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Human Medicines Research & Development Support

Questions and answers following the initial experience of the Adaptive Licensing Pilot project

Background

The Adaptive Licensing Pilot Project was launched by the EMA on 19 March 2014. At the time of publication of this document, three meetings of the Adaptive Licensing Discussion Group (ALDG) have taken place, including three teleconferences with applicants about specific development programs, selected from 26 submitted candidate applications.

This document summarises the initial experience, addresses some frequently asked questions and clarifies the terms of engagement and expected outputs for prospective applicants.

Questions and Answers on Adaptive Licensing (AL)

1. What is Adaptive Licensing and what does AL seek to achieve?

For the purposes of the pilot project, AL can be described as a prospectively planned, adaptive approach to bringing medicines to patients, and is intended 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.

AL aims to support product development by guiding applicants, through an early multi-stakeholder dialogue, to make the best use of all available regulatory tools and through strategic collection and use of real-world data. The AL approach is based on a prospectively designed development plan which is the subject of an early dialogue with stakeholders (regulatory authorities, patients' organisations, HTA bodies). The development plan would generally foresee an initial authorisation of a medicine, granted on the basis of the demonstration of a positive benefit/risk balance at the time of authorisation, most likely in a restricted patient population, possibly on basis of surrogate endpoints. This would be followed by iterative phases of evidence-gathering, including real world data, and the adaptation of the marketing authorisation to extend the access to the medicine to broader patient populations while gradually refining the knowledge of the benefit-risk balance during the post-authorisation phase.

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2. What is the objective of the AL pilot project?

The AL pilot project seeks to examine whether iterative, 'adaptive' approaches to medicine development and authorisation offer advantages in terms of achieving the best balance between the need for timely patient access with the importance of providing adequate, evolving information on a medicine's benefits and risks. In so doing it is expected to develop thinking in the following areas:

1. To encourage developers of medicines to consider all regulatory tools and flexibilities within the existing EU legal framework when planning the lifecycle of the medicine development.
2. To explore the extent to which regulatory demands for generation of evidence around efficacy and safety are compatible with demands around evidence generation from other stakeholders (e.g. HTA bodies, payers, patient organisations).
3. To investigate in a timely manner the hurdles that exist in realising the most efficient medicine development pathways, including the role and limitations of real-world data.

The confidential discussions intend to promote free exploration of the strengths and weaknesses of all options for development, assessment, authorisation, reimbursement, monitoring, and utilisation pathways in a confidential manner. The discussions should serve to guide the applicant through the next regulatory steps.

An aim of the pilot is to promote and establish early dialogue and not to pre-assess suitability of data that are already available for an early approval. Some submissions have been made to the pilot requesting early approval on the basis of available data without particular consideration of post-authorisation work, iterative changes to the product authorisation, HTA engagement or use of real-world data. Such submissions are not considered suitable for the pilot discussions. This does not preclude the suitability of such proposals for further dialogue with CHMP through SA/PA procedures or submission of a MAA.

3. What are the criteria for selection?

The following criteria are prioritised in evaluating the plausibility and feasibility of an Adaptive Licensing approach:

1. An iterative development pathway, most likely in terms of gradual expansion of the target patient population, alongside a gradual reduction of any uncertainties in benefits and risks associated with the initial authorisation decision.
2. Real-world monitoring, data collection and use, as a complement to RCT data, in subsequent regulatory decision making. This is assisted by good definition of the target population (e.g through restricted indication), and additional risk minimisation measures, such as educational programmes, controlled access programmes, including patients registries) that promote the likelihood of real-world data collection.
3. Ability to engage HTAs and other stakeholders (patients, learned societies) in multiple discussions along the development pathway; and with proposals for how the demands of these stakeholders can be met. The Applicant should identify, according to their development plan needs, the key stakeholders that they wish to involve in the discussions.

In addition to the criteria set out above, high unmet medical need is an important feature since this opens the possibility to use a wider set of regulatory tools and may justify a higher degree of uncertainty at the time of initial authorisation, in contrast to therapeutic areas with authorised treatment options available: companies should reflect on how to support this aspect. In all cases, however, the proposed development program must also meet the criteria mentioned above.

It is emphasised that development programmes that do 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 no use of real world data) and late stage development programmes are not suitable for inclusion in the pilot.

Prospective Applicants for the pilot exercise are invited to complete the application form by justifying in detail the criteria mentioned above, to support the rationale for selection into the pilot.

4. When should I apply for the Adaptive Licensing Pilot?

The early stages of development offer the highest opportunity for a meaningful dialogue and input from regulators, HTAs and patients. There is, however, flexibility as long as the indication and development plan fit the AL concept: the applicant may find that a different timing may offer the opportunity to better support the plausibility of the plan to demonstrate a positive benefit/risk in the initial, restricted population, without loss of equipoise. The type, extent and timing of data to be generated will depend on the product characteristics, the disease, and the chosen development pathway. The type of Marketing Authorisation obtained (full, conditional, under exceptional circumstances), including any potential restrictions or conditions, will depend on the level of evidence ultimately obtained.

5. Phase III studies are ongoing. Is my program suitable for Adaptive Licensing?

This is less likely. AL is a prospectively planned process, most likely starting with the early authorisation of a medicine in a restricted patient population, followed by iterative phases of evidence gathering and extensions of the marketing authorisation to expand access to the medicine to broader patient populations. If the Phase III trials already target an indication that fits the AL concept and if the opportunity still exists for multi-stakeholder dialogue to discuss the evidence base for the initial MA and to prospectively plan the post-authorisation clinical trials and real-world data collection, then the program may be considered for inclusion. Otherwise, the opportunities for input from regulators, HTAs and patients may be too limited.

6. Are the adaptive licensing discussions an in depth scientific discussion replacing Scientific Advice?

No. Scientific Advice / Protocol Assistance procedures remain the appropriate forum for detailed discussions concerning regulatory standards for a medicine development program. The AL pilot project is an opportunity for enhanced and prospective brainstorming interactions in a confidential environment with regulators and other downstream stakeholders (HTA, patients) prior to a formal regulatory interaction steps.

7. Are AL discussions confidential?

Yes. The only information to be disclosed pro-actively will be of a descriptive nature, e.g. the overall number of medicinal products discussed, the number of Orphan medicines, SMEs, ATMPs and the therapeutic area (not the proposed indication). The AL pilot project recognises the fact that discussions on a live asset are of an exploratory nature: a confidential environment allows open discussion of strengths and weaknesses of all options for iterative development, assessment and authorisation.

8. My program was selected (not selected) for the pilot. Does this mean a Marketing Authorisation is more (less) likely?

Since AL is based on the use of all tools within the existing EU legal framework, a medicine is neither more likely to achieve MA from inclusion into the pilot project, nor are chances of MA hampered by exclusion from the pilot project. Inclusion in the pilot reflects the existence of a plausible iterative development path.

An additional element to be considered for the selection is the nature of a pilot and the initial capacity to evaluate proposals: this may lead to prioritization of programs that offer the greater learning potential and ought not to be confused with regulatory interest in the medicinal product or regulatory acceptability of the proposed development program.

9. Is Adaptive Licensing based on a new regulatory framework?

AL uses the regulatory processes within the existing EU legal framework. Therefore, only existing regulatory tools will be used, including scientific advice (with participation of HTA bodies and/or payers and/or other stakeholders), centralised compassionate use assessment, the "standard" marketing authorisation, conditional marketing authorisation, marketing authorisation under exceptional circumstances, and other provisions of the pharmacovigilance legislation including risk management plans, patient registries, etc. Data protection and other relevant legal provisions remain unchanged.

At this stage, the pilot aims to assist Applicants to explore the feasibility of their proposals and to indicate alternative avenues that might be explored, within the existing legal framework, to optimize development pathways and achieve an optimal balance of patient access and increasing knowledge on benefits and risks.

A survey will be run with the participants, which will include feedback on regulatory aspects and may be used to inform on future steps.

10. What happens in practice in AL?

- As the aim of AL is timely access to new treatments for patients, the Agency takes the view that, in addition to the industry participants, all decision makers who ultimately influence patient access should ideally be involved in the pilot discussions; this includes HTA bodies that inform reimbursement decisions and, where applicable, organisations issuing clinical treatment guidelines, and patient organisations. Applicants are invited to consider this at the time of submission of their application.
- Once Applicants submit their application form, they will receive within 2 weeks confirmation of the date when their application will be discussed.
- The ALDG can review up to 10 products per month for suitability for the pilot. If more applications are submitted in a given month, they are postponed for consideration at the next meeting. This is because the project is currently a pilot, and therefore only a limited number of applications can be considered at this time.
- Products of particular interest in terms of learning about the AL concept, primarily based on the selection criteria mentioned above, are selected for a brainstorming teleconference with the applicant at the following ALDG meeting (normally during the following month): this consists of 1 hour (or more, depending on the content and complexity of the request) of high level discussion on the proposed plan with regulators and other downstream stakeholders identified by the Applicant. The discussion will focus on the adaptive elements of the proposed development plan, testing

whether other development and authorisation pathways are possible and discussing possible hurdles associated with each approach.

- For paediatric aspects, and should the development require the demonstration of Significant Benefit in the framework of Orphan Medicinal Products, it is advisable that discussions start in the initial proposal.
- The teleconference cannot be considered a formal advice: there is no in-depth discussion of scientific aspects, which is within the remit of a formal SA procedure. It is a high-level early dialogue led by the SAWP chair and assigned coordinators to review the plausibility of the development plan and guide to the next –more formal - regulatory steps. Given the nature of this discussion, the timelines for involvement of downstream stakeholders may be shorter than for other EMA procedures (e.g. parallel EMA/HTA advice) which require in-depth review.
- The output of the teleconference is a list of comments, similar to the one that results from an SA pre-submission meeting. The document is signed by Spiros Vamvakas, Head of Scientific Advice, and includes, as an attachment, the minutes of HTA and other stakeholder discussion commented upon by those participants for accuracy. It is the responsibility of to the sponsor to decide on how to take this feedback forward into their clinical development. If needed, depending on the outcome and content of the initial discussion, further confidential discussions with the Applicant and relevant experts can take place prior to a formal regulatory step.
- An HTA/SA parallel advice, shaped by this initial discussion, is expected to be the next regulatory step. Stakeholders to be involved in the procedure should be identified by the Applicant.
- The interaction process can be repeated several times prior to follow-up scientific/regulatory advice or submission of the marketing authorisation application.
- Participants will receive a questionnaire to provide their feedback, as the pilot is a learning exercise.

11. Where do we go from here?

- To optimise resources, future meetings will be conducted during SAWP week.
- After 5 meetings (approximately Q4 2014) the findings of the pilot will be reviewed, a report will be published and a decision will be taken on the next steps.
- As the project progresses, the European Commission will receive feedback from the EMA and examine the legal and policy aspects related to adaptive licensing in collaboration with the EU Member States and in consultation with relevant stakeholders, as necessary. This discussion has been already initiated with the Member States in the forum of the Pharmaceutical Committee.