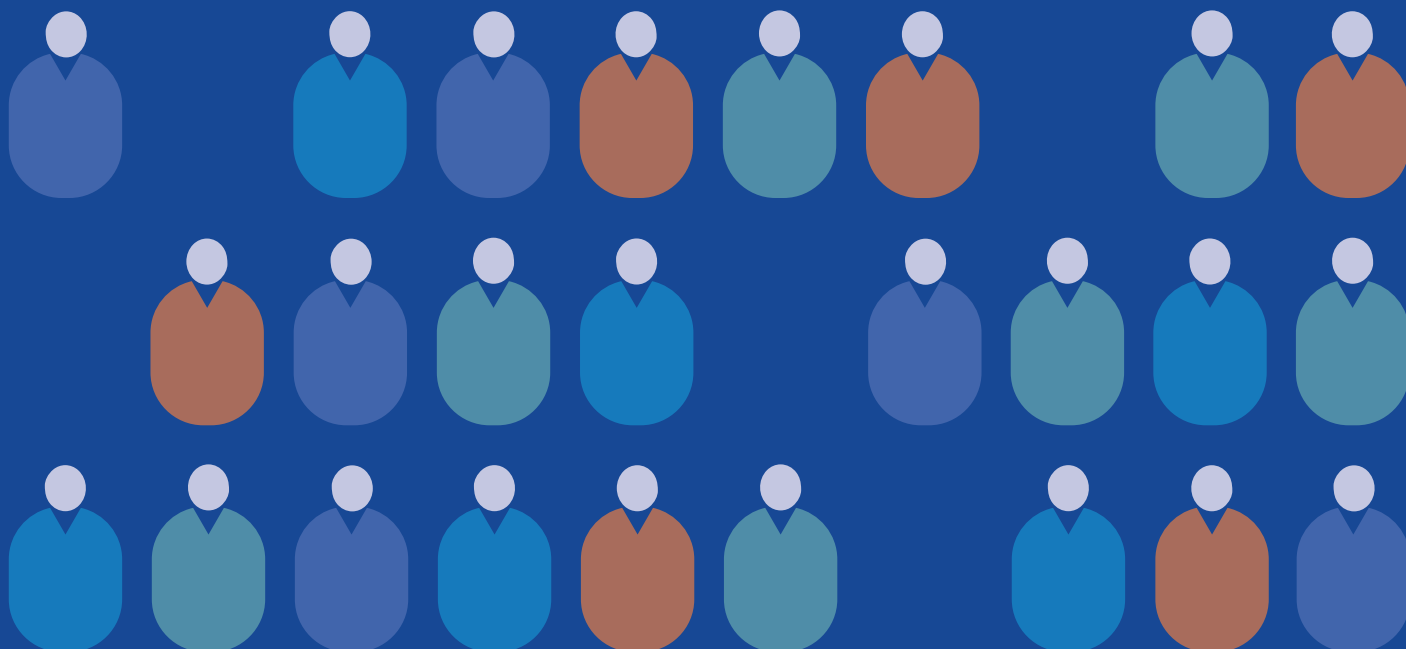




EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Adaptive Pathways Workshop

Report on a meeting with stakeholders held
at EMA on Thursday 8 December 2016



Introduction

Implementing the adaptive pathways concept

- ▶ Focus on areas of high unmet medical need
- ▶ Identify small populations with severe disease where benefit-risk balance may be favourable
- ▶ Identify in advance areas where real world evidence will be appropriate to support clinical trial data
- ▶ Involve stakeholders, such as HTA bodies, early in the development process
- ▶ Maintain highest standards of benefit-risk assessment

Over the past few years, the adaptive pathways concept has generated considerable interest among key stakeholders.^{1,2,3} While some stakeholders have supported the concept because of its potential to improve access to new medicines, others have voiced concerns about its possible impact on standards of evidence for medicines approval in the EU.

Much of the discussion has centred on how data are to be generated and evaluated for new medicines and whether the goals of adaptive pathways are indeed feasible. Crucially, there remains some confusion as to what the concept is, its scope and its aims, and how it is to be applied in practice.

The adaptive pathways concept is an approach to medicines approval that aims to improve patients' access to medicines in cases of high unmet medical need. To achieve this goal, several approaches are envisaged: identifying small populations with severe disease where a medicine's benefit-risk balance could be favourable; making more use of real world data where appropriate to support clinical trial data; and involving health technology

assessment (HTA) bodies early in development to increase the chance that medicines will be recommended for payment and ultimately covered by national healthcare systems.

Adaptive pathways are usually described as a concept or an approach, because they are not new regulatory routes for medicines and indeed are not strictly speaking separate pathways. Medicines are still expected to be authorised through the same legal routes as before and to benefit from incentives (such as orphan designation) that are already in place. In addition, the same standards of benefit-risk assessment will be maintained. The difference is in the way medicines development will be planned to better meet the needs of patients with serious conditions for whom there may be no suitable treatments.

Between 2014 and 2016, the European Medicines Agency (EMA) conducted a pilot project to explore how the adaptive pathways concept can be applied in practice and to develop guidance for companies considering using the adaptive pathways approach.^{4,5} Following the pilot, EMA and the European

1 Davis C, Lexchin J, Jefferson T, et al. "Adaptive pathways" to drug authorisation: adapting to industry? BMJ 2016;354:i4437.

2 Ermisch M, Bucsis A, Vella Bonanno P, et al. Payers' Views of the Changes Arising through the Possible Adoption of Adaptive Pathways. Front Pharmacol 2016;7:305.

3 Bouvy JC, Jonsson P, Longson C, et al. Health Technology Assessment in the Context of Adaptive Pathways for Medicines in Europe: Challenges and Opportunities. Clinical pharmacology and therapeutics 2016;100(6):594-97.

4 European Medicines Agency: EMA/276376/2016 - Final report on the adaptive pathways pilot. http://www.ema.europa.eu/docs/en_GB/document_library/Report/2016/08/WC500211526.pdf Accessed 3 January 2017.

5 European Medicines Agency: EMA/527726/2016 - Guidance for companies considering the adaptive pathways approach. http://www.ema.europa.eu/docs/en_GB/document_library/Report/2016/08/WC500211526.pdf Accessed 3 January 2017.

Commission (EC) organised a workshop in London on 8 December 2016, attended by representatives of patients' and healthcare professionals' organisations, academia, pharmaceutical companies, HTA bodies and payers, national competent authorities and the European Ombudsman. The workshop tackled important questions from stakeholders,

including how to generate appropriate data to aid medicines evaluation and ensure that the highest standards for approval in the EU continue to be met.

This report reflects the main issues discussed during the meeting ■

Why adaptive pathways?



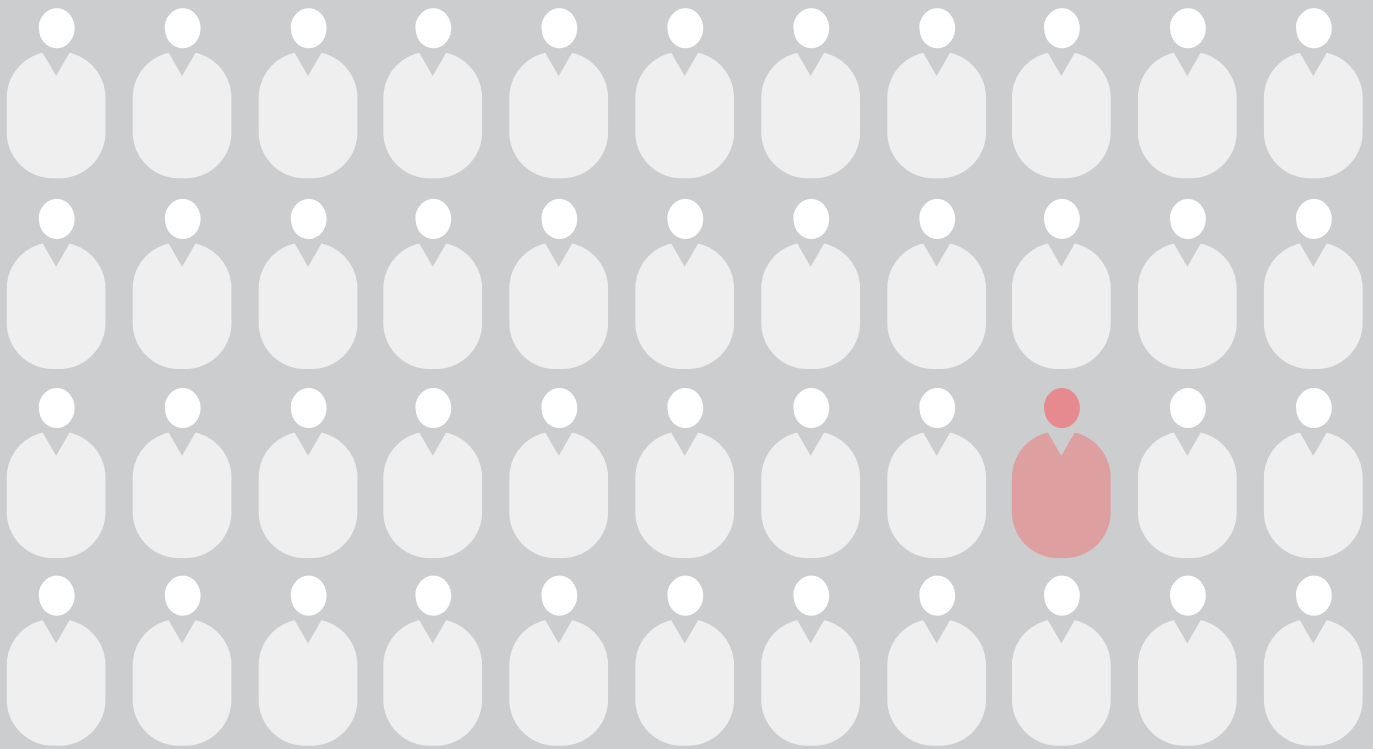
“The question people should be asking is, are we completely happy with how the system currently works for patients with urgent needs?”

Prof. Guido Rasi, EMA's Executive Director

According to Dr Hans-Georg Eichler, EMA's Senior Medical Officer, the adaptive pathways concept is a response to problems which have long existed in medicines regulation but have grown more acute in recent years. One such problem is the so-called access-versus-evidence conundrum, which describes the situation where, on the one hand, there are patients with serious illnesses today for whom time is of the essence, while on the other there is a broader society of patients in the future for whom complete knowledge of benefits and risks will be paramount.

One way of seeing this conundrum is through the prism of uncertainties and the challenges in managing them. As Dr Tomas Salmonson, Chair of the Committee for Medicinal Products for Human Use (CHMP), noted in his address, regulators must always accept some uncertainty in their benefit-risk assessments, and the amount of uncertainty they can tolerate will depend on both the strength of available data and patients' needs. The adaptive pathways concept aims to tackle the access-versus-evidence conundrum in cases of high unmet medical need by reducing uncertainty as rapidly as possible within the current regulatory framework, which means that the basic benefit-risk assessment will remain the same. This point about maintaining the highest standards of benefit-risk assessment within the current regulatory framework was stressed throughout the workshop; but it does raise the question as to why this new concept is needed if indeed the framework and standards of evaluations are to remain exactly the same.

The answer lies in how the current system has been working in practice. Dr Salmonson gave the example of conditional marketing authorisations, noting that they employ some of the same approaches as adaptive pathways, including the focus on unmet needs and small patient populations. The problem is that many conditional authorisations have been the result of late requests by applicants during EMA evaluations when it had already become clear that a standard authorisation or a broader indication would not be granted. Furthermore, the data sets used to approve



conditional marketing authorisations may differ from those normally required by HTA bodies in their assessments, a situation that could delay or prevent medicine reimbursement by national healthcare systems.

The adaptive pathways concept has the advantage of being planned in advance, with regulators and HTA bodies working with companies early in development to determine which data can be acceptable and to allow

for appropriate health technology assessment according to national requirements. It may not necessarily result in faster approval, but it could lead to a more efficient use of data and resources to meet the needs of the widest number of stakeholders.

Dr Eichler noted that current system is built on what he called the 'block-buster model', which works well for big sellers like statins and antihypertensives, but has not always worked

Concerns raised by stakeholders

- ▶ How will real world data be used and defined?
- ▶ Will standards be relaxed?
- ▶ How will companies be made to comply with data requirements once their products are on the market?
- ▶ Will restricted medicines be restricted in practice?
- ▶ How will high unmet medical needs be defined?

optimally in the area of 'non-conventional' products (such as advanced therapies and orphan medicines), where data may be more limited, treatments more urgent, and patient groups smaller. He stressed the need for more varied sources of evidence to support randomised controlled trials, which remain the best tool for measuring the effects of medicines, but cannot be used in all cases.

The problems that the adaptive pathways concept are intended to solve are not

themselves much disputed. The questions that have arisen concern whether, in aiming to improve access for patients, regulators can still maintain the highest standards of benefit-risk assessments. In this regard, many of the discussions around adaptive pathways have centred on the proposal to increase the use of real world data in the evaluation of new medicines and what this could mean for patients ■

Real world data

Real world data can be defined as data collected outside randomised controlled trials often, but not exclusively, during the delivery of normal clinical care, including data from post-marketing pharmacovigilance. The sources of real world data relevant to medicines regulation are numerous and include many traditional ones like prescription drug databases and registries, but could in the future include newer patient-driven data, such as social media data or data derived from smart phones and other technologies. In today's hi-tech world, new data are accumulating at an enormous rate (so-called 'big data') and represent great challenges and opportunities.

Dr Alison Cave of EMA's Pharmacovigilance and Epidemiology department explained that EMA already uses real world data in a variety of ways, including to refine and assess safety signals, to restrict indications and make labelling changes and to recommend, in cases of unfavourable benefit-risk assessments, the withdrawal of marketing authorisations. In recent years, around 20% of withdrawals of marketing authorisation in the EU have occurred partly on the basis of real world safety data.⁶

Real world data have also been used to evaluate extensions of indication. In 2015, Soliris (eculizumab), a medicine approved for paroxysmal nocturnal haemoglobinuria (PNH) in patients with a prior history of transfusions, had its indication extended to include patients without a prior history of transfusions on the basis of real world registry data.⁷ In this case, given the challenges of the disease and the known efficacy of eculizumab, a prospective randomised study involving a non-treatment group was not appropriate.

Dr Tom Jefferson of Cochrane was one of the workshop attendees who cautioned against the use of real world data to study effectiveness, saying that these data are traditionally used to generate hypotheses rather than to test them. The conclusions drawn from these data, he argued, will usually be open to alternative explanations. Dr Jefferson also queried the use of the descriptor 'real world', because, as defined, it could imply that the randomised controlled trials have little relevance to real world practice. His preferred term would be 'observational' data. Another suggestion put forward at the workshop was to describe them as data from 'every day clinical practice'.

6 McNaughton R, Huet G, Shakir S. An investigation into drug products withdrawn from the EU market between 2002 and 2011 for safety reasons and the evidence used to support the decision-making. *BMJ open* 2014;4(1):e004221.

7 European Medicines Agency: EMA/CHMP/204109/2015 - Extension of indication variation assessment report for Soliris http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Assessment_Report_-_Variation/human/000791/WC500186127.pdf Accessed 4 January 2017.



“What is clear is that not all medicines are suitable for adaptive pathways. In our pilot, we rejected the vast majority of applications.”

Francesca Cerreta of EMA’s Scientific Advice

Naming aside, what was agreed is that there is a need to be absolutely clear on the limitations (e.g. potential for bias and problems with design) and the strengths of these data (e.g. patient populations reflecting real world use) and how they can best support data from randomised studies. Professor Ashley Woodcock of the University of Manchester and Dr David Leather of GlaxoSmithKline presented the results of the Salford Lung Study (SLS) to illustrate the possibilities of real world data.

SLS was a randomised prospective study of the effectiveness of fluticasone furoate and vilanterol for an unlicensed indication - chronic obstructive pulmonary disease, COPD - in

every day clinical practice in the Salford area of Manchester, England.⁸ The study was designed to allow unobtrusive observation of a large number of patients during the delivery of normal clinical care and was well received at the workshop as a demonstration of how real world data can be obtained in a methodologically rigorous way and provide clinically relevant evidence. Some attendees however, noted that the approach used is not strictly applicable to adaptive pathways and may be difficult to replicate on a regular basis.

Professor Stephen Evans of the London School of Hygiene and Tropical Medicine and a statistics expert at the Pharmacovigilance

⁸ Vestbo J, Leather D, Diar Bakerly N, et al. Effectiveness of Fluticasone Furoate-Vilanterol for COPD in Clinical Practice. The New England journal of medicine 2016;375(13):1253-60.

Risk Assessment Committee (PRAC) cautioned that while there are some questions that can be reasonably answered with real world data with strong causal inference, there are many situations when we can make no sensible conclusions from these data.

In making his point, Professor Evans cited a warning from a recent article in the *New England Journal of Medicine*: "...the confluence of large data sets of uncertain quality and provenance, the facile analytic tools that can be used by nonexperts, and a shortage of researchers with adequate methodologic savvy could result in poorly conceived study and analytic designs that generate incorrect or unreliable conclusions."⁹

Given the limitations of real world data, which are not themselves controversial, randomised controlled trials remain central to the evaluation of medicines, despite there being situations where they are not appropriate or cannot be carried out. As Francesca Cerreta of EMA's

Scientific Advice who worked on the adaptive pathways pilot said, "Randomised controlled trials, if possible, would be the preferred way; but if it is not feasible, can we get data in another way?" The question therefore is not how real world data can replace clinical trial data but how they can best support them, and how methodologies for generating data can be improved.

Dr Rob Hemmings, CHMP member and Chair of EMA's Scientific Advice Working Party, noted that standards for making scientific conclusions, including accounting for bias and false positive results, are not changed for real world data and may be harder to meet with many studies relying on them. He emphasised that a clear understanding of the questions we want to answer is crucial to choosing and designing the studies and ensuring that their results are actionable. In this regard, effective dialogue among stakeholders is an essential part of the process, requiring great commitment from all sides ■

Patients and healthcare professionals

One of the findings of the adaptive pathways pilot was that it can bring a wide range of stakeholders around the table to discuss important aspects of medicines development, not least of which are the patients and healthcare professionals who will ultimately use them.

Dr Rafal Swierzewski of the European Cancer Patients Coalition (ECPC), an organisation representing over 400 cancer groups, was strongly in favour of patients being more involved in discussion with HTA bodies as part of adaptive pathways. Noting that the adaptive pathways concept could be life-saving for patients with rare and ultra-rare cancers, he also said that "the ultimate decision on medicine use should be left to the patient and

his or her doctor. Let the patient decide to accept or decline higher risk of treatment."

That is not to say that patients and civil society do not share some of the same concerns as other stakeholder groups. Francesca Cattarin of BEUC, the European consumer organisation, was pleased that the adaptive pathways concept was to be limited to cases of high unmet medical need, but called for a clearer definition of what constitutes such a need. She was also concerned about how restricted medicines would be restricted in practice, citing a recent OECD finding that a third of medicines are prescribed in the wrong way, illustrating the difficulty in controlling the use of medicines once they are on the market. Francesca Cattarin also noted concerns about evidence from real world data,

9 Sherman RE, Anderson SA, Dal Pan GJ, et al. Real-World Evidence - What Is It and What Can It Tell Us? The New England journal of medicine 2016;375(23):2293-97.

particularly the methodologies to be used to analyse them.

“BEUC’s objective is that consumers have timely access to safe, innovative and affordable treatments,” she said. “However we believe that so far many elements of adaptive pathways don’t really go in this direction and we maintain a cautious approach.”

The need to improve access to new medicines also raises the important issue of surrogate endpoints – those indirect measures of efficacy that are expected to correlate with real clinical benefit. Although the use of surrogate endpoints is not new and may speed up access to certain medicines, they require careful consideration. “We actually do have experience of accelerating approval on the basis of surrogate outcomes,” says Dr Courtney Davis of King’s College, London, “and subsequently finding that in 50% of cases where we have data, these [cancer] drugs fail to demonstrate an impact on overall survival.”

“We should not condemn adaptive pathways out of hand, but its assessment requires clear knowledge of the methods used in the pilot. These are not available at present.”

Dr Tom Jefferson of Cochrane, writing in the BMJ after the workshop¹⁰

Some of these concerns were addressed by another speaker, Dr Rosa Giuliani, a member of EMA’s Healthcare Professional Working Party (HCPWP), who gave an oncologist’s perspective on the adaptive pathways concept. She noted that the definition of high unmet medical need, which may be difficult in other fields, is less of a problem with cancers, where high mortality rates are all too common. She particularly welcomed the early engagement of relevant

stakeholders in adaptive pathways, which will help companies be aware of data that will be required by all parties further down in the development process.

In terms of data sources, while Dr Giuliani acknowledged the importance of randomised controlled trials, she did note that patients enrolled in cancer trials are not truly representative of patients she sees in the clinic. Many patients with cancers who suffer from other conditions, for example, will find themselves excluded from trials for both cancer and the other conditions that they may have. Furthermore, it is estimated that by 2030, 70% of all cancer diagnoses will be for elderly patients,¹¹ a population routinely excluded from many trials. Real world data can therefore play an important role in plugging the gaps in knowledge and dealing with uncertainty in treatments with new medicines.

Elizabeth Vroom of the Dutch Duchenne Parent Project (Duchenne muscular dystrophy being an urgent area of unmet need) noted that, although she saw adaptive pathways more in terms of making efficient use of scarce resources and improving access to medicines, the concept might potentially increase medicines safety by allowing the collection of more relevant data than could be obtained from randomised controlled trials.

Finally, patients and healthcare professionals agreed on the need for regulators to provide stakeholders with information and training about the strength of data used to approve medicines and the uncertainties surrounding them. This is of particular importance for patients’ representatives on whom many patients rely for information about their medicines. “If something goes wrong or if something goes well, patients will turn to us,” said Mathieu Boudes of Eurordis, the rare disease organisation. “We need to raise our capacities and that goes with time, money and training.” ■

10 Tom Jefferson: Adapting pharmaceutical regulation to more transparency. <http://blogs.bmj.com/bmj/2016/12/23/tom-jefferson-adapting-pharmaceutical-regulation-to-more-transparency/> Accessed 16 January 2017.

11 Smith BD, Smith GL, Hurria A, et al. Future of cancer incidence in the United States: burdens upon an aging, changing nation. J Clin Oncol 2009;27(17):2758-65.

Payers and HTA bodies

The workshop also addressed in depth the role of organisations such as health technology assessment (HTA) bodies and payers, who make the decisions about pricing and reimbursement that ultimately determine whether patients gain access to a medicine or not. It was also an opportunity for these organisations to discuss their positions on various aspects of the adaptive pathways concept.

Professor Sarah Garner of the UK's National Institute for Health and Care Excellence (NICE), an HTA body, envisages a system whereby regulators, HTA bodies and companies routinely engage in 'safe harbour' talks at early stages even before formal scientific advice discussions take place. Safe harbour talks are informal brainstorming discussions where companies can get insights into the requirements of HTA bodies before they have committed to a particular course of action and allow these companies to raise important questions early. (Feedback from company representatives at the workshop attests to the usefulness of these talks, at least in their own applications.)

With respect to real world data, many of the considerations on whether such data are appropriate are topic-specific. "It is only when you get down to specifics of a condition or a disease," said Professor Garner, "that you start to understand whether data sets are appropriate for answering questions or not." She agreed that evidence standards for real world data should not be relaxed.

Some workshop participants representing HTA bodies had concerns about specific aspects of the adaptive pathways concept. Dr Beate Wieseler of the Institute for Quality and Efficiency in Health Care (IQWiG), an HTA body in Germany, was concerned about the amount of information that would be available for certain medicines at the time of marketing authorisation. "We start treating patients at the point of market entry and ... we will have less information for a number of decisions," she said. These decisions concern not only the treatment of individual patients, but also



Dr Andrzej Ryś, DG SANTE

the development of clinical guidelines defining standards of care and reimbursement by national healthcare systems.

On the issue of real world data, Dr Wieseler noted the difficulties in evaluating treatment effect. "We just don't see how uncertainty in treatment effect can be solved by data that are inherently uncertain," she said, also noting that there was insufficient evidence from the adaptive pathways pilot of the use of real world data for estimating treatment effect.

Wim Goettsch from the Dutch HTA body Zorginstituut Nederland (ZIN) and coordinator of EUnetHTA Joint Action, an EU collaborative body, noted that the Dutch experience of parallel scientific advice has been positive. However, he emphasised the need to have clear criteria for selecting products entering adaptive pathways and for defining patient populations to ensure that products are used in the right setting and that post-marketing

data for efficacy as well as safety can and will be collected. He cautioned that achieving all these goals may require not only legislative changes but also significant changes in national healthcare systems.

Dr François Meyer of France's Haute Autorité de Santé (HAS) highlighted the importance of further developing parallel scientific advice and discussing data collection in the post-marketing phase, which may increase the value of real world data to be used by HTA bodies in their assessments.

Perhaps the most crucial, and sometimes overlooked, aspects of assessments of medicines are those concerning the actual dispensing of funds, without which many patients will be unable to access new treatments. Dr Ad Schuurman, Chair of the Medicine Evaluation Committee (MEDEV), who represented payers at the workshop, noted that, as with HTA bodies, views differ across the EU. "One third of the payers think we don't need anything new," he said. "One third doesn't know, and one third is really thinking about how we can do things differently."

Evert Jan van Lente of AOK-Bundesverband, a German payer organisation, stressed that he would like adaptive pathways to be restricted to exceptional cases of high unmet medical need where a medicine has a major therapeutic advantage and for EMA to have clear sanctions for companies that do not comply with conditions of authorisation.

On these points, there was broad agreement between HTA bodies, payers and EMA. The adaptive pathways concept has not been proposed for regular (i.e. non-urgent) marketing authorisation applications and, as noted in the workshop's briefing book,¹² compliance with legally binding post-marketing commitments has been good. (Since the workshop, EMA has published a report showing

how well companies have met conditions of conditional marketing authorisations over the past 10 years.)¹³

Dr Eichler noted that what is more likely than companies failing to fulfil conditions is post-authorisation data on safety or efficacy failing to meet expectations. For these situations, mechanisms are in place to re-evaluate medicines and take necessary regulatory action. He did, however, say that there is a need for an exit strategy, what some have dubbed 'adaptive disengagement', for products that are shown to be less efficacious or safe than previously thought.

A final word on HTA bodies and payers: Dr Andrzej Rys of the EC's Directorate-General for Health and Food Safety (DG SANTE) informed the workshop about the Commission's work to strengthen cooperation between HTA bodies, payers and regulators in line with a the recent call from the Council of the EU.¹⁴ As shown by the discussions around adaptive pathways, such cooperation is not only necessary for ensuring healthcare systems are sustainable and improving patients' access to medicines but also for improving the way individual medicines themselves are developed, taking into account the best possible data sources and the needs of patients ■

12 European Medicines Agency – Adaptive pathways workshop briefing book. http://www.ema.europa.eu/docs/en_GB/document_library/Other/2016/11/WC500216553.pdf Accessed 11 January 2017.

13 European Medicines Agency – Conditional marketing authorisation: Report on ten years of experience at the European Medicines Agency. http://www.ema.europa.eu/docs/en_GB/document_library/Report/2017/01/WC500219991.pdf Accessed 26 January 2017.

14 Council of the European Union: Council conclusions on strengthening the balance in the pharmaceutical systems in the EU and its Member States. <http://www.consilium.europa.eu/en/press/press-releases/2016/06/17-epsco-conclusions-balance-pharmaceutical-system/> Accessed 12 January 2017.

Conclusion

This report covers the main issues raised by speakers at the workshop on adaptive pathways. As Professor Guido Rasi, EMA's Executive Director, pointed out in his opening address, the workshop was as much a listening exercise as a forum to share ideas.

The workshop illustrated the wide range of views among patients, consumer representatives, HTA bodies, payers and healthcare professional organisations in the EU, and was an opportunity to clarify the aims and intended scope of the adaptive pathways concept.

There was broad agreement that the adaptive pathways concept should focus on meeting high unmet medical needs where data cannot be acquired via randomised clinical trials. The workshop also acknowledged the value of early involvement of stakeholders in critical discussions around medicines development and the need for careful decisions to meet urgent medical needs, without putting patients at risk. Finally, there was recognition of the need for continued efforts to improve access to medicines and ensure healthcare systems are sustainable.

EMA and the EC will now take stock of the different views expressed on the adaptive pathways concept and the lessons learnt from the pilot to determine ways to integrate proposals and address concerns within the existing regulatory system. EMA will also build on the experience gained from the adaptive pathways pilot within the existing mechanism of scientific advice, which provides for early multi-stakeholder dialogue. There will be further opportunities for discussion with stakeholders at various forums.

The workshop was attended by over 170 delegates, with 155 others logging in remotely. Due to the depth of the discussions that took place, not all statements made are included or attributed in this report. However, the slide presentations and video recordings of the talks, including a summing up by EMA's Spiros Vamvakas, are now available on EMA's website ■

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Adaptive Pathways Workshop

EMA/650/2017

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