EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

# Adaptive pathways workshop briefing book

## Readers' guidance

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**About this briefing book**

This document is preparatory reading material for the adaptive pathways workshop. It is meant to be a working tool to support productive discussion at the workshop.
It presents anonymised examples of the products discussed in the EMA parallel regulatory-HTA scientific advice, and reflections on the issues raised by civil society on the pilot.

The workshop consists of three sessions covering the three areas for further discussion identified in the final report on the adaptive pathways pilot. A full report on the workshop will be made available on the EMA website.

We advise you to read the briefing book in full prior to the meeting. To assist participants in preparing for the floor discussion following each session's presentations, some sections of the briefing document where these areas are discussed are linked below (Ctrl+click):

• *Agenda Topic 1: Patients and healthcare professionals' involvement and perspective on unmet need*

Patient involvement and input (e.g. A, B, C, D, E, F, G)

Unmet need (e.g. A, B, C, D, E)

• *Agenda Topic 2: Methodological challenges to the use of Real World Data (RWD)*

e.g. A, B, C, D, E, F, G

• *Agenda topic 3: Conditions to facilitate input from downstream decision makers.*

e.g. A, B, C, D, E, F, G

**Suggested background reading**:

These documents on the EMA website provide information on early access tools and the EMA position on adaptive pathways.
Early access tools at EMA
Report on the adaptive pathways pilot

# Adaptive pathways workshop, 8 December 2016

Participant briefing book

## 1. Introduction

**Why this workshop?**

Adaptive pathways is a scientific concept of medicines development and data generation intended for medicines that address patients' unmet medical needs. It can be defined as a prospectively planned, iterative approach to bringing new medicines to patients.

Between 2014 and 2016 EMA conducted a pilot project to explore the practical implications of the adaptive pathways concept with medicines under development, prospectively looking at actual development programmes submitted to the Agency for advice on the design of the clinical trials[1] (report on the adaptive Pathways pilot).

The initiative aims to look at how to optimise clinical data collection of beneficial medicines, to meet both regulatory and Health Technology Assessment (HTA) requirements so that the need for redundant/additional studies is reduced, and the lag time between regulatory approval and subsequent steps before patients access is reduced. It also explores the potential for real world data to increase the knowledge on the actual performance of treatments in the daily clinical setting. It recognises the existence of an increasingly complex regulatory and medicines' access environment and seeks to maximise the value of prospectively planned post-authorisation activities.

This is considered important especially in the case of products with a conditional marketing authorisation, where reimbursement and patient access may be delayed by the lack of elements supporting HTA and payers' decision-making; in areas of high public health need where research is lagging or the design of randomised clinical trials (RCTs) is difficult (e.g. new antimicrobials, Alzheimer's and other degenerative diseases, and rare cancers); and in situations that present challenges to the traditional value proposition and reimbursement models, as could be the case for newly emerging treatment modalities such as gene therapy.

During this period, stakeholders' interest has been high: feedback expressed by civil society and researchers on the concept and the methodological validity and feasibility of the data collection approaches must be given the appropriate weight.

**This workshop is organised in collaboration with the European Commission to explain aspects of the adaptive pathways concept, as examined by EMA, in light of the practical experience gained during the pilot project; to gather the views and proposals from stakeholders on the adaptive pathways approach; and to plan the next steps in the exploration of this concept.**

**What is expected at the workshop?**

The workshop will consist of three sessions covering the areas for further discussion identified in the final report on the adaptive pathways pilot: patients and healthcare professionals involvement and perspective on unmet need; methodological challenges to the use of real world evidence (RWE); conditions to facilitate input from downstream decision makers.

[1]Interactions between stakeholders took place in a 'safe harbour' environment so that strengths and weaknesses of all options for development, licensing and value assessment were explored openly and informally without binding commitments.

Each session will have three speakers on the subject, followed by a 60-minute open discussion with the audience, which consists of around 200 people from all stakeholder groups. The workshop will also be publicly broadcast.

Speakers at the workshop are encouraged to frame the discussion in light of the practical experience gained during the pilot. This document presents anonymised cases of products submitted for the pilot where the conduct of RCTs was difficult, conditional marketing authorisation (CMA) could be considered, and the collection of RWE was considered feasible to support medicine development.

These cases are discussed in light of the type of questions posed by the different stakeholders and of the areas prioritised by the Patients and Consumers and Working Party (PCWP) and the Health Care Professionals Working Party (HCPWP) - see section 4 for further details. During the discussion, attendees will also be encouraged to comment in relation to the clinical developments presented in this briefing book, and, if desired, to suggest potential alternative solutions.

## 2. Development support and early access tools at EMA

EMA is committed to enabling timely patient access to beneficial medicines, particularly those that target an unmet medical need or are of major public health interest. The Agency seeks to support the medicine development process from an early stage and to offer regulatory mechanisms to help promising new medicines reach patients in a timely manner[2].

Support can be provided in two ways, which are not mutually exclusive[3]:

- Through legal provisions in the European Union (EU) pharmaceutical legislation;
- Through regulatory support schemes such as PRIME and Innovation Task Force (ITF), which advise, strengthen and streamline the use of regulatory support.

Scientific advice is the legally-established platform where the proposed product development is discussed at EMA. Such discussions can involve, in addition to EU regulators, other stakeholders (e.g. HTAs, EU payers, non-EU regulators, patients, WHO).

The pilot showed that the adaptive pathways approach can be embedded within the existing regulatory framework using available tools and processes.

**The pilot showed that the adaptive approach can take place within the existing regulatory tools and processes.**

Therefore medicines development plans that fulfil the below characteristics of the adaptive pathways approach are now accepted for parallel regulatory-HTA scientific advice, with the inclusion of other stakeholders who are relevant decision makers for the specific issues under discussion. This provides a more structured, sustainable and tested framework, and may increase the availability of relevant expertise from all stakeholders. An additional pre-submission meeting (two for SMEs) is granted as compared to the parallel regulatory-HTA scientific advice.

Adaptive pathways is a specific type of scientific advice discussion, where, in order to indicate which elements would be necessary for their evaluation, decision makers and stakeholders offer their views on development programmes that foresee:

[2] For an overview of access tools refer also to section 4 of the SME guidance http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2009/10/WC500004134.pdf

[3] http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000856.jsp&mid=WC0b01ac058096f643

1. A development plan that is iterative in terms of evidence generation and decision points, prospectively designed;

2. The involvement of HTA bodies and other downstream decision-makers;

3. Real world evidence as a complement to RCTs; in particular in the post-authorisation phase where RCTs might become less feasible and might not be an appropriate method to address the question of interest.

## 3. Anonymised examples of adaptive pathways pilot discussions

Specific examples of submissions cannot be presented due to the need to maintain confidentiality in the early stages of product development discussions. This is the same approach as for all early stage discussions at EMA (e.g. scientific advice, ITF, business pipeline).

The following anonymised examples are intended to provide background insights to the type of discussions that take place during the adaptive pathways meetings: discussions on possible different development scenarios, the questions put to different stakeholders according to their remit, the limitations to the possible input (lack of relevant stakeholders around the table; discussion only on the approach to data collection, not assessment of data).

**The examples illustrate the type of discussions taking place during the pilot.**

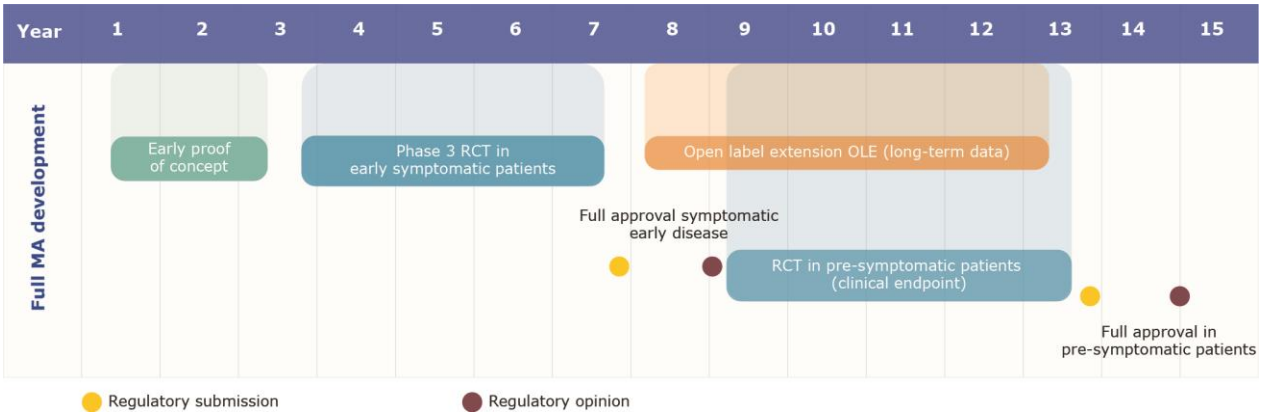
The number of examples is fewer than six EMA parallel regulatory-HTA scientific advices (which was the target for the pilot conclusion), as the content of some discussions was rather similar once anonymised. The more salient examples are presented to exemplify learnings.

*Example 1: Disease-modifying drug for a degenerative disease*

Consider the case of a disease modifying drug for a degenerative disease, where the progression is well documented in the medical literature, and a number of registries (or long term epidemiological studies) exist.

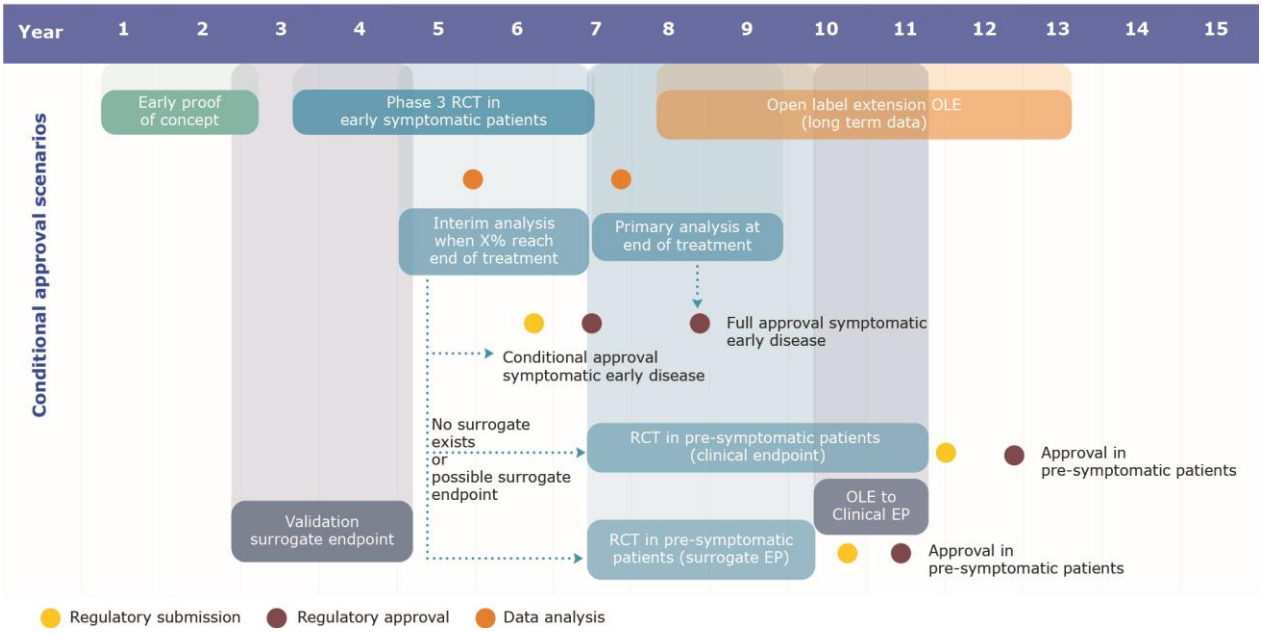
In order to capture progression in a reasonable timeframe, early symptomatic patients are likely to be studied first. Only when there is reassurance of beneficial effect in symptomatic patients, would the trials in pre-symptomatic patients start. In a traditional development approach (Figure 1), the sequential approach to the trials means that a long time is needed for this development.

**Figure 1.** *Development approach based on initial full approval*



In an adaptive pathways approach (Figure 2), different scenarios are discussed to define the conditions under which it may be possible to initiate trials earlier, and to design these trials to address the needs of all stakeholders. From the figure below, for example, at the time of interim analysis the level of evidence for the decision whether to apply for CMA could be discussed. The interim analysis, if the benefit/risk is positive, may support an earlier start of RCTs in the pre-symptomatic patients. If a validated surrogate endpoint exists, approval in pre-symptomatic patients may be granted even earlier.

**Figure 2.** *Adaptive scenario: initial conditional approval*



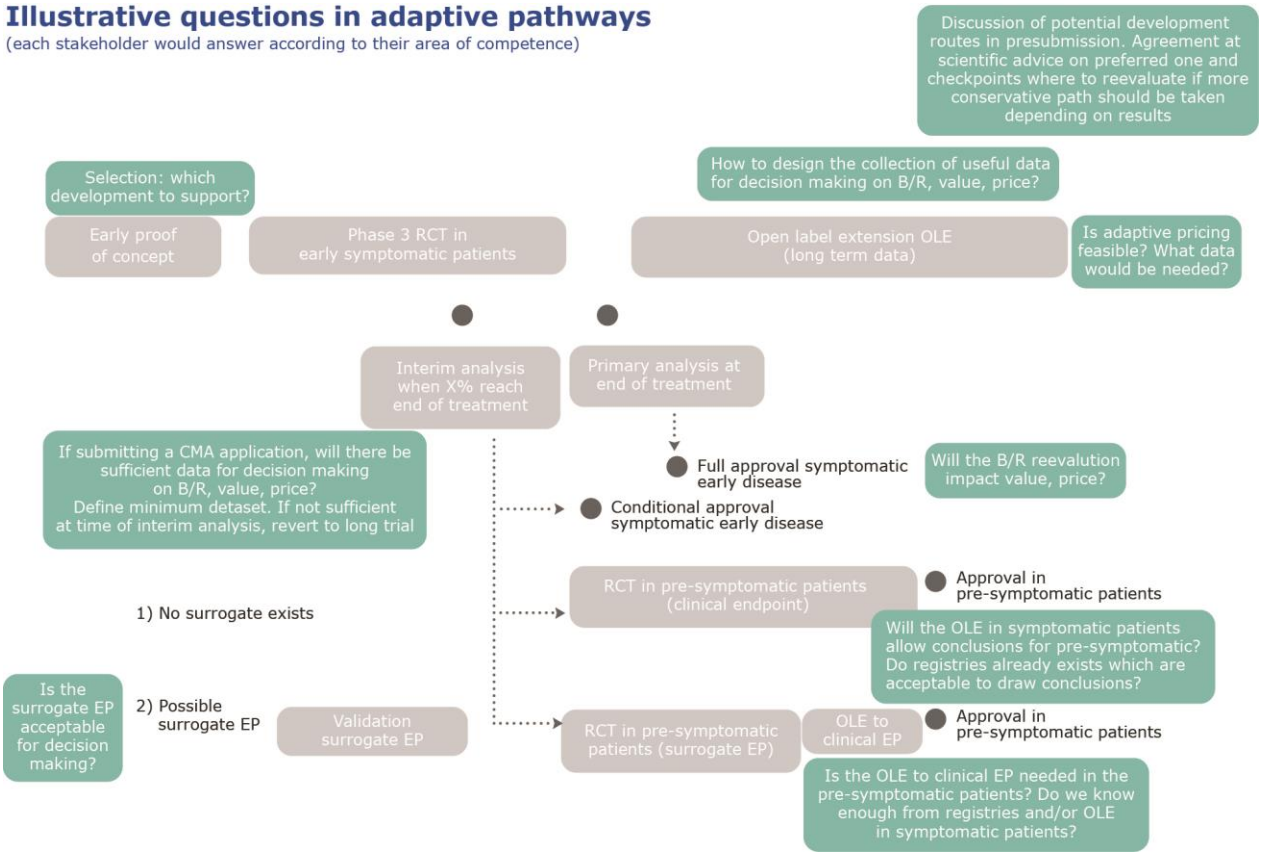

In this specific example, the criteria for adaptive pathways are fulfilled as follows: iteration comprises both the possibility of an initial CMA (should the results of the interim analysis be positive) and the expansion to a wider population of pre-symptomatic patients); the use of real world data could be made in several ways (use of existing registries to predict progression of the disease; helping towards validation of surrogate endpoints; designing the open label extension as a registry - with or without additional patients to the ones enrolled in the RCT; utilising the Open Label Extension (OLE) data as a possible basis to extrapolate progression of the disease in pre-symptomatic patients; designing a pay-per performance registry to capture the long term outcomes, etc.).

To understand more in detail the type of discussion that can take place in an adaptive pathways approach, potential stakeholder questions on the different steps of this adaptive scenario are highlighted in Figure 3.

These considerations may well be discussed outside an adaptive pathway scenario, in either scientific advice or an EMA parallel regulatory-HTA scientific advice, though the scope of routine discussions in those fora are usually restricted to the questions posed by the company. The adaptive pathway discussions are necessarily broad in scope, both in terms of stakeholder groups and in terms of product lifecycle. What the proposed EMA adaptive pathways approach adds, is that the potential scenarios can be preliminarily discussed without commitment on the part of either the stakeholders or the company, and before the full protocols for the chosen pathway are developed. Sample questions asked at this stage, which allow the company to choose which one of the development pathways they will develop further for an EMA parallel regulatory-HTA scientific advice, are exemplified in Figure 3. One of the findings of the pilot is that not all stakeholders currently involved in the EMA parallel regulatory-HTA

scientific advice are competent to address these questions: according to the Council conclusions[4], the exploration of possible synergies between the work of regulatory bodies, HTA bodies and payers is encouraged.

**Figure 3.** *Illustrative questions for stakeholders' input on the pilot scenarios described in figure 2*




In the absence of reassurance on the acceptability of the data collection plan to the various decision makers, the company may want to choose the more conservative and lengthy approach, thus delaying patient access. It is again emphasized that the discussion focuses on the elements that would be required for decision making, while the decisions on benefit-risk and on value will depend on the data generated and submitted to the relevant bodies once the studies are completed: checkpoints along the development plan allow companies and stakeholders to revise and adjust the development pathway if the acquired data differ from the initial plan.

*Example 2: Lentiglobin*[5]

In the case of LentiGlobin BB305 (a gene therapy medicinal product for the treatment of transfusion dependent beta-thalassemia) 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] http://www.consilium.europa.eu/en/press/press-releases/2016/06/17-epsco-conclusions-balance-pharmaceutical-system/
[5] Not anonymised as it was disclosed by the company.

*Example 3: Rare cancer*

This medicine was intended to treat a rare paediatric cancer with poor prognosis and limited treatment options (unmet need). For this cancer, healthcare practice/ academic registries exist, recording survival data.

A long-term follow-up and reanalysis of patients from an investigator-initiated study showed that a significantly longer unexpected survival appeared to have occurred (promise to address an unmet need based on a hard clinical endpoint). The survival follow up was ten years, making the performance of a new trial of such duration a complex endeavour.

The proposal from the company was to match this retrospective cohort with an historic control group from the existing registries, seek a CMA, and set up a prospective single arm confirmatory trial vs historical controls (use of real world data in the proposal).

In this case the company was advised not to follow this route, but to design a two arm prospective randomised clinical trial vs best physician choice. The reason for this suggestion is that a positive benefit/risk balance is a prerequisite to grant a marketing authorisation, and the proposed plan did not offer sufficiently high plausibility to provide robust and definitive evidence to reach a conclusion on the benefit/risk: patient numbers are very low due to the rarity of the disease, there was no randomisation in the original study, history of previous treatment was difficult to track, population homogeneity and matching with the databases was a further complication. Collection of data supporting the prospective study through compassionate use programs was welcome.

It was acknowledged that the conduct of a two-arm trial is very difficult, but the blinding difficulties due to the different administration can be overcome by an appropriate design, and patient associations may assist in informing and recruiting patients in this rare setting.

In this case, even in the presence of undeniable unmet need and of an unquestionable endpoint (overall survival), the methodological doubts both in the existing databases and in the early clinical results made accepting the use of historical controls in an adaptive pathways approach a unacceptably risky strategy: patient welfare and reliability of data must be ensured before the data can be considered in support of a marketing authorisation application.

*Example 4: anti-infective for uncommon infectious diseases*

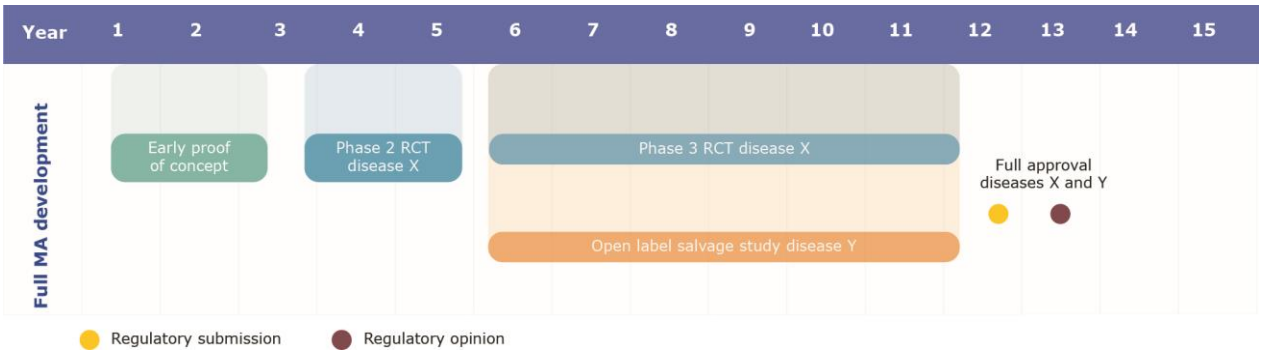
This medicine was a first in class anti-infective for uncommon infectious diseases (X and Y) of relatively high mortality. Disease Y is of orphan-drug prevalence. The treatment options available are limited, and present important ADRs. Resistance towards available treatments is emerging (unmet need).

The proof of concept studies, supported by PK, PD and microbiology, showed an effect size large enough to give reassurance of the promise to address the unmet need.

It is difficult to obtain positive cultures from patients to confirm the infection, and survival data are preferred as an endpoint, with supportive microbiology.

Given the incidence of the disease, a fully powered Phase 3 study would not be feasible within a reasonable timescale. The projected study duration indicate that a traditional route would take around ten years, including regulatory evaluation time (Figure 4).

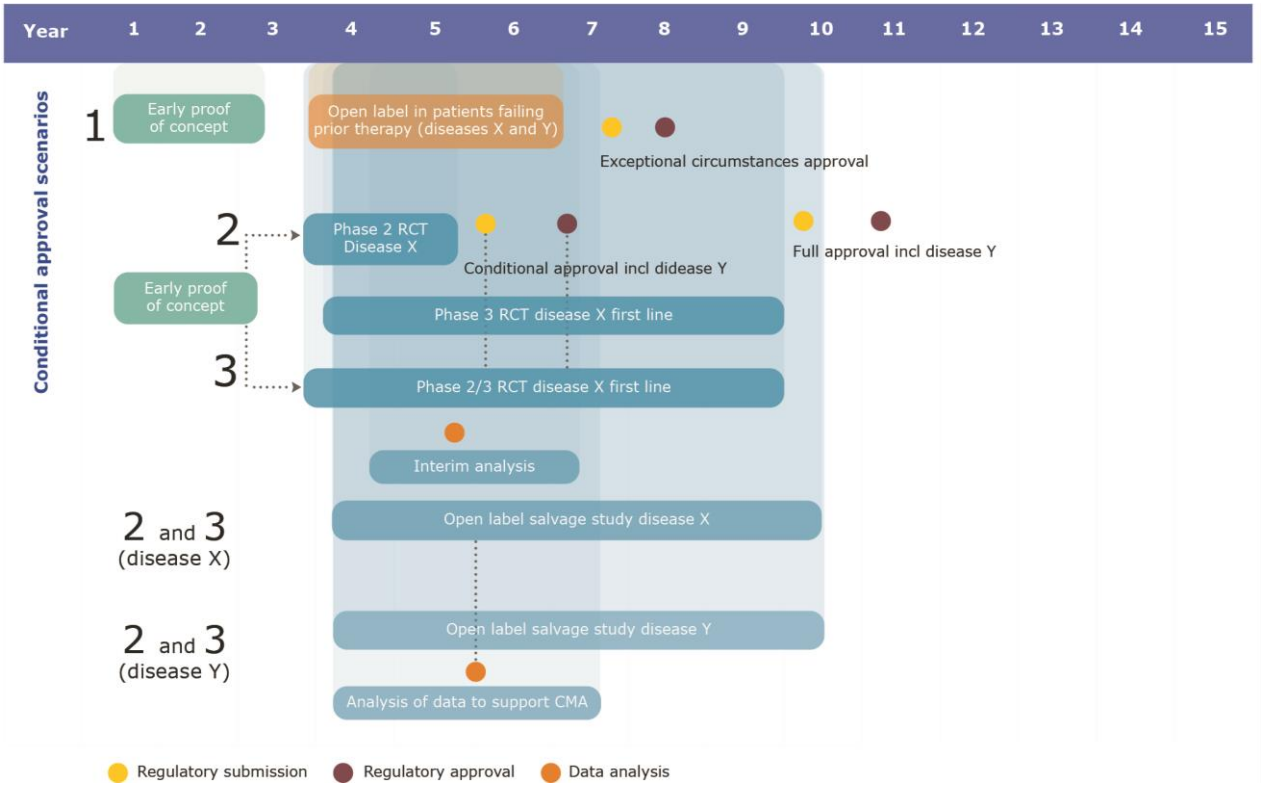
**Figure 4.** *Development approach based on full initial approval*




The product is expected to be used in specialised centres, and its usage limited (aspect relevant to the HTA/payer discussion).

Several different scenarios are possible (Figure 5). Both the company and EMA's Committee for Medicinal Products for Human use (CHMP) agreed that scenario 1 is not advisable: fully open label data would be difficult to interpret, and the feasibility of post-authorisation studies once an approval is granted could be difficult, resulting in the need for an MAA under exceptional circumstances.

**Figure 5.** *Adaptive scenarios: initial conditional approval*




Scenario 2 (two separate phase 2 and 3 studies randomised non inferiority vs active comparator , with enrolment of the phase 3 well under way at the time of CMA) and scenario 3 (a phase 2/3 study with an interim analysis) would allow an earlier approval while continuing to acquire data in a randomised fashion for disease X.

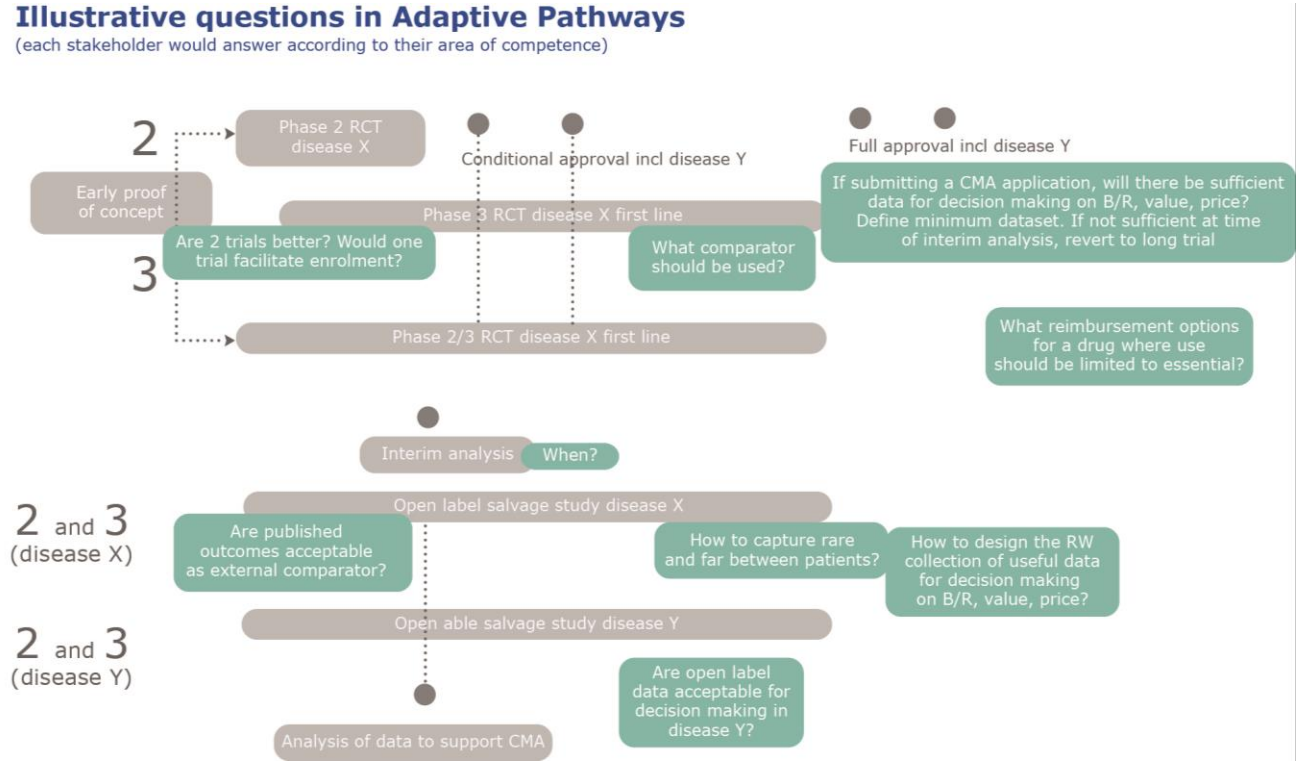
It is accepted that, in both scenarios, the data in disease X would be supported by open label salvage studies.

Due to its rarity, randomised clinical trials would not be feasible for disease Y, which therefore unavoidably needs to rely on the collection of open label salvage data for efficacy. These would be compared to literature-reported outcomes as an external comparator, and supported by the safety data from disease X programme and in vitro microbiology data.

The marketing authorisation would switch to full upon completion of the fully powered phase 3 RCT, and open label data from larger salvage groups. These trials would be feasible in a more reasonable timeframe and provide elements from a randomised clinical trial population supported by a real life one, reflecting standards of care.

The open label salvage studies provide an example where real world data can usefully supplement the results from randomised clinical trials with a population where data collection would be challenging.

**Figure 6.** *Illustrative questions in adaptive pathways*




*Example 5: ATMP for potential use in a number of degenerative conditions*

The mechanism of action of this medicine could potentially be useful to address a number of different degenerative conditions. Indications A and B (for both no pharmacological intervention is currently authorised, and the current Standard of Care (SOC) is deemed to provide unsatisfactory outcomes) were discussed in two separate advices.

Different subpopulations and degrees of unmet need exist depending on patient classification according to well established scales and diagnostic criteria. Clinically relevant outcomes are however multifactorial and vary depending on the degree of severity. Posology may also vary with degree of severity. There are registries but also a history of failed development programmes in the area. The initial focus on patients with highest unmet need was welcomed but recovery of the most severe patients might be unlikely due to the advanced disease status, and the medicine might offer greater benefit in less advanced stages.

The company was advised to follow a traditional RCT route: the proposed composite endpoint included components less easy to standardise and more subjective, hence less reliable as a basis for decision making based on collection of real world data, and is unlikely to be able to conclusively show a 'major therapeutic advantage' as required by CMA.

Although registries exist that were considered for integration with the internal controls to reduce the size of the comparator arm, associated comorbidities often found in these populations are a confounder, and collection of data from several registries across different regions with different SOC was also deemed problematic.

## 4. Topics raised by civil society in relation to adaptive pathways

During the conduct of the pilot, a number of publications and letters from civil society representatives addressed to EMA and the European Commission raised conceptual and methodological questions.

Ten recurring topics were identified:

a) How is 'unmet need' to be understood for the selection of AP products[6]?

b) Are real world data an adequate source of information for marketing authorisation and reimbursement decisions?

c) How can it be ensured that post marketing obligations will be honoured by industry?

d) Is it possible to ensure appropriate utilisation after initial marketing authorisation?

e) Is the process reversible if information is not forthcoming or if the benefit-risk balance does not meet expectations? (Are there exit strategies?)

f) How can patients be optimally involved in the discussion?

g) Will patients be exposed to increased risk?

h) Is there a risk of lowering the regulatory requirements for applications going through adaptive pathways?

i) Is affordability a criterion to be taken into account for adaptive pathways?

j) Is the objective to apply adaptive pathways to all marketing authorisation applications at a later stage?

One of the purposes of the workshop is to discuss civil society priorities in light of the actual experience of products submitted in the pilot.

In order to gauge stakeholders' views on their relative importance, the ten topics were presented to PCWP and HCPWP on 19 September 2016, asking the working-party members to rank the top five according to their opinion.

Overall, 17 responses were received. Assigning a weight to the answer's ranking, the following priorities emerged:

**Patients and civil society representatives' ranking:**

1st: Unmet need
2nd: How can patients be optimally involved in the discussion?

3rd: Post-marketing obligations fulfilment
4th: Potentially increased risk
5th (joint): Lowering standards & real world data

**Health care professionals' ranking:**

1st: Potentially increased risk
2nd: Reversibility of decision
3rd: Post marketing obligations fulfilment
4th: Lowering standards
5th: Real world data

**Adaptive pathways is not intended to be applicable to all products.**

The message by EMA that adaptive pathways is not intended to be applicable to all products seems to have been clearly understood, as this was ranked the lowest by both groups, therefore it will not be discussed in this briefing book.

Affordability was raised in several publications recognising that marketing authorisation is not equivalent to patient access, as the price of new medicines can be unaffordable to health systems and individual patients[7]. It received a high number of hits in our survey, but for fifth place, indicating that it might be more of an issue for consumer bodies and payers rather than for patients and healthcare professionals (HCPs). It will not be discussed in the briefing book, but it may be raised at the workshop discussion by the competent stakeholders.

## 5. Civil society priorities and experience in the adaptive pathways pilot

This chapter discusses the top ranked civil society priorities in light of the actual experience of products submitted in the pilot. The considerations presented in this chapter are intended to assist an open discussion within each workshop's session.

**Unmet need**

The adaptive pathways concept is not meant to be applicable to all medicines, and unmet medical need is a necessary driver to invoke the possibility to use all the tools and flexibilities available to the public stakeholder bodies. Speeding up a development *per se*, in the absence of addressing an unmet need, is not a goal of the discussion.

From the regulatory point of view, Commission Regulation (EC) No 507/2006 on Conditional marketing Authorisation defines 'unmet medical need' as *a condition for which there exists no satisfactory method of diagnosis, prevention or treatment authorised in the Community or, even if such a method exists, in relation to which the medicinal product concerned will be of major therapeutic advantage to those affected.*

**Speeding up a development *per se*, in the absence of addressing an unmet need, is not a goal.**

All products accepted in the pilot were for conditions with major impact on quality of life / life-shortening / debilitating; AND showed a credible promise of relevant improvements in patient-relevant outcome(s) with an acceptably high probability of a relevant effect size.

A significant proportion of the proposals received in the pilot were not accepted as they related to areas without unmet need.

On the other hand, during the discussions applicants have been advised not to use unmet need as an argument to reduce the data package, but to focus on the requirements for a minimum data package

[7] Adaptive pathways: deregulation under the guise of earlier access http://www.isdbweb.org/publications/download/210

to support a positive benefit/risk balance according to the current CMA legal requirements in the case where immediate availability outweighs the fact that additional data are still to be generated.

The criteria for unmet medical need in order for the regulatory decision to apply CMA remain unchanged.

As the adaptive pathways discussion takes into account the decision-making framework of the involved downstream stakeholders, additional elements to the ones for medicines' authorisation in the EU regulatory framework are brought to the table. There is no universally agreed definition of major therapeutic advantage or added therapeutic value, and different stakeholders (medical journals, HTA bodies, payers) apply different definitions according to their remit: some of these consider parameters that go beyond the current legal framework for medicines. Stakeholders have commented that unmet need can also be defined from a healthcare systems perspective: "*when financial resources are limited, a medicine presenting a benefit risk balance approaching the one of the reference product, but available at a markedly reduced price, can constitute a progress to facilitate patient access.*"[8]

The adaptive pathways pilot was designed to operate within the existing framework and rules applicable to the stakeholders. All accepted products showed promise to address an unmet need, and the discussions involving further decision-makers have allowed them to bring to the table the additional requirements on which they base their decision-making.

The pilot was a voluntary exercise, and showed that questions can only be answered by those who have the remit to do so[9]. To optimise the design of development programmes EMA would like to continue to offer a wide and flexible platform within scientific advice, to involve a variety of relevant decision makers.

**Involvement of patients in the discussion**

Beyond the scientific assessment, there is an increasing need to understand the day-to-day use of the medicines and to better inform the users about the medicines in order to promote their safe and rational use. To achieve this objective, the Agency engages in close cooperation and partnership with its various stakeholders including healthcare professionals' organisations, patients' and consumers' organisations, scientific and academic societies, and the pharmaceutical industry, as mandated by Regulation (EC) No 726/2004. These stakeholder relations have evolved over time, and the type and degree of interaction varies depending upon the stakeholder group concerned and the field of Agency activity.

The experience acquired to date demonstrates that the participation of patients in the Agency's activities has resulted in increased transparency and trust in regulatory processes and mutual respect between regulators and the community of patients and consumers. It is also acknowledged that their contribution to the evaluation of medicines enriches the quality of the opinion given by the scientific committees. This positive experience confirms the importance for the Agency to continue supporting and facilitating patient contribution to its work.

In the pilot discussions, patients' input was sought in trials and registries design (feasibility, ethical aspects, support to enrolment) and to provide input on risk aspects and prioritisation of products.

A presentation in the workshop is dedicated to this experience.

Future submission will be within the framework of EMA's parallel regulatory-HTA scientific advice, where the need for patients' involvement is routinely sought as additional expertise in the discussions.

[8] (translated from the French) *Evaluer le progres Therapeuthique: avec methode, au service des patients.* La revue Prescrire August 2015 page 569

9 Final report on the adaptive pathways pilot, EMA/276376/2016 pages 21-22

Patients are also providing input in the evolution of the adaptive pathways concept through the IMI ADAPT SMART project[10].

**Post-marketing obligations fulfilment**

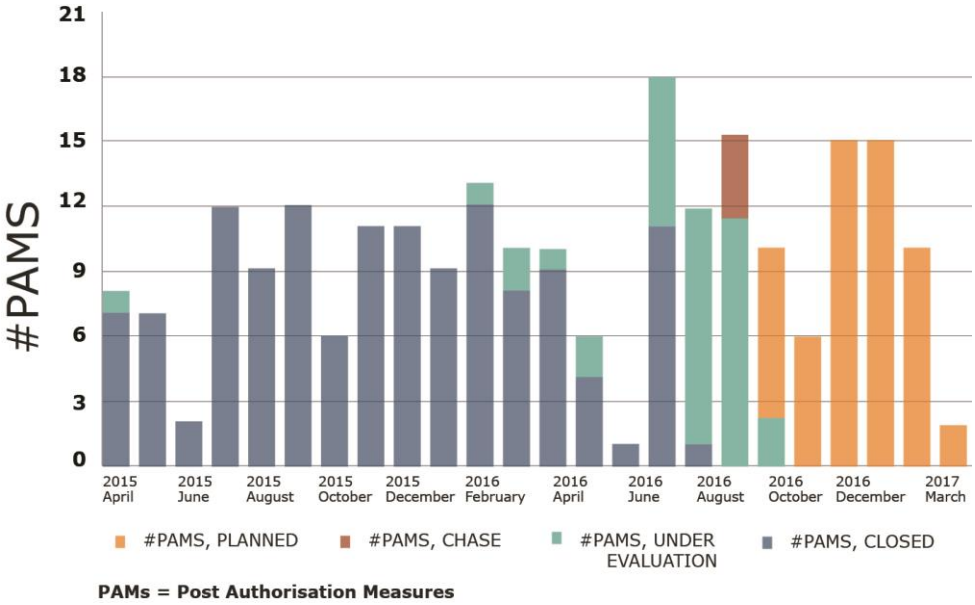
In all cases submitted to the pilot, the discussion has put a firm emphasis on the feasibility and methodological rigour of the proposed study design and on the plausibility that the expected data to confirm the positive benefit/risk will be delivered. Elements that have been considered are: timing of the start and enrolment of the clinical trials, feasibility aspects including consulting patient representatives, the robustness of data sources, endpoints (clear-cut, actionable, methodologically reliable) and methodology (e.g. ability to make reliable treatment comparisons to quantify therapeutic efficacy).

As the examples show, where a convincing case was not presented, applicants have been advised to pursue more traditional development routes.

**There is added benefit in well-planned post authorisation activities.**

On the other hand, there is added benefit in well planned post-authorisation activities: early interaction between stakeholders maximises the opportunity for relevant, comprehensive and efficient data collection. The aim is to design studies based on objectively measurable and quantifiable outcome parameters, to minimise gaps for decision making, so that a decision on value can be taken as well. An adaptive pathways type discussion offers the opportunity to avoid an insufficient data set, or allows redirecting resources away from the development of a medicine that is not likely to offer a therapeutic advantage.

An analysis of fulfilment of post-authorisation measures since 2015 shows generally good compliance of the applicant toward their obligations. This includes postponed submissions that have been agreed by the CHMP systematically through an assessment evaluation procedure based on data presented by the applicant. Detailed analysis of these findings will be published shortly, but a snapshot is presented below:




**PAMs = Post Authorisation Measures**

Data as of October 1st 2016

10 http://adaptsmart.eu/

While a full analysis is ongoing, delays or granted extensions of timeframe over one year were below 15%, of which a few were attributable to better than expected results that led to study prolongation to collect additional data.

Concerns have been expressed (Banzi et al.2015) that switch of conditional marketing authorisations to full marketing authorisations is a slow process: the results reported in the paper show that all products that had not undergone a switch were authorised in the last four to five years. When looking at the time usually required for the completion of a clinical trial this is not an excessive timeframe. The duration of a given study also relates to the type of data that need to be collected: the obligations relating to influenza pandemic vaccines can be postponed for obvious reasons, and for two products where the timeframe was considerably extended, studies required either collection of data in an orphan setting[11] or longer time due to a first-line setting[12]. It is reasonable to conclude that a prospectively planned post-authorisation evidence generation plan, with protocols and their feasibility discussed well in advance of the CHMP opinion, would be of added benefit to shorten this timeframe.

**Reversibility of decision**

With the adaptive pathways concept, EMA acknowledges the existence of an increasingly complex regulatory environment and the emergence of products that challenge the established access paradigms (e.g. ATMPs, antibiotics, disease-modifying drugs).

As a general rule, the benefit/risk profile and the value of a medicine evolve in time as new data are acquired and new treatments reach patients. We seek to use the tools and flexibilities that are available to each stakeholder body, and the potential to learn about medicines from real world data / data generated in clinical practice, to define a strategy for a beneficial medicine to reach patients with the minimum time lag between decisions leading to access.

Regulatory, reimbursement and clinical recommendations all have an impact on patient's access to a medicine, and the relevant tools at the disposal of the different decision makers can be used. From the regulatory point of view, any new negative information that becomes available post-authorisation as well as non-compliance of the marketing authorisation holder with the obligations and conditions linked to the authorisation can lead to a regulatory action (including modification of product information, imposition of obligations, suspension or revocation of the marketing authorisation). Regulatory supervision is particularly close for CMAs, which are valid for one year only and therefore are subject to annual renewal, which re-assesses the benefit-risk balance of the product on the basis of information generated in the imposed specific obligations.

**Real world data**

Publications[13] have cited examples where observational studies have suggested a treatment benefit only to be overturned by RCT. The opposite can also be true, and real world data should be seen as an opportunity to capture the effects of a medicine in a real population and clinical setting.

**Real world data were considered in the pilot as a complement to RCTs**

Real-world data were considered in the pilot as a complement to RCTs: in an adaptive pathways proposal, a coherent, prospective plan for real-world evidence is designed, to inform the design of clinical trials, provide

[11] http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Scientific_Discussion/human/000664/WC500036521.pdf (page 31)
[12] http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Assessment_Report_-_Variation/human/000741/WC500187313.pdf
[13] Ermisch et al Payers view of the changes arising through the possible adoption of Adaptive pathways, Frontiers in pharmacology Sept 2016

context for clinical trial data and to collect high-quality data to further refine the benefit/risk profile, the therapeutic value and the price of a medicine.

One session of the workshop is dedicated to the methodological challenges posed by real world data collection. The issue, together with the point on reversibility of decision, is also depending on the nature of the selected endpoints, on the relative timing of the studies, and on the company's capacity to conduct them: the questions raised in the pilot examples show that when the proposed plan for the collection of post-authorisation data was not considered robust enough, the programme was not considered suitable for the adaptive pathways approach.

The issue of feasibility, cost and data access was raised by the Member States[14] and must be considered before advising a company to pursue a route involving this type of data collection.

There is a need for a framework which provides the EU regulatory network with access to and analysis of an extensive range of multi-national observational data. Components of this framework considered by the EMA include developing sustainable multi-stakeholder governance and funding mechanisms, a comprehensive characterisation of EU-wide sources of real world evidence, identification, or development, of methods to integrate and analyse data and collaboration across stakeholders and borders. In parallel, EMA continues to deliver to its Committees the results of observational studies performed through the EMA-funded studies framework.

**Will patients be exposed to increased risk?**

The introduction of all new medicines into national health services is about finding the right balance between efficacy, safety, certainty, time of access and cost. The same framework applies to adaptive pathways, where no new regulatory standards are proposed.

The examples from the pilot show that it is incorrect to assume that medicines undergoing adaptive pathways will be approved on the basis of Phase 2 data only. In the case of CMA (when immediate availability of a medicine outweighs the fact that additional data are still to be generated), a plan to demonstrate a positive benefit/risk, and a study design commensurate to the required outcomes and the incidence of the disease are required: these were the subject of the adaptive pathways discussions.

Clear-cut, methodologically reliable endpoints are also important for a medicine to be suitable for the adaptive approach, as explained more in detail in the final report of the pilot, as they more easily support decision makers taking action.

The safety datasets are not reduced from current practice and are mutually reinforced across indications and with collection of data from all sources, including compassionate use, which could be used more efficiently as an opportunity for data collection.

For new medicinal products, at the time of marketing authorisation the experience is mostly limited to the population enrolled in clinical trials. Proactive post-authorisation real world data collection, as foreseen by an adaptive pathways approach, would provide more relevant information in subgroups currently underrepresented (e.g. older, co morbid population) in the clinical trials. Early dialogue is beneficial to plan access and risk monitoring measures at Member State level[15].

Regarding the potential for off- label use, the Court of Justice of the European Union ruled that EU law does not prohibit physicians from prescribing medicinal products off-label. Member States apply a variety of policy options to deal with off-label use, including reimbursement policies. Direct Health Care Professional letters are used by EMA in case guidance to prescribers is deemed necessary to ensure optimal use of a product.

[14] http://ec.europa.eu/health/documents/pharmaceutical-committee/stamp/index_en.htm
[15] Godman 2012

**Is there a risk of lowering the regulatory requirements for applications going through adaptive pathways?**

The adaptive pathways product examples show that these development plans fit within the current regulatory framework. What the adaptive pathways offers is the opportunity to avoid a situation where a CMA is granted but a decision on value and reimbursement cannot be reached without collection of additional data. Timely patient access means designing a programme that satisfies the decision making needs of different stakeholders, and this is best done by prospective planning of the pre and post authorisation in a multi-stakeholder forum, to facilitate downstream decision making.

**Adaptive pathways offers the opportunity to avoid a situation where a CMA is granted but a decision on value and reimbursement cannot be reached without collection of additional data**

The development plans are discussed aiming at consolidating and optimising these requirements to reduce the gap between regulatory and reimbursement decisions, not at changing the requirements to grant a marketing authorisation. Offering a platform for this discussion is important, whether it be called adaptive pathways or not.