, Chief Regulatory Officer at GlaxoSmithKline**. Given this, Dr Huckle said he was “heartened” by Lord O’Shaughnessy’s commitment that the government will protect public health and maintain access to new and existing medicines. “This isn’t just a trade issue,” said Dr Huckle. “UK and EU patients need access: we must find a way [for this] to continue.”



As **Chair of the BIA’s Regulatory Affairs Committee and of the European Federation of Pharmaceutical Industries and Associations’ Brexit Taskforce, Alan Morrison** has been involved in work on Brexit scenarios from day one. The industry operates in an environment of extreme complexity, with long development cycles and a requirement for supply chains to be planned years in advance.

As a result, there is a need for clarity to ensure business continuity, Mr Morrison said, calling for a swift decision on the new location of the EMA; an agreement on future collaboration between the UK and the EU; and for a transition period. Whatever the terms of withdrawal, “It is not going to be easy because we are a long cycle business,” said Mr Morrison.

What should companies do now?

The government may have made its preferences clear, but with negotiations ongoing, it remains unclear how and when companies should activate their Brexit plans. The EU/EMA notices to make preparations to relocate marketing authorisations from the UK seems unequivocal, but it will be costly, and in the end may not be necessary.

As Dr Huckle noted, moving products from one regulatory system to another is a huge undertaking, not only for companies, but also for EMA. “This drives you to the logical conclusion that there has to be collaboration and transition,” he said.

Mr Bates agreed, saying while the only way to buy certainty is to invest, it is unlikely EMA can complete the work it has set itself by March 2019. Now there is constructive engagement, his advice is to hold off for this year and see what progress is made. Similarly, on the single market, there are signs that the government’s firm line that the UK will withdraw seems to be softening.

Mr Gregory too, advised companies to wait until the principles for the negotiations are agreed. In terms of testing and inspection, there are off the shelf options that could be rapidly deployed if necessary, and in any case a transition period now seems more likely. On marketing authorisations, the MHRA will aim to remain part of the peer review network. The extended timeframes in the EU approval process, in particular the time between EMA recommending approval and the European Commission giving the rubber stamp, means MHRA can ensure there is no time lag between an EU-27 approval and a UK approval.

How do the requirements of pharma and biotech industry get more attention in Brexit negotiations?

At £2.6 billion per annum, pharmaceutical exports from the North East of England are not far short of the £2.7 billion of Nissan cars exported from the region. Since Nissan has received assurances from the government, what can pharmaceutical and biotech companies do to attract similar attention?

One route will be through the Life Sciences Industrial Strategy. But it is important to recognise that whereas car production can be arbitrated to the lowest-cost location, the UK is positioned to compete globally for pharmaceutical R&D and manufacturing investment, with an attractive fiscal environment, a high level of skills and a track record. This will remain the case after the UK leaves the EU. “The expertise and capacity won’t walk out of the door because of Brexit,” Mr Bates said.

Sustain the lobbying

Now the industry has the attention of government, it is critical to maintain the momentum. Suggestions for how to do this include:

- Draw up a series of specific messages from sub sectors and specialist areas, such as cell and gene therapy;
- Get the issue of medicines regulation on the European Commission’s agenda by explaining the mutual dependence and why the EU-27 need a deal with the UK;
- Ride the coat tails of EMA’s relocation to force a debate not just on where the agency resides, but how European medicines regulation will work in practice if the MHRA was no longer able to make its current significant contribution;
- Strengthen the understanding of the UK government and the EU-27 about what is at stake and what outcomes the industry needs by drawing up more data-driven scenarios;
- Keep stressing why regulatory alignment and cooperation is important to patients in the UK and the EU-27.



Personalised medicines and companion diagnostics in an evolving regulatory framework

The new EU in vitro diagnostic medical devices Regulation: Overview and expectation for the regulation of companion diagnostics



Companion diagnostics that indicate if a patient is likely to respond to a medicine are central to delivering the clinical and commercial value of innovative targeted medicines. As **Stephen Lee, Biosciences Team Manager in the MHRA Devices Division**, described, big changes are in the pipeline on how companion diagnostics are regulated, following the entering into force on 25 May of the new EU medical devices Regulations.

The new rules, which will see a change from a largely self-certified system to one with far greater oversight, will not fully apply to medical devices until May 2020 and to in vitro diagnostic medical devices (IVDs) by May 2022. Devices covered by the Regulations include products for the delivery and administration of medicines, digital health apps, and diagnostic devices including ones based on next-generation DNA sequencing and bioinformatics.

Highlights of the new Regulations

A new rules-based risk classification for IVDs means that in future 80 - 90 % of devices will need to go through Notified Bodies designated by EU Member States. To back up this greater role, Notified Bodies are developing more expertise. The European Commission is setting up reference laboratories and expert panels. At the same time, companies will be required to provide more evidence and documentation on the performance of a device.

One objective of the Regulations is to secure the supply chain and prevent counterfeit or non-qualified devices getting into the system. To achieve this, regulatory responsibilities have been broadened from a focus on manufacturers to include authorised representatives, importers and distributors – who are collectively termed ‘economic operators’. Reinforcing this move to ensure the integrity of the supply chain, there will be a requirement for traceability through unique device identification and greater market surveillance/post market surveillance.

There will also be greater oversight of devices that are put into service in laboratories but not placed on the open market, including devices made or modified and used within a health institution.

Companion Diagnostics

Of particular interest to the pharma and biotech industry, the new EU IVD Regulation includes a new definition of, and assessment route for, companion diagnostics. According to the definition, a companion diagnostic is a device which is essential for the safe and effective use

of a corresponding medicinal product, to identify before and/or during treatment patients who are most likely to benefit from the drug in question, or to identify patients at risk of a serious adverse event. The definition covers diagnostics used to stratify patients in clinical trials.

The rules on conformity assessment will require interaction between a national medicines regulator and a Notified Body. Handily, in the case of the UK, both sit under MHRA, Mr Lee noted.

According to his interpretation of the conformity rules, Mr Lee said that following an analytical study, the clinical performance of a proposed companion diagnostic could be tested during Phase II/III trials. The medicines regulator will give an opinion on the suitability of the test for use with the corresponding medicinal product to feed into the Notified Body's review, hopefully with coordination between the two, so that the medicine and accompanying diagnostic are approved at similar times.

Mr Lee set out the general requirements for IVD performance studies, the specific requirements relating to companion diagnostics and the different stages of the application process (these can be seen in the slides presentation).

The diagnostics industry "has got a lot of regulations to get to grips with," Mr Lee said. The MHRA will soon publish guidance on co-development of medicines and IVDs. For help in navigating the new rules, companies should seek early advice from MHRA and can approach the MHRA Innovation Office.

Pursuing precision in immuno-oncology – Biology, big data and biomarkers



The remarkable activity of MSD's pembrolizumab (Keytruda), both as a monotherapy and in combination with a variety of other types of cancer therapies, highlights the need for companion diagnostics that will give patients, physicians and payers a rational means of assessing the best regimen, as **Dr Tom Lillie, Vice President, Head of European Clinical Development at MSD**, described to delegates.

While to date pembrolizumab has shown an effect as a monotherapy in more than 20 tumour types, the level of response varies, with Hodgkin's lymphoma, for example, showing a complete response, whereas ovarian cancer has a low response. Pembrolizumab has also demonstrated better overall survival in both first and second line treatment of non-small cell lung cancer, melanoma and cancer of the bladder.

Building on such results, MSD now has more than 480 clinical studies underway, the largest PD-1/PD-L1 check point inhibitor programme in the industry. At the same time, the company is working to understand the side effect profile of pembrolizumab. Although effective, tumours can develop mechanisms to circumvent check point blockade and as a result the clinical trial programme involves assessing combination therapies to overcome resistance.

Such combinations are showing response rates of 60 - 70 - 80 %. "There are multiple [combination] strategies that may work, the question is, can we put them in framework?" Dr Lillie said. Such a framework would encompass different regimens, including T-cell priming, inhibiting targets in the microenvironment of the tumour that allow it to suppress the

patient's immune system, and the direct killing of tumours with products including traditional chemotherapy, tyrosine kinase inhibitors and oncolytic viruses.

Dr Lillie said there are encouraging signs of efficacy of pembrolizumab/chemotherapy combinations in non-small cell lung cancer and triple negative breast cancer. This has prompted moves to reopen the "lexicon of all cancer treatments" to see if they work with PD-1 inhibitors, and to test PD-1 inhibitors with compounds that previously failed in clinical development.

There are also encouraging responses in studies combining pembrolizumab with other immune modulators. For example, combining the IDO (indoleamine 2,3 dioxygenase) inhibitor epacadostat (which like pembrolizumab inhibits a pathway used by tumours to escape detection by T-cells) with pembrolizumab has been shown to boost overall response rates in melanoma by 58 %.

In renal cell carcinoma, combining pembrolizumab with the tyrosine kinase inhibitor axitinib induced an overall response rate of 71 %, compared to 32 % for axitinib alone. Meanwhile, the combination of pembrolizumab with the oncolytic virus T-Vec has led to remarkably high response rates in melanoma.

The challenge now lies in bringing these positive findings in combination therapy into a scientific rationale, enabling the development of biomarkers that will ensure patients are given the best combination.

Multiple biomarkers predict who will respond to pembrolizumab, including expression of PD-L1 and PD-L2 ligands on a tumour; gene expression signatures that indicate whether a tumour microenvironment is immunogenic; and an increase in antigen presentation due to a high DNA mutation load.

All these biomarkers are predictive, but no single one works across all tumours in all patients. "The biology of tumour immune response is complicated," said Dr Lillie. "Trying to go for a single biomarker won't work." MSD's vision is to develop multiplexed diagnostics that identify the option most likely to benefit the patient. Such tests would then underpin a decision tree allowing for the precision use of immuno-oncology products. The currently approved PD-L1 biomarkers are a starting point, but more complex markers of tumour inflammation, mutational load and the resistance profile of a tumour, are needed to underpin a truly precision approach.

That will require translational biomarker research to be integrated into clinical trials and for the use of clinical genomics to become routine practice. The need for multiple biomarkers raises questions of whether the current regulator/payer paradigms are able to support a precision approach in immuno-oncology, Dr Lillie concluded.

Enhanced support for the development of promising new medicines: PRIME one year on

Regulators' learning

The Priority Medicines (PRIME) scheme was launched by EMA in March 2016, building on the existing regulatory tools to accelerate the development of medicines with the potential to make a significant clinical impact in areas of unmet medical need, and to support patient access to these innovative products.



The “badge” of PRIME to a candidate medicine is a written confirmation from EMA of eligibility to the scheme and the potential for accelerated assessment at the time of application for a marketing authorisation, said **Rob Hemmings, Manager, Licensing Division, MHRA; member of the EMA's Committee for Medicinal Products for Human Use (CHMP) and Chair of CHMP's Scientific Advice Working Party.** In addition to demonstrating the unmet medical need, applicants must provide a scientific justification that the unmet need might be addressed based on early clinical data to secure eligibility. Sponsors of eligible products are then assigned a CHMP and/or CAT Rapporteur and subsequently invited to a kick-off meeting with multidisciplinary experts from the EU network to discuss development plans.

By the first anniversary of the launch of PRIME there had been 108 requests to enter the scheme, of which 91 had completed assessment of eligibility and 20 were successful. More than 50 % of applications were from SMEs, with submissions coming in at a rate of 8 - 10 per month. “There was overall a good quality of applications in the first year,” Mr Hemmings said.

While 70 % of applications were in oncology/haematology, a fairly broad spectrum of conditions and of different types of products were covered, with 34 % categorised as Advanced Therapy Medicinal Products.

The assessment of eligibility for PRIME designation is a short, lean, 40-day process involving multiple EMA committees. This includes a PRIME Oversight Group, which looks at issues arising from a policy perspective. Issues over which the group has deliberated include permitting entry regardless of the stage of development. Since the aim of PRIME is to enhance support to optimise development plans for early stage products, it would seem on the face of it that later stage products are not eligible. But, said Mr Hemmings, “There are cases where post-authorisation activities look so complicated we think even though [a product] is late stage, additional regulatory support including appointment of Rapporteur can add value.”

There have been instances of EMA receiving a PRIME application in a condition in which other products are known to be in development. However, Mr Hemmings noted, the unmet medical need is there until a product is approved, and given this, the second or third application in a class could still be eligible for PRIME.

Entry points to PRIME

There are two points of entry to PRIME, with SMEs and academics able to apply once they have proof of principle in Phase I, while any sponsor can apply once they have reached Phase II proof of concept. By the end of the first year of the scheme, EMA had received five applications at proof of principle, of which only one was assessed as having sufficient data to qualify for PRIME.

Reasons for denying PRIME designation to products with proof of concept included trial design issues; a failed study; inconsistency of results across studies, study groups or endpoints; a claim in a subgroup of patients not being sufficiently justified; issues with the heterogeneity or stage of disease at baseline; and the comparison of study data to inadequate historical controls.

There have been five re-submissions, but the products have again failed to secure PRIME eligibility. In one case there was no new data, for three there was limited new data and for one the programme had become too late in development for value to be added. Mr Hemmings said that different reviewers are appointed to assess re-submissions, adding, "it is important to bring new evidence, not just re-discussion."

The kick-off meetings, taking place around four months after a product has received PRIME designation, give sponsors the opportunity to get access to the full range of EMA Committees expertise. "We hold a broad discussion on development and regulatory strategy to raise awareness of issues and develop a plan for future regulatory interactions," Mr Hemmings said. This includes aspects that may not be on a company's horizon at this point, such as GMP inspections, the risk management plan (RMP) and interactions with health technology assessment (HTA) bodies and other post-approval stakeholders.

Companies submit a briefing document three to four weeks in advance of the kick-off meeting. This informs an internal EMA teleconference and the drawing up of a tailored agenda for the meeting. Following the kick-off meetings, there have been 11 requests for enhanced scientific advice relating to seven products.

On 19 May, the EMA held a workshop on the first anniversary of PRIME to discuss experience of the scheme to date with the industry. Based on the feedback EMA is looking at ways to provide more comprehensive explanations of why a product has been rejected and working on further improving interactions to ensure EMA can get updates from applicants and to allow applicants to interact with the Rapporteur outside formal Scientific Advice procedures, in particular towards the time of marketing authorisation.

Having post-authorisation discussions in advance of approval, "will be one of the most interesting challenges for the PRIME scheme," Mr Hemmings said. There are a couple of products where post-authorisation work is under discussion.

Industry experience of PRIME: Case study 1 – Gene therapy for the treatment of haemophilia A



Chay Morgan, Head of EU Regulatory Affairs at BioMarin, described the company's experience of applying for PRIME designation for BMN 270, a gene therapy for treating the inherited blood clotting disorder haemophilia A. While plasma-derived or recombinant forms of the missing Factor VIII coagulation factor are available, they must be administered by intravenous injection, either at the time of a bleed and if undergoing surgery, or in severe cases prophylactically, to prevent spontaneous bleeds.

As a single gene defect, haemophilia A is well-suited to a gene therapy approach, Mr Morgan noted. "There is the potential for continuous endogenous production of Factor VIII, altering the phenotype and eliminating the need for frequent infusions."

BMN 270 is an AAV5-based gene therapy that transduces liver cells, resulting in expression of a specific liver promoter. The product is administered by a single intravenous dose and is designed to promote stable and potentially life-long expression.

The PRIME designation was awarded to BMN 270 on the basis that there is an unmet medical need to stop spontaneous bleeds and because the company had Phase I data showing expression of Factor VIII in the normal range.

Why apply for PRIME designation for BMN 270?

The goal of PRIME – to get really innovative products to patients sooner – fits with BioMarin's mission of developing treatments for rare diseases, and the scheme offers important benefits, Mr Morgan said. The opportunity that the kick-off meeting provides to have a holistic and strategic dialogue on the development plan and regulatory strategy with senior regulators and the possibility of accelerated assessment are "real attractions."

After applying for PRIME designation in November 2016, BMN 270 was accepted in January 2017, with the kick-off meeting taking place on 10 April. In parallel, BioMarin sought Protocol Assistance, and the Protocol Assistance letter was signed off in May.

The experience was very positive, Mr Morgan said. There was a good interaction with the Rapporteur, which enabled BioMarin to maximise the value of the kick-off meeting and get a clear understanding of what was required. At the same time, there was useful dialogue around what was in the scope of PRIME and what fell into Scientific Advice/ Protocol Assistance.

Industry experience of PRIME: Case study 2 – Aducanumab for Alzheimer’s Disease



For Simon Bennett, Regulatory Policy Director at Biogen, the potential benefit of receiving PRIME designation for aducanumab, currently in Phase III development for the treatment of Alzheimer’s disease, is the added value of accessing a number of EMA tools under a single scheme.

Following the application to PRIME in April 2016, aducanumab was accepted in May, the rapporteur assigned and the kick-off meeting took place in September. From the start, the dialogue has been very constructive, Mr Bennett said. “There is definite value in having a dedicated EMA contact who is always available to answer questions.” A further benefit is that PRIME allowed Biogen to integrate other aspects such as manufacturing and early engagement with value and access stakeholders into the plan.

“The kick off meeting was good with full engagement by the EMA and the aim to try and facilitate a smooth regulatory path and to identify any problems,” said Mr Bennett. The post-authorisation strategy was a key element of the discussion, an aspect that is important for a treatment that has the potential to address unmet need in a large patient population.

In terms of potential improvements based on the experience to-date, the ability to have informal discussions with the Rapporteur to identify areas/concerns that should be raised through scientific advice would be helpful. Although it is EMA’s preference to work at a centralised level, Mr Bennett believes it is important that the option of access to national expertise in specific areas should remain available in PRIME.

Looking to the future, Mr Bennett said the umbrella which PRIME provides to bring together HTA bodies, patients groups and EMA committees during development will be important in making aducanumab available to patients. “As a company, we are very excited to be in PRIME and are pleased with progress to-date, and the ability to engage different stakeholders with the scientific rigour necessary to meet all stakeholders’ needs,” Mr Bennett concluded.



The research charity perspective on PRIME



Because the burden of Alzheimer’s disease is so great, new disease-modifying treatments that – on the face of it – lead to modest improvements could have a significant impact for individuals and society, said **Dr Matt Norton, Director of Policy and Strategy at Alzheimer’s Research UK**. Delaying the onset of dementia by two years would mean there are 400,000 fewer cases by 2050; a delay of five years would mean 650,000 fewer cases. “Set against the massive unmet need, the potential for disease-modifying therapies is huge,” Dr Norton said.

Given this, factoring the views of patients’ groups and medical research charities into PRIME discussions on shaping the development path to deliver data for post-authorisation discussions, is hugely important. Patient involvement should allow aspects including the outcomes that matter most; what constitutes success from a patient’s perspective; and patient preferences on the benefit - risk, to be considered.

It is apparent that we do not understand enough about patient preferences in relation to the types of outcomes that would be most important for new treatments to deliver. To fill this data gap, Alzheimer’s Research UK is setting up a project with University of Edinburgh looking at the outcomes that matter most to people who are known to be at risk of developing Alzheimer’s disease. This will, for example, provide inputs for HTA assessments of cost-effectiveness. Beyond that, there will be challenges of affordability, with a high price per patient and a large patient population. There may also be the need to change care pathways. “It will not be easy to get access,” said Dr Norton.



Panel Discussion and Q&A on PRIME

Delegates posed questions to the Panel comprised of Rob Hemmings, Manager, Licensing Division, MHRA, and Chair of CHMP's Scientific Advice Working Party; Chay Morgan, Head of EU Regulatory Affairs, BioMarin; Simon Bennett, Director, Regulatory Policy, EU and Global Emerging Markets, Biogen; and Dr Matt Norton, Director of Policy and Strategy, Alzheimer's Research UK.

Q: How does PRIME compare/contrast with FDA's Breakthrough Therapy Designation?

A: EMA has made a comparison of the schemes: the PRIME scheme reflects the EU regulatory framework. However, a presentation at the PRIME workshop in May comparing experience of PRIME versus Breakthrough Therapy Designation pointed to more flexibility in interactions in the FDA scheme.

Q: Do kick-off meetings involve HTA bodies and patients' groups?

A: No, HTA bodies and patients are not involved as yet, though they are a subject of the meeting. Companies are asked about interactions to date and the kick-off meeting is the forum for planning future interactions.

Q: How do companion diagnostics fit into the PRIME scheme?

A: There have to be conversations about companion diagnostics that are under development, but this is to understand how they perform and sit alongside the medicine. An EMA concept paper is due soon on issues around the co-development of companion diagnostics.

Q: Can MHRA's Early Access to Medicines Scheme learn from PRIME?

A: There is a shared intent of accelerating access, but the two are different in scope, one being a national scheme for medicines not currently authorised but having completed confirmatory trials versus a centralised scheme to support marketing authorisation. The three years of experience of EAMS provides a pathfinder for multi-stakeholder engagement that is required to ensure access and uptake.

Q: Could PRIME be used to accelerate access to a drug that is being repurposed?

A: If there is an unmet medical need such an application would be eligible. That a drug is licensed by another company in one condition does not mean that it may not address an unmet medical need in another condition.

Q: Given that the ability to apply for PRIME at proof of principle was intended to attract SMEs but only five have applied, what can be done to get more to come forward?

A: There needs to be awareness raising about PRIME. There are a lot of SMEs, often with only one product and the timing needs to be right. Small companies represent more than 50 percent of applications at proof of concept stage.

Q: Are the short PRIME timelines comfortable?

A: Yes, they are workable and predictable, but do require companies to involve parts of the business that would typically not have a role in progressing products at Phase I/II. Companies have reported that PRIME has been a good "forcing function" to get the whole organisation to engage at an earlier stage in the development process.



For photos from the day, check out BIA Flickr <http://bia.me/BIAMHRA17>

