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Adaptive pathways to patients: report on the initial experience of the pilot project

1. Introduction

On 19 March 2014, the European Medicines Agency launched the Adaptive Licensing Pilot project (from now on referred to as Adaptive Pathways, or AP). This report aims to summarise the experience gained in the period March to December 2014, and outline the next steps of the pilot.

2. Executive summary

Adaptive Pathways is an opportunity for early brainstorming discussion among all relevant stakeholders, including regulators, companies Health Technology Assessment bodies (HTAs) and patient representatives, to explore ways to optimise development pathways and potentially accelerate patients' access to medicines. This faster access may be achieved by shorter time to approval and/or reimbursement decision for targeted groups of patients.

With the publication of this report, the project changes its name from Adaptive Licensing to Adaptive Pathways, to emphasise the fact that its aim is to foster and facilitate the pathway of product development to potentially achieve earlier access to medicines through an early dialogue involving all stakeholders. The term "licensing" has generated confusion about the scope of this project, which is not establishing a new regulatory tool.

This report also announces the closure of the Stage I of the pilot on 28 February 2015, the deadline for submission of new proposals which are not developed enough to proceed directly to Stage II. This is to allow the focusing of resources into the in-depth discussions that will constitute Stage II meetings.

The final evaluation of the impact of the Adaptive Pathways initiative will be undertaken once at least 6 products selected for the pilot have received a parallel Scientific-HTA advice.

3. The Adaptive Pathways concept

The Adaptive Pathways approach intends to maximise the positive impact of new medicines on public health by balancing the need for timely patient access with the importance of providing adequate, evolving information on a medicine's benefits and risks.

Criteria that identify a good candidate product for Adaptive Pathways are:

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1. An **iterative** development plan (e.g. either by gradual **expansion** of the target population, perhaps starting from a population with high(est) medical need, or progressive reduction of uncertainty after initial authorisation based on surrogate endpoints)

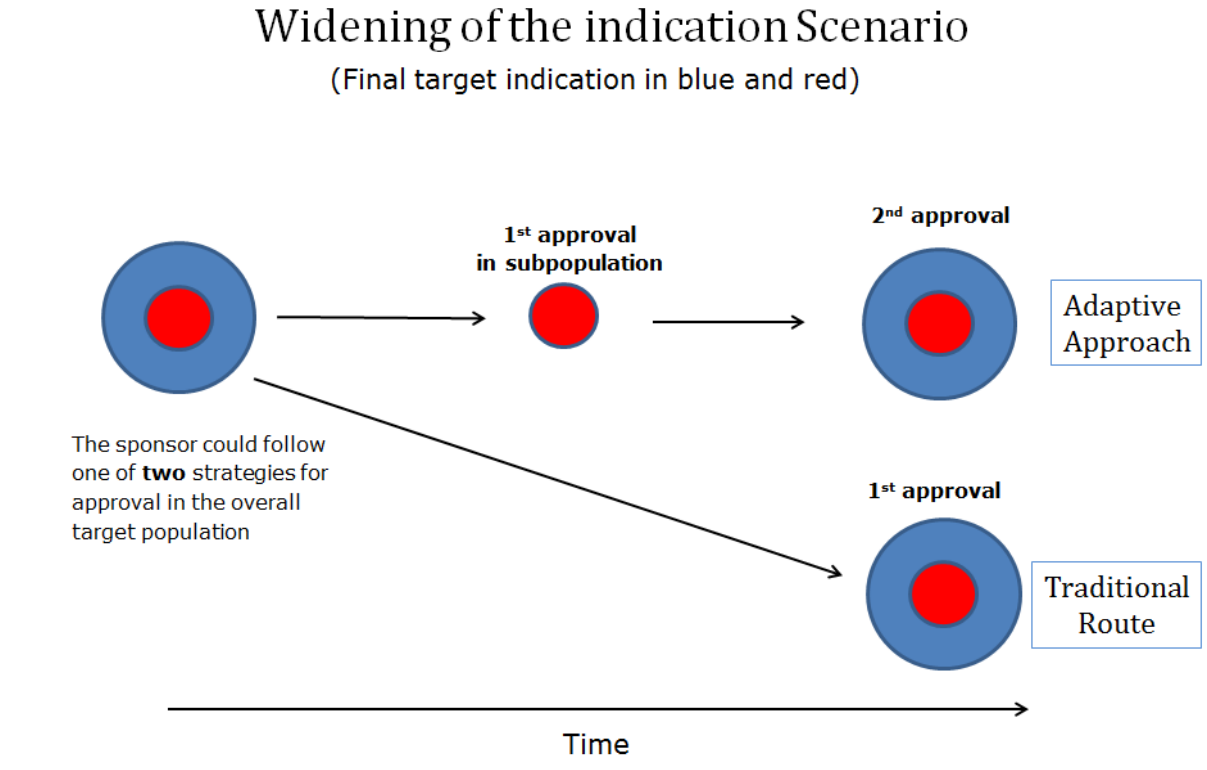
2. Ability to engage **HTAs and other downstream stakeholders,** with proposals for how the demands of these stakeholders can be met.

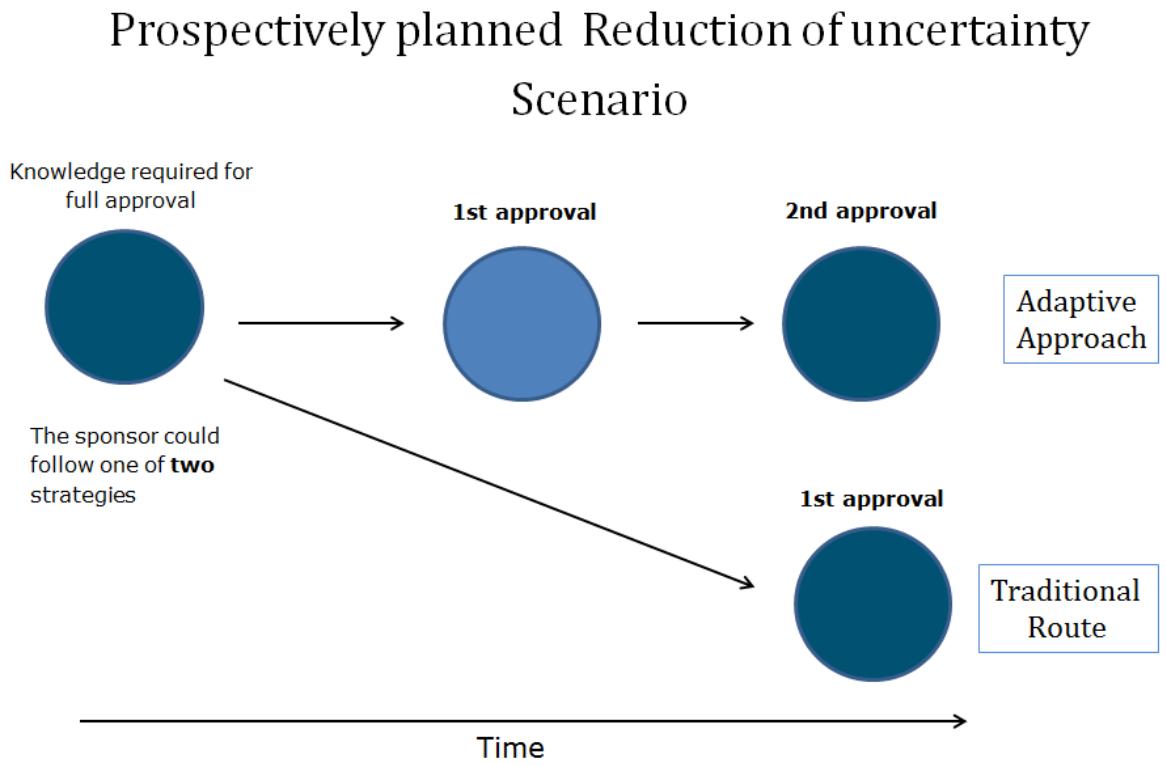
3. Proposals for the monitoring, collection and use of **real-world data**, post-authorisation, as a complement to RCT data, to inform updates to the regulatory label and to the positions of other stakeholders.

Adaptive Pathways is a prospectively-planned lifespan approach, therefore discussions will involve experts from various EMA Committees as applicable. The Adaptive Licensing Discussion Group (ALDG), includes representatives from the CHMP, CAT, PRAC, PDCO, SAWP, COMP and the Agency's Secretariat. ALDG will be renamed Adaptive Pathways Discussion Group (APDG).

AP does not aim at instituting new regulatory tools, but at increasing awareness and optimising the use of all tools and flexibilities within the existing regulatory framework. The type of Marketing Authorisation obtained (full, conditional, under exceptional circumstances), including any potential restrictions or conditions, will be determined case-by-case depending on the level of evidence ultimately obtained.

Two scenarios can be envisaged that would allow earlier access to patients. In the first, approval is granted in a well-defined, high medical need subgroup, and subsequently the indication is widened to a larger patient population. In the second case, an early (perhaps conditional) approval is prospectively planned, for example on the basis of surrogate endpoints, and uncertainty is planned to be reduced through obligations to collect data post-approval with the marketing authorisation potentially converting to 'full' approval once more data are available. Under both scenarios, there is potential for earlier access to patients both through an early first approval, and also through streamlined health economic appraisal, if the HTAs have given input on their requirements for evidence generation during the development phase.





The AP discussions are conducted in a safe harbour environment and all submissions are strictly confidential. As this is an exploratory framework, inclusion or exclusion from the pilot has no bearing either on the regulatory tools and approaches available, or on the future likelihood of receiving a Marketing Authorisation.

4. Agency activities during the reporting period

Due to the interest raised by the launch of the pilot, a Question and Answer document was published in September 2014 to offer further guidance, and an updated application form was published in October.

As of the beginning of December, the Agency has received 34 applications for the pilot project. Of the received proposals, 6 concerned ATMPs, 12 concerned orphan products, 11 came from SME companies and 14 concerned anticancer medicinal products.

Ten candidate products fulfilling the criteria for Adaptive Pathways were selected for a Stage I discussion, an initial 1-hour teleconference.

A broad range of therapeutic areas were represented by the indications of the 10 selected products, together with large and small patient populations: 5 were orphans, 2 ATMPs, 4 were from SMEs. Stage I teleconferences relating to 7 products had taken place by mid-December 2014.

The ALDG also revisited 9 applications which were not initially selected: these were classic CMA cases, where iteration in terms of population expansion was limited, and were considered as offering limited learning potential for the pilot (e.g. in terms of optimal use of regulatory tools, use of real-world data, label extensions). It is however considered valuable to foster proactive use of the Conditional Marketing Authorisation pathway, where reimbursement decisions have historically been shown to be difficult, by trying to design a program that addresses HTA needs. The concerned companies have been invited to develop their proposals in terms of HTA requirements and plans for real world data acquisition. Following review of the amended proposals, these products may qualify for a Stage I discussion.

Following the initial Stage I discussions, 6 well-designed submissions have been selected so far for a Stage II meeting: this consists of one (or more) longer, in-depth discussion(s) with the participation of all stakeholders. The first of these discussions, on the quality aspects of an ATMP product, took place in December 2014, with others already planned during 2015.
The other 4 submissions are either being expanded by the applicants, or have proceeded directly to a Scientific Advice or parallel SA/HTA advice.

In December 2014 there was a teleconference among EMA and 13 HTA bodies to discuss general issues such as opportunities and hurdles to the implementation of the Adaptive Pathways paradigm in the different public bodies, together with procedural interaction improvements. After the teleconference, a questionnaire was sent to all the HTA bodies that have been involved in EMA procedures, to determine interest in being involved in the Adaptive Pathways pilot and to collect further feedback. Such meetings will continue in the future.

5. Lessons learned

Content of the submitted applications

EMA has carefully considered all products fulfilling the Adaptive Pathways criteria, prioritising for inclusion those offering maximum learning potential for a pilot. Several requests were not included in the pilot as the proposals were not well developed in terms of HTA and real world data approach, or did not present a well-developed plan concerning the indications (populations) initially and subsequently sought.

We have clarified the criteria in the Q&A document and the revised application form, and the quality of applications has improved as a result.

Applicants are reminded that general statements (e.g. "a registry will be set up to collect post authorisation data" or "we anticipate a high level of interest from HTAs") do not provide sufficient elements to evaluate the suitability of an approach for the Adaptive Pathways, and should be avoided when filling the application form. Also, the safe harbour discussions are not concerned with evaluating data and results, but to provide advice to the Applicant on the plan and principles underlying the proposed development pathway(s), and assist in the preparation of a parallel SA/HTA advice submission. Therefore, it should be indicated why, for example, a registry is planned, and in which way it is expected to supplement the RCT data (safety, efficacy effectiveness?); or how a certain endpoint could satisfy both regulatory and HTA requirements. Also, the Applicant should try and indicate as clearly as possible which initial indication (or subpopulation) will be the subject of the initial MAA request, and how confirmation or (expansion) of the population will be investigated (via RCT or registries).

Examples of adaptive elements that have been discussed also include quality aspects (particularly for ATMP products, and their impact on the timing of the clinical trials); clinical trial adaptation following interim analyses, subpopulations (paediatric), and adaptive health economic appraisal approaches following the acquisition of post-authorisation data.

A Gantt chart outlining the timing of the studies, of the planned regulatory and HTA interactions, and any other elements that could influence the conduct of the clinical trials (PIP, Orphan designation, quality development milestones), is very useful for inclusion in the submission.

Scenario-planning, based on "what-if" scenarios, is welcome so that multiple pathways can be discussed.

Extent of the dialogue

The initial phase of the Adaptive Licensing project saw a learning curve on the part of all stakeholders involved. A strong link to the Scientific Advice Working Party has provided optimisation of resource use and facilitates high quality input.

A number of interesting proposals have emerged during the initial Stage I discussions, which offered an opportunity to clarify the elements of interest to the stakeholders. These were outlined in the Q&A document.

To complete the learning curve of the pilot, and to assess the value of the exercise, efforts will now concentrate on the more elaborate proposals for discussion in stage II. This is the reason why the EMA from February 28 will accept only very well-developed proposals, which include scenarios requiring input from different stakeholders, for Stage II meetings. This includes potential CMA cases where HTA aspects are developed. Stage II consists of a 2-4 hour meeting for a detailed exploration of proposals (and their possible alternatives) for the design of a parallel SA/HTA advice. The experts and stakeholders involved in these meetings will depend on the nature of the proposal. It has to be reiterated that these safe harbour discussions are not a substitute of a parallel SA/HTA advice, and they do not focus on data and results, rather on the exploration of a proposed plan and its different options. Another way to see the AP discussion is as a preparatory brainstorming meeting to an SA/HTA advice, where a wider range of proposals is discussed in an informal manner, providing elements to inform the preparation of an SA/HTA advice.

Among the proposals received so far, none were elaborate enough to proceed straight from submission to Stage II discussion, without an initial Stage I discussion: after the 28 February deadline, applicants with well-developed proposals who could be the subject of a meaningful Stage II face-to-face meeting are invited to contact the EMA (adaptivepathways@ema.europa.eu) for advice on the content and suitability of their request to be considered for the pilot, as preparatory Stage I discussions will no longer be held.

Patient input

Whenever possible, input from patients should be sought: examples of areas where this is particularly valuable are Patient Reported Outcomes, the design of clinical trials, the relevance of clinical outcomes in a given patient population. The Stage II discussions planned at the beginning of 2015 foresee patients' involvement.

Partnership with HTAs

Some HTA bodies have had a more in-depth involvement than others in the pilot phase so far. There are two main reasons: the applicant has the choice of which HTA to involve; secondly, some HTA bodies had been involved in the design phase of the Adaptive Pathways project, and had therefore more interest in participating. EMA together with these experienced HTAs are working hard to increase participation and identify stumbling blocks: in December a meeting with HTAs was held to tackle some of these issues.

Synergies and experience stemming from the numerous initiatives currently ongoing in the HTA field should be fed into the pilot.

An earlier HTA involvement would be very beneficial in terms of choice of candidates, prioritisations, involvement of appropriate partners depending on the national frameworks for reimbursement of certain categories of products.

HTAs can also contribute to discussions around real-world monitoring, data collection and use, as a complement to randomised controlled clinical trial data, and controls over prescribing in the initial subpopulation.

Feedback on the Adaptive Pathways experience

EMA will provide input to the Safe and Timely Access of Medicines to Patients expert group (STAMP) of the Pharmaceutical Committee on the lessons learned from the case studies discussed.

6. Conclusions and next steps

Adaptive Pathways is a lifespan approach, with the distinctive characteristics of HTA involvement and consideration to the use of real world data. For this reason, input is sought from various EMA committees, and all stakeholders including patients, as appropriate.

At this early stage of product identification (Stage I), the pilot has successfully identified 10 products which fulfil the criteria of iteration, acquisition of real world data, and HTA interaction. These are all cases where the development pathway and the value decisions present difficult questions. Of these, so far 6 products have been selected to undergo detailed discussions with the participation of all stakeholders (Stage II): with the aim of offering companies elements to inform the design of a parallel SA/HTA about the next steps of development, which is the next step expected in the process. The first Stage II in-depth meeting took place in December 2014.

From February 28th 2015, the EMA will accept in the pilot only very well developed proposals which present elements for discussion by all stakeholders, to allow the concentration of resources for the in-depth Stage II meetings.

The evaluation of the impact and usefulness of the Adaptive Pathways project will be conducted after at least 6 procedures have completed a parallel formal SA/HTA advice procedure following the safe-harbour discussion.