



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

28 July 2016
EMA/276376/2016
European Medicines Agency

Final report on the adaptive pathways pilot

Summary

In March 2014 EMA launched a pilot project to explore the adaptive pathways approach, a scientific concept of medicines development and data generation intended for medicines that address patients' unmet medical needs.

Adaptive pathways seeks to balance timely access for patients who are likely to benefit most from the medicine with the need to provide adequate evolving information on the benefits and risks of the medicine itself.

Adaptive pathways is not a new route of approval for medicines. It makes use of existing approval tools, in particular conditional marketing authorisation, which has been in operation in the European Union (EU) since 2006. It also builds on the experience gained with strengthened post-marketing monitoring tools introduced by the 2012 pharmacovigilance legislation (e.g., post-authorisation studies and patient registries).

The adaptive pathways concept is not meant to be applicable to all medicines, but only to medicines that are likely to offer help for a patient population with an unmet medical need, and where the criteria for adaptive pathways apply.

As for any medicine, a marketing authorisation will only be granted if the balance of benefits and risks for a defined patient population is found to be positive; the same principles and legal tools apply as for any other new medicine.

Adaptive pathways can be defined as a prospectively planned, iterative approach to bringing medicines to market. The iterative development plan will initially target the development to a well-defined group of patients that is likely to benefit most from the treatment. This is followed by iterative phases of evidence gathering and progressive licensing adaptations, concerning both the authorised indication and the potential further therapeutic uses of the medicine, to expand its use to a wider patient population as more data become available.

A key aspect of adaptive pathways is the involvement of all relevant decision-makers in the process across the life span of the medicine, including those who decide about patient access in the Member States: to help determine which medicines could be appropriate for adaptive (iterative) development; to jointly agree a data generation plan to meet the needs of regulators and health technology assessment bodies (HTAs) and to ensure that the use of the medicine is well monitored and managed.

The aim of this collaboration is to achieve better patient access to important medicines.



All involved stakeholders agree upfront on a plan of post-licensing knowledge generation for a medicine, before it is authorised, and the marketing authorisation holder commits to carrying out this plan. Once a marketing authorisation has been granted, the post-authorisation plan becomes a legally binding regulatory obligation.

The cooperation between stakeholders and a strong pharmacovigilance system are the basis for the systematic monitoring of the safety and the overall performance of a medicine in clinical practice; these are the two key elements underpinning the adaptive pathways concept which makes use of the tools provided by the pharmacovigilance legislation to their fullest extent..

The pilot

In March 2014 EMA launched a pilot project to explore the practical implications of the adaptive pathways concept with medicines under development. The pilot was designed as a learning exercise providing insight into the characteristics of development programmes where the adaptive pathways concept could be applied. EMA invited companies to submit ongoing medicine development programmes that met the following criteria:

1. **An iterative development plan, prospectively planned.** This means that evidence can be acquired step-wise to either expand the target population from an initial approval in the population with high(est) medical need, or to progressively reduce uncertainty with additional data collection after an initial (conditional) marketing authorisation based on surrogate endpoints, early time points, or a smaller population sample.
2. **The involvement of HTAs and other downstream stakeholders, with proposals for how the demands of these stakeholders can be met.** As the adaptive pathways development will be iterative, aspects like plans for demonstration and change of the value proposition within an evolving data set can be discussed with HTAs; while control of prescription, relevance of early endpoints and risk management can be discussed with patient representatives.
3. **Real-world data as a complement to RCTs.** In an adaptive pathways proposal, a coherent, prospective plan for real world evidence is designed to collect high-quality data to further refine the benefit/risk profile, the therapeutic value and the price of a medicine.

EMA's adaptive pathways pilot is now closed, as it has reached the target planned in the interim report of six products going through parallel EMA-HTA advice.

This report reflects the experience gained in the pilot project, discusses the practical findings and outlines the next steps to further explore the concept. The report also reflects the different perspectives on the adaptive pathways concept that were collected through a questionnaire circulated via the European Commission Expert Group on Safe and Timely Access to Medicines for Patients (STAMP) to the Member States, EUNetHTA and network of Competent Authorities for Pricing and Reimbursement (nCAPR), and a company survey conducted within the ADAPT-SMART IMI project.

Key figures

EMA received 62 applications. Eighteen proposals were selected for in-depth, face-to-face meetings with the participation of other stakeholders. At the end of the pilot, seven of these applications had progressed to a formal scientific advice (one) or parallel regulatory-HTA scientific advice (six).

The pilot received applications covering a wide range of therapeutic areas, with oncology accounting for a third of the total initial submissions.

The majority of the proposals received did not fulfil the eligibility criteria for the pilot, and applicants have been advised to pursue traditional development routes. Reasons for non-acceptance in the pilot included:

- development programmes that did not afford scope for expansion and iteration;
- proposals for areas without unmet need; and
- late stage development programmes (where no changes to the plan could be effected).

Of the proposals accepted into the pilot, some did not progress beyond the initial discussions because the subsequent scientific advice on more detailed protocols cast doubt on the feasibility and methodological robustness of the development plan. If the adaptive pathways approach is no longer deemed appropriate at a certain point in the medicine's development, it is possible to revert to traditional development routes.

Key learnings

The pilot showed that:

- adaptive pathways can foster multi-stakeholder dialogue, bringing regulators, interested HTAs, healthcare professionals and patients around the same table to discuss a product development paradigm for medicines addressing unmet medical needs. Agreement between stakeholders can be reached on a prospective approach to evidence generation across the lifespan of a medicine in areas of high unmet need, with a view to optimising and aligning their requirements as much as possible;
- the benefit of adaptive pathways lies in appropriate prospective planning to incorporate multiple stakeholders' requirements upfront to avoid the need to request additional studies later in development, and in exploring the full potential of utilising the real world evidence generated in clinical practice to refine regulators' and other stakeholders' decisions;
- as the proposed evidence set makes use of different data sources aiming to create a common evidence base to address both regulators' and HTAs' needs, consulting all concerned decision makers on their respective requirements is essential;
- adaptive pathways can support medicine development in therapeutic areas where evidence generation is challenging, such as infectious diseases, Alzheimer's disease, degenerative diseases, and rare cancers;
- adaptive pathways should focus on medicines that can plausibly address an unmet medical need in a defined population, where there is scope to explore feasible data collection plans (randomised controlled trials (RCTs) and registries) based on reliable, clear-cut and actionable endpoints;
- adaptive Pathways is not a suitable approach for the development of all products. Certain pre-conditions have to be met for adaptive pathways, such as:
 - the availability of clear-cut, actionable endpoints for post-authorisation decision making of regulators and HTAs (and - if relevant - payers);
 - the setting of checkpoints across the development pathway to revise and adjust the development programme to the level of evidence required by the decision makers;
 - controllable prescription so that the medicine can only be prescribed to the patient population for which the benefit/risk has been demonstrated;

- the ability to arrange managed entry agreements and entry and exit strategies if these are considered relevant by the concerned stakeholders.

- the regulatory framework offers robust mechanisms to ensure close monitoring of a medicine's benefits and risks once it is on the market, and that prompt regulatory reassessment and action can be taken if needed. Development plans should make use of these tools in an optimal and convincing way in order to be accepted by regulators. When the proposed plan for the collection of post-authorisation data is not considered feasible or robust enough, companies have been advised to pursue a traditional development route.
- pre-requisites for companies to come forward and discuss early developments in the setting of adaptive pathways include trust in the non-binding nature of adaptive pathways, and an open mindset to consider a flexible lifecycle development, including the discussion of potential scenarios. These qualities enable productive interaction and facilitate the understanding of the advantages, requirements and constraints behind each proposed development route.

Issues identified for further reflection

- Involvement of patients and healthcare professionals

Increased patient participation in the future will assist in the selection of candidates for which accelerating access is particularly desirable, and to provide insights on feasibility and ethical aspects, and to support enrolment in trials and registries. Input from healthcare professionals on the feasibility of implementing patient registries in clinical practice and on the control of prescription should be sought.

Further discussions on the application of the current definition of unmet need in the adaptive pathways setting (unmet medical need, public health need, healthcare cost savings) with the competent stakeholders would be helpful.

- Post-authorisation data gathering plans

The challenge remains to identify methodologically sound strategies of real-world evidence collection to support the assessment of both efficacy and effectiveness. These issues need to be discussed further in appropriate stakeholder fora and research programmes.

- Involvement of payers

Member States' organisations and entities responsible for decisions on pricing and reimbursement on the basis of HTA body recommendations (referred to as 'payers' in this report) were not part of the pilot discussions. In some cases, which needed input on the design, acceptability and feasibility of adaptive pricing strategies linked to the data collection, payers' input on the principles and feasibility of such schemes would be important early in the process if they are envisaged as part of the development plan. In line with the Council conclusions¹, possible synergies between the work of regulatory bodies, HTA bodies and payers, in order to ensure timely and affordable access of patients to innovative medicines, may be explored in the future.

Next steps

EMA will further explore the adaptive pathways concept as an approach to bringing promising medicines to patients with an unmet need in a timely manner.

¹ Council conclusions on strengthening the balance in the pharmaceutical system in the EU and its Member States <http://www.consilium.europa.eu/en/press/press-releases/2016/06/17-epsco-conclusions-balance-pharmaceutical-system/>

Future discussions on adaptive pathways will be incorporated into the existing operational platform of EMA parallel regulatory-HTA scientific advice, with the inclusion of other stakeholders (patients, interested HTAs and, if relevant, payers will also be invited) relevant to the specific issues under discussion. An additional pre-submission meeting (two for SMEs) will be granted as compared to the parallel regulatory-HTA scientific advice.

Adaptive pathways is still a concept in development which will be fine-tuned as more medicines in development are considered for this approach.

EMA values contributions from stakeholders on its initiatives, as feedback and open debate are essential for adapting and fine-tuning concepts and approaches and ensuring that they meet stakeholders' expectations.

EMA will organise a workshop in the fourth quarter of 2016 to gather the views and proposals from its stakeholders on the adaptive pathways approach.

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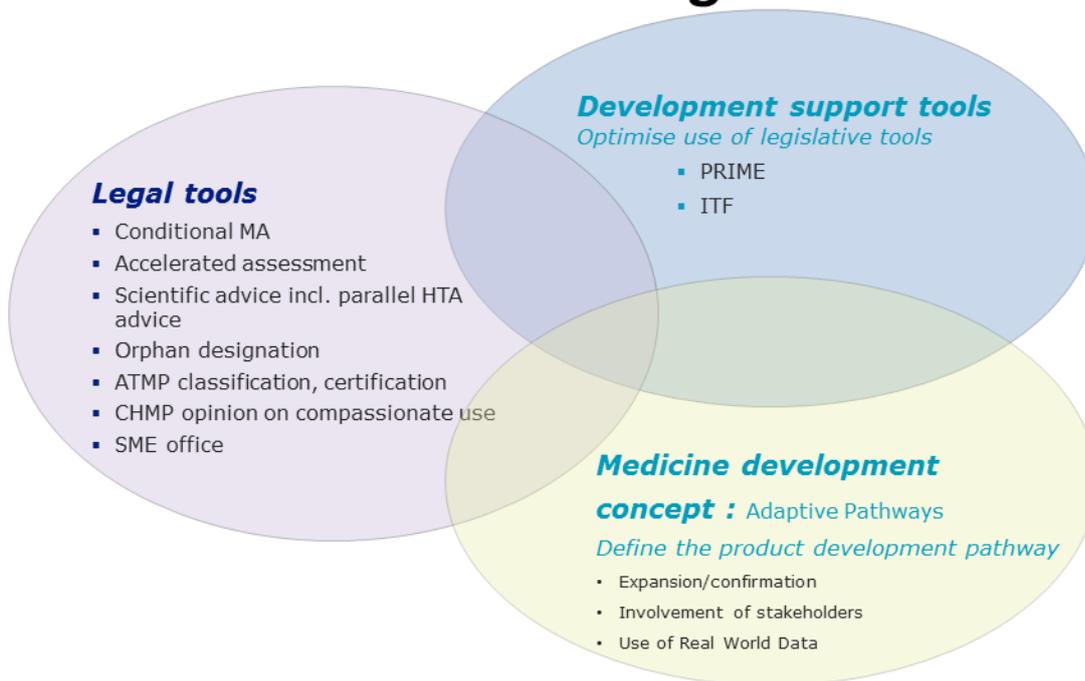
1. Introduction and background

Striving to ensure that patients have timely access to promising medicines is an important goal for public health and should be undertaken in a way that does not compromise patients' safety. The Agency uses a wide range of regulatory mechanisms to achieve these aims, and continuously reviews and improves its processes. A number of early access tools for medicines addressing unmet medical needs have been available in the EU for many years. These include, compassionate use programmes², accelerated assessment, reinforced recently with the introduction of the PRIME scheme, and conditional marketing authorisation (CMA). An overview of existing tools is available on the EMA website.

In March 2014 EMA launched a pilot project to explore a concept of medicines development and data generation intended for medicines that address patients' unmet medical needs – the adaptive pathways approach. This report provides further information on the adaptive pathways concept and experience gained with the pilot.

Figure 1

Development support and early access for medicines addressing unmet need



What is adaptive pathways?

Adaptive pathways can be defined as a prospectively planned, iterative approach to bringing medicines to market. The iterative development plan initially targets the development to a well-defined group of patients that is likely to benefit most from the treatment. This is followed by iterative phases of

² http://www.ema.europa.eu/docs/en_GB/document_library/Other/2016/03/WC500202631.pdf

evidence gathering and progressive licensing adaptations, concerning both the authorised indication and the potential further therapeutic uses of the medicine, to expand its use to a wider patient population as more data become available.

Adaptive pathways seeks to balance timely access for patients who are likely to benefit most from the medicine with the need to provide adequate evolving information on the benefits and risks of the medicine itself.

Adaptive pathways is not a new route of approval for medicines. It makes use of existing approval tools (Figure 1), in particular conditional marketing authorisation, which has been in operation in the EU since 2006. It also builds on the experience gained with strengthened post-marketing monitoring tools introduced by the 2012 pharmacovigilance legislation (e.g. post-authorisation studies, patient registries) that facilitate the gathering of real-world data post-authorisation.

As for any medicine, a marketing authorisation will only be granted if the balance of benefits and risks for a defined patient population is found to be positive; in other words, the same criteria and legal tools will apply as for any other new medicine.

The adaptive pathways concept is not meant to be applicable to all medicines, but only to medicines that are likely to address an unmet medical need, and where the criteria of adaptive pathways apply: a staggered approval from very small, restricted patient populations to increasingly wider populations; a binding plan of post-licensing evidence gathering; and involvement of key stakeholders in the process.

A key aspect of adaptive pathways is the involvement of all relevant decision makers in the medicine's lifecycle. Dialogue between all these actors is important across the life span of the medicine to help determine which medicines could be appropriate for adaptive (iterative) development; to jointly agree a data generation plan to meet the needs of regulators and HTA bodies and to ensure that the use of the medicines (i.e. restricted prescribing) is well monitored and managed.

This allows for agreement to be reached upfront on a development plan that meets the data requirements for the benefit-risk assessment carried out by regulators and also for the assessment of a medicine's added value carried out by HTA bodies. The aim of this collaboration is better patient access to important medicines.

All involved stakeholders agree upfront on a plan of post-licensing knowledge generation for a medicine, before it is authorised, and the marketing authorisation holder commits to carrying out this plan. Once a marketing authorisation has been granted, the post-authorisation plan becomes a legally binding regulatory obligation.

It should be noted that if the adaptive pathways approach is no longer deemed appropriate at a certain point in the medicine's development, it is possible to revert to traditional development routes.

The necessary discussion of post-authorisation data generation and monitoring is what differentiates the adaptive pathways approach from EMA parallel scientific advice with HTA bodies, which generally focuses on the initial marketing authorisation.

The cooperation between stakeholders and a strong pharmacovigilance system are the basis for the monitoring of the safety and the overall performance of a medicine in clinical practice; these are the two key elements underpinning the adaptive pathways concept which makes use of the tools provided by the pharmacovigilance legislation to the fullest extent.

Drivers

Patients' demand for timely access and emphasis on unmet medical need are the key drivers of adaptive pathways³. The urgent need for access to new medicines is underlined in many cases where patients face rapidly deteriorating conditions or chronic, slow, irreversibly progressing diseases for which there are currently no satisfactory treatment options.

Another key driver is a better understanding of pathologies which has led to the identification of subgroups of patients who are likely to better respond to certain medicines than others, as well as the growing financial pressure on healthcare systems and the call for more targeted use of medicines to increase their therapeutic value.

Experience with the adaptive pathways approach

In March 2014, EMA launched a pilot project to explore with medicines in development the adaptive pathways approach. The objective is to support timely patient access for new and important medicines which have the potential to fulfil an unmet medical need.

Unmet medical need refers to a disease area for which patients have no or unsatisfactory treatment options. In the context of AP, a broader acceptance of the term unmet medical need, including potential future need (as in the case of antibiotic development), is considered. It should be noted that this definition does not mandate the use of a particular marketing authorisation route.

EMA's adaptive pathways pilot was meant to be a learning exercise providing insight into the characteristics of development programmes that could be suitable for an adaptive pathways approach. EMA's pilot is now closed. This report reflects the experience gathered in the pilot project, the discussion on the selected cases, and the experience gained with the six parallel HTA-EMA advice procedures that followed. The report discusses the practical findings and outlines the next steps to further explore the concept.

Discussions on a possible adaptive pathways approach in the pilot have taken place at the early stages of medicine development (i.e. Phase I and II), and as is the case for all scientific advice discussions, deal with commercially sensitive information. This report does therefore not contain detailed information on the products and issues discussed in the "safe harbour setting"; however, it captures a number of common findings and trends identified.

Different perspectives on the adaptive pathways concept were also collected by sending a questionnaire via the European Commission Expert Group on Safe and Timely Access to Medicines for Patients (STAMP)⁴ to the Member States, EUNetHTA and nCAPR; and a company survey was conducted within the ADAPT-SMART IMI project. The outcomes are incorporated in the relevant sections of this report.

2. Experience from the pilot

Criteria

As part of the pilot, EMA invited companies to submit ongoing medicine development programmes that meet the following criteria:

1. An iterative development plan, prospectively planned. This means that evidence can be acquired step-wise to either expand the target population from an initial approval in the population with

³ <http://onlinelibrary.wiley.com/enhanced/doi/10.1002/cpt.59>

⁴ http://ec.europa.eu/health/files/committee/stamp/2016-03_stamp4/5a_adaptive_pathways_stamp_questionnaire_summary_of_responses.pdf

high(est) medical need; or to progressively reduce uncertainty with additional data collection after an initial (conditional) marketing authorisation based on surrogate endpoints, early time points, or a smaller population sample.

2. The involvement of HTAs and other downstream stakeholders, with proposals for how the demands of these stakeholders can be met. As the adaptive pathways development will be iterative, aspects like plans for demonstration and change of the value proposition within an evolving data set can be discussed with HTAs; while control of prescription, relevance of early endpoints and risk management can be discussed with patient representatives.

3. Real-world data as a complement to RCTs: in an adaptive pathways proposal, a coherent, prospective plan for real-world evidence is designed, to collect high-quality data to further refine the benefit/risk profile, the therapeutic value and the price of a medicine.

Safe harbour environment

Since discussions on possible adaptive pathways are of an exploratory nature, interactions between stakeholders took place in a safe harbour environment so that strengths and weaknesses of all options for development, licensing and assessment were explored openly and informally in advance of more formal interactions that might eventually be undertaken such as scientific advice/protocol assistance or a marketing authorisation application. As such, none of the stakeholders represented in the discussion were asked to make binding commitments.

2.1. Medicines in development submitted in the pilot

At the date of this report, EMA had received 62 proposals for inclusion in the pilot.

Twenty were accepted for a Stage I meeting, a short meeting with regulators intended to improve the understanding of the concept and the design of the proposal. These discussions aimed to identify the topics that warranted further discussion by stakeholders, to clarify the adaptive pathways process and the areas for improvement, and to provide the basis for the criteria to progress to the extended adaptive pathways meetings involving HTAs and patients (i.e. Stage II meetings).

Eighteen proposals were selected for Stage II at the time of writing, of these seven progressed to formal scientific advice (1) or parallel regulatory-HTA scientific advice (6).

Submitted proposals	Stage I discussions	Stage II discussions	Advice requests submitted
62	20	18	6 HTA/SA 1 SA

The majority of the proposals received did not fulfil the eligibility criteria for the pilot, and applicants have been advised to pursue traditional development routes. This happened at the stage of submission to the pilot, but also when subsequent scientific advice discussions on more detailed protocols cast doubt on the feasibility of the development plan.

The reasons for non-acceptance in the pilot:

- development programmes that did not afford scope for expansion and iteration (for example, programs where addition of indications would be achieved through standard variations supported by a self-contained development, and not through use of real-world data);
- proposals for areas without unmet need (where treatments already existed); and
- late stage development programmes (where no changes to the plan could be effected).

Of the proposals accepted in the pilot, some did not progress beyond the initial discussions, because the subsequent scientific advice on more detailed protocols cast doubt on the feasibility of the development plan.

Type of applicants

All applications for the pilot came from the pharmaceutical industry. Small and medium-sized enterprises (SMEs) accounted for 23% of the initial applications submitted to the pilot (14/62). Of these, four products were selected for a Stage I meeting, representing 20% of the total selected for this phase.

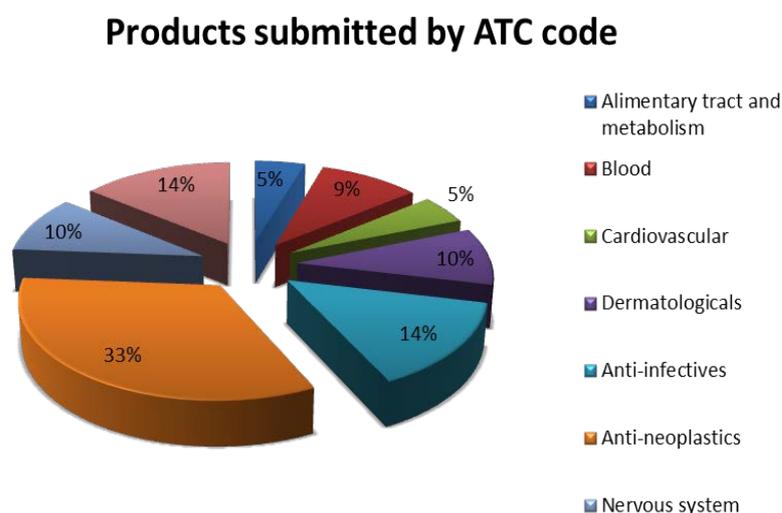
Approximately half of the products invited for a Stage I meeting were developed by biotechnology companies, three of them being spin-offs from academic and research institutions.

Therapeutic area

The pilot received applications covering a wide range of therapeutic areas, with oncology amounting to around one third of the total initial submissions (Figure 2). This was not unexpected, as cancer medicines, which receive a large proportion of conditional marketing authorisations and command a high price, represented a large proportion of submissions. Other therapeutic areas, which were highly represented, included infectious and respiratory diseases, neurodegenerative diseases, and hereditary genetic disorders.

The indications proposed in the applications received addressed diseases for which no, or no satisfactory, treatment is currently available, as well as where there are high unmet medical need sub-groups of broader indications where the prevailing standard of care is not effective or does not produce satisfactory results, resulting in limited therapeutic options.

Figure 2



Orphan status

One in four products had been granted orphan designation by the European Commission at the time of submission (15/62). Of these, five were accepted in the pilot's Stage I meetings.

For Stage II (meetings with regulators and other stakeholders) the proportion of orphan products was similar. Committee for Orphan Medicinal Products (COMP) representatives were involved in the discussions on these products.

2.2. Involvement of stakeholders

HTAs and other downstream stakeholders

HTA bodies took part in the 18 stage II discussions with the applicants on a voluntary basis.

The identification of participating HTAs was done on the basis of the company's proposal.

The following HTAs (in alphabetical order) participated in at least one of the adaptive pathways discussions:

- AEMPS (Agencia Española de Medicamentos y Productos Sanitarios, Spain)
- AIFA (Agenzia Italiana del Farmaco, Italy)
- G-Ba (Gemeinsame Bundesausschuss, Germany)
- HAS (Haute Autorité de Santé, France)
- HVB (Hauptverband der Österreichischen Sozialversicherungsträger, Austria)
- NICE (National Institute for Health and Care Excellence, UK)
- NoMA (Statens legemiddelverk / Norwegian Medicines Agency, Norway)
- TLV (Tandvårds- och läkemedelsförmånsverket, Sweden)
- ZINL (Zorginstituut Nederland, The Netherlands).

For one product (a vaccine) where national competences differed, the UK Department of Health participated in addition to NICE.

Involvement of patient representatives

Patient representatives were involved according to the current process for parallel HTA/SA advice and participated in four (out of 18) Stage II discussion meetings. The issues where patient input was needed included: balancing unmet medical need with accelerating development to safeguard patients' safety, relevance of endpoints, development of Patient Reported Outcomes (PROs), risk management and prescription control discussions. Patients also participated in the subsequent SA/HTA procedure.

The input of patients also facilitated contact with patient organisations to provide insights on feasibility, ethical aspects, and to support enrolment in trials and registries.

From the practical perspective, the pilot highlighted some difficulty in identifying suitable patient representatives due to the short timelines of the process. The move to a more formal setting in scientific advice may help increase future participation.

Involvement of EMA committees and other groups

When applicable, representatives of EMA committees (CAT, PDCO, COMP) were involved in the discussion to maximise the opportunity for flexible application of the regulatory framework.

For selected proposals, additional dedicated discussions with the EMA Registries Pilot group were held, to look at the suitability of existing registries, to avoid duplication of work, and to define the characteristics of the planned registries. The input from healthcare professionals included in this group was helpful to assess the quality of existing disease registries as a data source, and the feasibility of developing new registries.

The other area where the potential need for broader stakeholder participation was highlighted is where the requirements of other stakeholders could have significant impact on the global development plan: parallel FDA advice or advice involving WHO should then be considered, and EMA will facilitate the

involvement of these stakeholders if required. A framework for parallel EMA-FDA advice has already been in place for several years. One company participating in the pilot had planned to request parallel FDA advice, but, having separately received FDA agreement on their plans, opted for a regular scientific advice request instead.

2.3. Use of Real-world data

“Real-world data” can be defined⁵ as data collected both prospectively and retrospectively from observations of routine clinical practice. Real-world data can be obtained from many sources including patient registries, electronic medical records, and observational studies.

In the pilot, the concept of real-world evidence was expressly intended as wide ranging, encompassing different types of observational research that may be utilised to supplement randomised clinical trials. This was to encourage the submission of different approaches, not all of which could be foreseen at the conceptual stage, with the intent to highlight possibilities, needs and maximise the learning potential.

EMA considers that real-world data are a crucial element in the monitoring of medicines; these data can also complement and enhance the evidence collected in a randomised controlled trial (RCT) setting and can:

- capture real clinical practice, adherence, compliance and the performance of a medication in real life;
- capture rare, long-term events (for safety and/or efficacy);
- reduce the cost of monitoring long-term outcomes – important for degenerative and chronic diseases;
- be useful for geriatrics and paediatrics (examples from Paediatric Investigation Plans (PIPs) of acceptable real-world data use: historical control arms, safety and tolerability investigation if efficacy could be extrapolated from the adult trials);
- support the validation of biomarkers;
- allow the capture of more strata than RCT in the context of personalised medicine.

To design a plan for iterative evidence generation, the following aspects are considered to be important for companies wishing to pursue adaptive pathways:

- defining the purpose of the real-world data collection (regulatory, HTA, both?); why is this proposed and necessary, instead of, or in addition to an RCT?
- specifying the type and timing of real-world data (prospective disease registries; follow-up drug registries);
- critiquing the quality of the real-world data, particularly in case of utilisation of existing disease registries, and fitness of the data for the intended purpose;
- setting up milestones for results checking and development of potential different scenarios depending on the emerging level of efficacy of the product (e.g., heavier reliance on post-authorisation real-world data may be possible for a higher level of efficacy).

All of the 18 proposals accepted in Stage II of the pilot included plans for the use of real-world data to supplement randomised clinical trials, with a plan that went beyond the traditional use of a registry to investigate safety aspects. Proposals which were accepted include:

- Use of existing disease registries to identify natural history of the disease, current standard of care, resource utilisation, adherence to treatment;
- Single arm studies for rare diseases compared with outcomes and time-points inferred from disease registries;
- Open label salvage studies in patients with no therapeutic options remaining, with the purpose of obtaining an expansion of the indication;
- Collection of efficacy and safety data from early access/compassionate use programs to supplement RCTs in small populations;
- Post-authorisation drug registries for effectiveness, long-term outcomes, drug utilisation, Patient Reported Outcomes (PROs), time to treatment failure, diagnosis confirmation;

⁵ <http://adaptsmart.eu/adapt-smart-glossary-published/>

- Linking drug registries to risk-sharing schemes for reimbursement (pay-per-performance, annuity payments)
- Expansion of the indication based on a mixture of disease registries and compassionate use data (for rare, severe diseases, where RCT data were available for less severe forms of the disease);
- Post authorisation studies to investigate biomarkers' (or other subpopulation selection criterion) status of an all-comer population;
- Investigation of non-serological outcomes for vaccines.

An area that was identified for improvement related to the level of detail presented in the applications.

The majority of the plans were vague in terms of the purpose of collection of real world data to supplement RCTs, and on the practical elements for implementation there was insufficient detail in the submitted proposals to explore the refinement of the safety profile, and even less about to what extent efficacy could be confirmed or augmented in the post-authorisation phase. A critical discussion on the quality, potential for bias, and reliability of the data acquired in the post authorisation setting, and their suitability for regulatory and HTA purpose, was lacking. The few submitted proposals relied mostly on a traditional registry paradigm, geared towards the confirmation of conditional marketing authorisation or the reimbursement/effectiveness link.

Some of the proposals included the design of a pay-per-performance scheme linked to the long-term outcomes, and in some cases the question could not be addressed as the participating HTA bodies were not competent on the feasibility of the proposed reimbursement schemes in the Member States.

2.4. Marketing authorisation route

Well-established tools are available to regulators and medicine developers to support timely access to new medications: accelerated assessment, authorisation under exceptional circumstances and conditional marketing authorisation with legally-binding post-authorisation obligations. At the European Commission level, work is under way within the STAMP expert group to seek further improvement of the use of the existing regulatory framework, including if possible a better use of compassionate use programs, which are coordinated and implemented by Member States, under their own rules and procedures.

Ten out of the 20 submissions accepted for the Stage I meeting explicitly included plans to prospectively use conditional marketing authorisation in their development. As the medicines included in the pilot were in early stages of their development it is not possible in all other cases to draw firm conclusions with regards to the best possible marketing authorisation route, as this will depend on the data generated.

2.5. Prescription control

The iterative nature of adaptive pathways requires that consideration is given to prescription control if a medicine is initially licensed in a restricted subpopulation for which a positive benefit/risk balance has been demonstrated. This limits the risk of exposure of patients for which a benefit/risk balance is still under investigation, and, in the case of prescription linked to a registry, could allow for better quality data to be collected.

From the experience gained in the pilot, unequivocal definition of the population to be treated needs to be thoroughly discussed to allow accurate diagnosis and the establishment of prescription controls. Once initial indications is granted for a sub-population of high-need patients, patients could be followed in registries, and provide long-term data to supplement the safety profile of the medicine as the development programme progresses in other patient subgroups.

Certain therapeutic areas (e.g., hepatitis C, oncology) are more viable for effective prescription control, as there is a need to strike a balance between the resources required to achieve the control and the

cost of the drugs. From the discussions at STAMP it appears that for high cost medicines, or specialised healthcare areas, registers and electronic prescription methods are more likely to have been set up in the Member States, facilitating controls.

2.6. Chemical, Manufacturing and Controls (CMC) issues

EMA recognises that CMC evolves continuously, both pre- and post-authorisation. At the time of approval, however, regulators require a product of good quality based on a robust manufacturing process according to legal requirements, so that the product can be reliably supplied to the patient. In the context of the lifecycle approach, certain validation and/or upscaling/change activities may be agreed to be conducted post-marketing with the use of appropriate regulatory tools available (e.g., post approval change management protocols).

The acceleration of development time presents challenges in delivering a product of appropriate quality for the conduct of clinical studies and reliable supply to the patient. The product used for the clinical trial needs to be representative of the product that will be submitted for approval. The impact of any manufacturing changes must be proactively explored. This is particularly true for advanced therapy medicinal products (ATMPs), where initial development costs are high, and logistics complex.

Applicants for two ATMPs which entered the pilot had dedicated discussions with the Biologicals working party (BWP) and experts from EMA's Committee for Advanced Therapies (CAT) to discuss expectations and impact on the conduct of clinical studies of changes and delays in the manufacturing process and quality specifications. This initial informal discussion of the options was then followed by a more detailed scientific advice procedure on quality.

Adaptive pathways is a lifecycle approach that seeks to explore flexibilities within the regulatory framework, and involve the relevant expertise from all committees. If companies foresee an impact of manufacturing on the clinical trials, they are invited to discuss specific CMC aspects and how they impact on the development timelines.

Particularly in the case of ATMPs, where initial development costs are substantial, it is important to agree a strategy that ensures that initial clinical data are not invalidated by subsequent manufacturing changes.

3. Products submitting a parallel regulatory-HTA scientific advice

The early discussions in the framework of adaptive pathways are made on the basis of the principles of data collection and study design, and do not constitute official scientific advice from EMA.

Six products accepted for stage II progressed to parallel regulatory-HTA scientific advice. They pertained to the following therapeutic areas:

- Oncology (2)
- Haematology (2)
- Anti-infective (1)
- Cardiovascular (1)

Three of the companies were SMEs, and four indications were either designated as orphan or potentially qualified as such (designation yet to be granted).

In the six cases, once the advice request containing the detailed protocols was submitted, it was possible to reach an agreement on a progressive development plan only in those cases where reliable surrogate endpoints existed, where the population to be initially treated could be clearly identified, and

where there was trust that a reliable post authorisation data collection plan could be put in place to record long-term endpoints.

When, at the time of the advice, the more detailed discussion of the proof-of-principle/mode of action of the medicine showed that there was no convincing case to support an accelerated approval pathway, the company was advised to follow a traditional development pathway.

A concrete example

The case of LentiGlobin BB305 (a gene therapy medicinal product for the treatment of transfusion dependent beta-thalassemia) can be described in some detail, as the company itself has published information on the development of the product. The development plan is currently designed for once-only administration, and an initial conditional approval route is foreseen in the EU. This would provide the initial basis for the labelling and the value proposition. Long-term follow-up of patients will provide information on the duration of the effect and the long-term safety of the treatment. This information will be used by regulators, HTA bodies and payers in their assessment and decision making. Therefore, it is of interest to all parties, including patients, that a prospective discussion takes place on the data elements and design of long-term evidence generation to collect relevant and high quality data, and on the corresponding feasibility of the proposed reimbursement schemes in the Member States.

4. Key learnings and issues identified for further reflection

Key learnings

The pilot showed that:

- Adaptive pathways can bring together regulators, interested HTAs, healthcare professionals and patients to discuss a product development paradigm for medicines addressing unmet medical needs. Agreement between stakeholders can be reached on a **prospective** look at the evidence generation **across the lifespan** of a medicine in areas of high unmet need, with a view to optimising and aligning their requirements to the largest possible extent.
- Adaptive pathways can support medicine development in areas of high unmet medical need, and could help foster innovation in areas of public health need where research is lagging or the design of randomised clinical trials is difficult, such as anti-infectives, Alzheimer's and other degenerative diseases, and rare cancers; and in situations (such as for gene therapy) that present challenges to the traditional value proposition and reimbursement models. As expected, cancer medicines, which receive a large proportion of conditional marketing authorisations and command a high price, represented a large proportion of submissions. The discussions focussed on comparison with existing treatments, particularly where it is not possible to directly test against every possible comparator; and on alternative trial design (basket trials). In the context of disease-modifying and gene therapy products requiring long-term follow-up, the possibility of approval on the basis of early endpoints or surrogates, with follow-up of patients in open label study extensions or registries was discussed.
- The added value of adaptive pathways lies in the incorporation of other stakeholder requirements to address additional studies that could be avoided by appropriate prospective planning, and in exploring the full potential of utilising the real-world evidence generated in clinical practice to refine regulatory decisions.

- The regulatory framework offers robust mechanisms to ensure close monitoring of a medicine's benefits and risks once it is on the market and prompt regulatory reassessment and action if needed. Development plans should make use of these tools in an optimal and convincing way in order to be accepted by regulators. When the proposed plan for the collection of post- authorisation data is not considered robust enough, the programme is not suitable for the adaptive pathways approach.
- Collection of real-world data should be used to help regulators refine the benefit/risk balance of the medicine and support HTA bodies in their assessment of the added value outside the controlled environment of a clinical trial. Discussions at STAMP have revealed that recent experience in some Member States has shown that this is possible, but additional evidence generation should not only be limited to pricing and reimbursement. If it can be streamlined to meet the needs of multiple stakeholders, it would allow fairer and more efficient decision making by regulators, HTA and payers. To allow such decision making, the endpoints selected for the real-world data collection should be clear-cut and actionable (e.g., viral load clearance, overall survival) so as to be able to confirm and possibly improve the initial level of evidence. Milestones should be set for the review of the results and adjustment of the data generation plan accordingly.
- As the proposed evidence set makes use of different data sources aiming to create a common evidence base to address both regulator and HTA needs, consulting the decision makers on the requirements to demonstrate an added benefit over existing treatments is even more important in adaptive pathways than in a conventional EMA/HTA advice.
- Adaptive pathways should focus on medicines that offer plausibility to address an unmet medical need in a defined population, where there is scope to explore feasible data collection plans (RCTs and registries) based on reliable and actionable endpoints.
- Adaptive pathways is not a suitable approach for the development of all products. Certain pre-conditions had to be met for adaptive pathways , such as:
 - the availability of clear-cut, actionable endpoints for post-authorisation decision making of regulators and HTAs (and, if relevant, payers);
 - the setting of checkpoints across the development pathway to revise and adjust the development programme to the level of evidence required by the stakeholders;
 - a controllable prescription; and
 - the ability to arrange managed entry agreements and entry and exit strategies if these are considered relevant by the concerned stakeholders.
- For companies to come forward and discuss early developments in the setting of adaptive pathways, trust in the informal nature of the preliminary discussions is essential to explore the different possibilities. Trust in the non-binding nature of adaptive pathways, and a mindset prepared to consider a flexible lifecycle development, including the discussion of potential scenarios, are very important for a productive interaction and the understanding of the advantages, requirements and constraints behind each proposed development route. While it is important for stakeholders to keep a flexible mindset throughout the interactions, the evaluation of the final proposal in the SA/HTA advice is performed on a more detailed set of information, and needs to provide reassurance that the sponsor will be committed to implementing the proposed

plan. At that stage, certain aspects that were not apparent in the earlier discussion may warrant the suggestion to follow a traditional development pathway.

- As the scope of the adaptive pathways safe harbour is to refine the content of the subsequent scientific advice request, participation of the different representatives relevant to address the questions is important. This includes the involvement of EMA's CAT, PDCO and registries pilot group. For selected proposals, additional dedicated discussions with the registries pilot group were held, to look at the suitability of existing registries, to avoid duplication of work, and at the desirable characteristics of planned ones. Adequate infrastructure for data collection is an important element and existing best practice offers a learning potential. The careful prospective planning of a registry would support the expected accrual, as it would allow consultation on feasibility aspects, including the participation of healthcare professionals.

Points for further reflection

- *Involvement of patients and healthcare professionals*

The choice of candidate products for which timely and affordable access is desirable: different aspects of unmet need could be relevant (unmet medical need, public health need, healthcare cost savings), and the competent stakeholders should give input on these aspects.

Increased patient participation in the future will assist in the selection of candidates for which accelerating access is particularly desirable, and to provide insights on feasibility, ethical aspects, and to support enrolment in trials and registries.

Input from healthcare professionals on the feasibility of implementing patient registries in clinical practice and on the control of prescriptions is useful.

- *Post-authorisation data gathering plans*

The challenge remains to identify methodologically sound strategies of real-world evidence collection to support the assessment of efficacy, to make them as acceptable to decision makers as real-world evidence is at present to support the assessment of safety. These issues need to be discussed further in appropriate fora of stakeholders and research programmes.

Most companies were not ready to describe real-world data plans, or value proposition strategies in detail at a stage when they do not yet know whether the product will prove effective. Companies are nevertheless encouraged to plan different scenarios stemming from different efficacy levels, adapting the amount and type of data to be collected according to the data generated at various milestones along the development pathway. For example a more accelerated licensing and re-imburement strategy may be possible in case of compelling data in the early stages of development, indicating the potential for substantial contribution to patient care, while a more traditional, RCT based approach should be followed in case of more marginal results.

On a conceptual level, the work of IMI projects such as GetReal may shed greater clarity on stakeholders' expectations and limitations of real-world data use. This may result in more elaborated proposals in future.

- *Preparatory discussion at advice pre-submission stage*

Good preparation by medicine developers of a set of potential development avenues that could be followed is essential to enhance the value of the exchange at the advice stage. Companies should provide an analysis of the feasibility of the various proposals and scenarios, with a clear timeframe in

mind. This is helpful for the discussion as it would be expected that post authorisation studies be conducted in the agreed timeframe.

- *Marketing authorisation route*

The submitted proposals did not highlight any impediments in the regulatory tools, processes or mindset that would make an adaptive approach unfeasible. There were, however, a number of issues identified that may warrant further discussion:

- the current situation where it is not possible to vary an existing marketing authorisation to give a conditional marketing authorisation for a new indication;
- The difficulty of demonstrating significant benefit for very early approvals of orphan medicines;
- The timing of paediatric development when adult studies are accelerated;
- The necessity to implement reliable prescription controls for the initially licensed population;
- Specific challenges of quality development for ATMPs when clinical development is accelerated.

EMA supports prospective discussion of the conditional marketing authorisation route and the earlier access it may provide, and believes that early discussion of the development plan with downstream stakeholders, and inclusion of their requirements in the data collection plan, may allow faster reimbursement decisions.

Regulators are very committed to seeing the obligation for follow-on studies to be carried through, and experience has shown that the delays seen so far with conditional marketing authorisation are not excessive. Early planning of any proposed registry or post-authorisation study may also result in a more feasible, better designed study and increase the chances of meeting the desired patient accrual within shorter timelines.

In addition to early stage dialogue, EMA is also interested in investigating the possibility of safe-harbour multi-stakeholder dialogue in the peri-approval (or immediate pre-approval) setting, in particular for applications that might target conditional marketing authorisation. If any such studies were required for the confirmation of the safety or efficacy profile of a medicine, this may provide an opportunity for alignment and consolidation of other post authorisation investigations that may be requested at Member State level.

- *Involvement of HTA bodies*

In line with the existing EMA-HTA parallel advice process, the participation of HTAs in the adaptive pathways discussions and subsequent advice is voluntary, and only a subset of HTAs have participated so far. The downstream impact of adaptive pathways on a wider set of HTA bodies and on payers should be further assessed and discussed.

Generally, HTAs which had the conceptual interest and the resource capability engaged in the pilot once approached by the company, but the fit within existing mechanisms and procedures has proven burdensome in terms of resources (both for EMA and HTAs), due to the number of simultaneous applications received, the concomitant pressure on resources exercised by the dramatic increase in the volume of parallel regulatory-HTA scientific advice requests in the same time period, and the flexible and iterative nature of the discussions, which was difficult to accommodate into streamlined existing workflows.

Fully tapping into specialist resources with therapeutic area expertise has been difficult within the flexible framework and tight timelines of the pilot's discussions. Therefore, HTA input on the design of protocols to be submitted for the subsequent parallel regulatory-HTA scientific advice has, at this stage, focused on more general issues, such as national policies and approaches to HTA assessment,

including the best use of national support schemes to early access, and on the principles of the collection of real-world data on clinical outcomes and quality of life against appropriate comparators.

Future submissions from the date of this report will be treated as parallel HTA/scientific advice requests. In this way a well-tested and established framework will be utilised, where patient participation is already established.

- *Communication to prescribers and appropriateness of prescription*

A clearly identifiable and controllable patient population is a prerequisite for the adaptive pathways approach. For some of the proposals controlled prescription was feasible, while others were difficult to implement and manage. Factors that may influence prescription and its control include frequency of disease, precision of diagnosis, availability of therapeutic alternatives, price and reimbursement, point of dispensing (hospital, specialised doctor), societal pressure and expectations.

The use of restricted prescribing/controlled access as a risk minimisation measure and as a channel to collect post-authorisation data requires prescribers to be trained, patients to be included in a registry, and perhaps even the setting up of controlled distribution schemes.

This will require further discussion at Member State level, taking into account national differences (e.g. cultural differences about physician autonomy and practical differences relating to how the positive and negative lists operate), coordination and investment in electronic prescribing, diagnostic data linkage and innovative models of controlled prescribing.

- *Perception of increased risks for patients⁶*

While it is reiterated that only products for which a positive benefit/risk balance is demonstrated according to the current legal framework will receive a marketing authorisation, there is a need to build confidence in the concept of adaptive pathways by supporting methodologically sound cases in areas of high medical need, and through open dialogue and transparent communication.

- *Value proposition*

The aim of adaptive pathways is to design development plans that support regulators' benefit-risk assessments and HTA bodies' assessment of value. However, the submission of plans on value proposition and reimbursement strategies has been limited in most cases. Submitted examples included the possibility of annuity payments for one-off treatments, with the aim of reducing the budget impact, and the possibility of linking registries to reimbursement and the feasibility of adaptive pricing upon demonstration of longer-term effectiveness.

To meet the needs of HTA bodies, the value proposition strategy should identify how the product can add value compared to existing options, for example by addressing an unmet need or reducing high healthcare burden. Some companies merely provided evidenced statements regarding need, burden of disease or shortcomings or costs of existing treatments. The shortcomings of currently available treatment options are not a valid value proposition. A company will need to specify how it plans to show that the intervention is superior to currently available options. Reduction in health care resource use is a valid part of a value proposition and the approach to demonstrate expected savings through the use of the intervention may be discussed. A number of safe-harbour discussions centred on the need for companies to consult with health-outcomes specialists or health economists in addition to the

⁶ BMJ 2016;353:i3060

usual clinical considerations. This will ensure the development strategy collects the necessary evidence.

Comparative effectiveness is what ultimately matters for the decision to support reimbursement of one treatment over another, and the parallel regulatory-HTA scientific advice has seen a rapid increase in numbers of requests in the past year. While reimbursement is and remains a national decision, consulting the decision makers on the requirements to demonstrate an added benefit is even more important in adaptive pathways, where the evidence set makes use of different data sources aiming to create a common evidence base to address both regulator and HTA needs.

The fact that some value proposition proposals were not well-developed was explored in a questionnaire sent to companies. This may be partly due to different perspectives and risk-aversion between the market access and medical departments of companies, to the belief that these discussions were premature due to the early stage of development, and to the fact that payers were not among the involved stakeholders, therefore lowering the predictability of the proposed approach. This difficulty was particularly pronounced for SMEs, and for this reason two preparatory meetings, instead of one, will be offered to SMEs in the future.

- *Involvement of payers*

Payers did not participate in the pilot. The submission of plans on value proposition and reimbursement strategies has been limited in most cases. In some cases when input on the design, acceptability and feasibility of adaptive pricing strategies linked to the data collection was needed, the involved HTAs were not in a position to provide an answer. This has highlighted that in specific cases payers' input on the principles and feasibility of such schemes would be important early in the process if these schemes are envisaged as part of the development plan.

The involvement of payers may be important in cases where there is a need to give increased certainty on the suitability of the proposed scenarios, or where some novel aspect of evidence, appraisal, pricing or re-imbursement are proposed (e.g., up/down pricing as evidence accumulates, how annuity payments fit within the different national framework, experiences and lessons learned at national level on how to use registries for effectiveness and reimbursement).

The importance of payers' input has also been highlighted in the context of the feasibility of designing an optimised registry which could be useful for decision-making of all stakeholders (regulators, HTAs and payers).

The specificities of some products (e.g., for ultra-rare diseases) which are within the remit of other national bodies or have different decision making pathways, may require the involvement of those decision makers in future discussions too.

In line with the Council conclusions⁷, possible synergies between the work of regulatory bodies, HTA bodies and payers, in order to ensure timely and affordable access of patients to innovative medicines, should be explored.

Payers will be invited to participate in discussions where specific relevant questions will be raised by the company, with the aim of providing feedback on the acceptability of the principles underlying the chosen approach. Additionally, within the framework of ADAPT-SMART, a number of theoretical scenarios will be analysed for acceptability. Reimbursement is, and remains, a national decision.

⁷ Council conclusions on strengthening the balance in the pharmaceutical system in the EU and its Member States <http://www.consilium.europa.eu/en/press/press-releases/2016/06/17-epsco-conclusions-balance-pharmaceutical-system/>

5. Next steps

EMA will further explore the adaptive pathways concept as an approach to bringing promising medicines to patients with an unmet need in a timely manner. Relevant outcomes of ongoing initiatives in the area of “early access” (STAMP, EMA registries pilot, IMI GetReal and ADAPT_SMART) will also need to be considered in the adaptive pathways concept to avoid duplication of efforts and build the best synergies.

Future adaptive pathways discussions, including proposals already submitted, will be incorporated in the existing operational platform of a parallel regulatory-HTA scientific advice, with the inclusion of other stakeholders (patients, interested HTAs and, if relevant, payers will also be invited) which are relevant decision makers for the specific issues under discussion. This will provide a more structured, sustainable and tested framework, and may increase the availability of relevant expertise from all stakeholders. An additional presubmission meeting (two for SMEs) will be granted as compared to the parallel regulatory-HTA scientific advice.

The type of stakeholders to be involved in the presubmission discussions should be determined on the basis of the issues to be addressed. As for all parallel regulatory-HTA scientific advice, it is the responsibility of the company to contact the desired participants, and the EMA will assist in identifying the patient representatives according to the existing process. It is possible that interested payers’ organisations may agree to the participation to the preliminary discussions, under the understanding that they would provide feedback on the feasibility of the proposed reimbursement schemes but in no case will pricing discussions be undertaken.

The number of advice requests undergoing preparatory AP discussions will be reported in quarterly reports, and an analysis provided annually in the EMA annual report.

Adaptive pathways is still a concept in development which will be fine-tuned as more medicines in development are considered for this approach, in particular where clinical trial design is difficult or too lengthy and where novel approaches to evidence generation and decision-making might lead to accelerated patient access.

EMA values contributions from stakeholders on its initiatives, as feedback and open debate are essential for adapting and fine-tuning concepts and approaches and ensuring that they meet stakeholders’ expectations.

EMA will organise a workshop in the fourth quarter of 2016 to gather views and proposals from its stakeholders on the adaptive pathways approach.

6. List of abbreviations

ADAPT-SMART Accelerated Development of Appropriate Patient Therapies: a Sustainable, Multi-stakeholder Approach from Research to Treatment-outcomes (an IMI project)

ATMP: Advanced Therapy Medicinal Product

CAT: EMA Committee for Advanced Therapies

EMA: European Medicines Agency

EUNetHTA European Network for Health Technology assessment

HTA: Health technology assessment

ITF: EMA Innovation Task Force

NCA: National Competent Authorities

nCAPR: network of Competent Authorities for Pricing and Reimbursement

PDCO: EMA Paediatric Committee

PRIME: PRIority MEdicines

RCT: Randomised Clinical Trial

RWE: Real World Evidence

RWD: Real World Data

SME: Micro, small and medium-sized enterprises

STAMP: European Commission Expert Group on Safe and Timely Access to Medicines for Patients