



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

19 March 2014
EMA/254350/2012
Senior Medical Officer

Pilot project on adaptive licensing

There is currently much debate about adaptive pathways for new medicinal products to come to the market. The terms 'staggered approval', 'progressive licensing', and 'adaptive licensing' have been used, often interchangeably, to describe the same broad concept. More recently, the term 'Medicines Adaptive Pathways' (MAPs) or 'Medicines Adaptive Pathways to Patients' (MAPPs) is discussed as potentially more appropriate terminology. For the time being, and in the interest of internal consistency, the term 'adaptive licensing' (AL) is used throughout this document.

AL can be defined as a prospectively planned, adaptive approach to bringing drugs to market. Starting from an authorised indication (most likely a "niche" indication) for a given drug, through iterative phases of evidence gathering and progressive licensing adaptations concerning both the authorised indication and the potential further therapeutic uses of the drug concerned AL seeks to maximize the positive impact of new drugs on public health by balancing timely access for patients with the need to provide adequate evolving information on benefits and harms.

In addressing the 'evidence versus access' balance, and consistent with a staged approach to collection of evidence and consequent licence adaptations, AL aims at a life-cycle approach to evaluation and licensing of medicines.

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

The Agency is aware that representatives from different stakeholder groups, including patients, academicians, research-based industry, HTA experts, and regulators from several jurisdictions have expressed an interest in exploring how the concepts of AL could be further explored and developed.

The potential benefits and risks of AL, as well as the issues that need to be addressed have been discussed in publications^{1 2 3} and at international conferences. Retrospective and hypothetical case

¹ Eichler HG et al. Adaptive Licensing: Taking the Next Step in the Evolution of Drug Approval. Clin Pharm & Ther 2012, Vol 91 (3), 426-437

² Woodcock J. Evidence vs. access: can twenty-first-century drug regulation refine the tradeoffs? Clin Pharmacol Ther. 2012 Mar;91(3):378-80

³ Forda SR et al. Priorities for improving drug research, development and regulation. Nat Rev Drug Discov. 2013 Apr;12(4):247-8. doi: 10.1038/nrd3981.



studies have been developed by external groups^{4 5} and at the Agency (please see Annex II) to clarify the understanding of AL pathways.

The Agency takes the view that it will be useful to also discuss *prospective* case studies and wishes to initiate a **Pilot Project on Adaptive Licensing**. The purpose of this pilot is to provide a framework for informal interactions: by discussing 'live assets', i.e. medicines currently under development, it is hoped that all stakeholders will be able to address a range of technical and scientific questions (outlined in Annex I) which will help refine their understanding of how future AL pathways might be designed for different products and indications, what might be achieved by AL, how best to address the potential blocking factors and, possibly, to identify additional hurdles or issues that may not have become apparent yet.

Recalling that the aim of AL is timely access for patients to treatments that promise to address serious conditions where there is an unmet medical need, especially when there are no satisfactory alternative therapies, the Agency takes the view that all decision makers who ultimately determine patient access should ideally be involved in the pilot projects; this includes HTA bodies that inform reimbursement decisions and, where applicable, organisations issuing clinical treatment guidelines, and patient organisations. This is not intended to preempt current discussions with member states' HTA bodies or with member states in the Pharmaceutical Committee coordinated by the European Commission but shall focus only on the technical and scientific issues of the 'live asset' under consideration. The examination of any legal aspects or potential legal limitations of AL within the existing EU legal framework is the competence of the European Commission who is carrying out this task in collaboration with the Member States and by consultation of relevant stakeholders, as necessary.

Giving due recognition to the fact that discussions on possible AL pathways of a live asset are of an exploratory nature, interactions between stakeholders will take place in a safe harbour environment so that strengths and weaknesses of all options for development, licensing and assessment may be explored openly and discussed without fear or favour in advance of more formal interactions that might eventually be undertaken such as Scientific Advice / Protocol Assistance or Marketing Authorisation Application; this is to ensure that none of the stakeholders represented at the table will be asked to make binding commitments or suffer unforeseen consequences.

⁴ Baird L et al. New medicines eight years faster to patients: blazing a new trail in drug development with adaptive licensing. *Scrip Regulatory Affairs* June 2013, 9-12

⁵ Baird L et al. Comparison of Stakeholder Metrics for Traditional and Adaptive Development and Licensing Approaches to Drug Development. *Therapeutic Innovation & Regulatory Science*, July 2013 vol. 47 no. 4 474-483

Invitation to sponsors to submit live assets to the Adaptive Licensing pilot project

Sponsors are invited to submit to the European Medicines Agency on-going medicines development programmes ('live assets') for consideration in the context of the Agency's Adaptive Licensing (AL) pilot project.

- Live assets shall be experimental drugs or biologicals which a sponsor company volunteers to make available as a prospective AL pilot case. Live assets should be drugs or biologicals in the early stage of clinical development to enable actionable input from stakeholders into the planning of the development, licensing, monitoring, reimbursement and utilisation pathways. 'Early stage' would normally mean prior to initiation of confirmatory studies (i.e. during or prior to phase II), though this should be considered on a case-by-case basis.
- Discussions about a live asset should involve not just the sponsor and regulator but, from the earliest planning stage, should also include EU payers (or HTA bodies which advise payers) and, whenever possible, patients groups and provider groups, (e.g. learned societies).
- Discussions will take place in a 'safe harbour' environment that will enable all participants to freely explore different pathways and solutions without fear of early commitments. The rules of engagement are currently under development.
- It is emphasised that these exploratory discussions should not be equated with a 'Scientific Advice' procedure. However, some drug candidates may subsequently progress to more formal interactions, such as a regulatory scientific advice procedure and equivalent procedures offered by payers or HTA bodies.
- Sponsors interested in submitting a live asset are kindly requested to consider Annex I of this document when submitting a product for the AL pilot project.
- For further information or to initiate a pilot case, please contact adaptivelicensing@ema.europa.eu

ANNEX I

Framework for individual pilot studies (to download Annex I in Word format, [click here](#))

ANNEX II

Retrospective case studies.

Annex I – Framework for individual pilot studies

The document presents a high-level framework on which to base the pilot study. This template should facilitate discussion of pilot studies, but should not be restrictive.

Product name/identifier

Summary of relevant product data and development to date (please include licensing history and interactions with health authorities/payers/HTA bodies, including non-EU – if applicable)

Proposal for development under adaptive licensing

Please propose 'adaptive' strategies for development, licensing, patient access, appropriate utilization, and monitoring that could be considered, using existing regulatory tools. Please address the following questions where relevant to the proposal:

- a. Does the drug hold sufficient promise to address an unmet need (e.g. based on convincing Mode of Action, impressive preliminary animal/human data)?
- b. What evidence would support a positive benefit-risk in a defined (sub-) population at the time of initial licensing, including surrogacy of early, pharmacodynamic endpoints and compatibility with legislation for 'normal' marketing authorisation (MA), Conditional MA (or MA under Exceptional Circumstances)? Also, what is the risk of failing to identify an important adverse effect based on early phase clinical trial data?
- c. What assurance of commitment from sponsor will there be to conduct further studies after the initial marketing authorisation. What is the feasibility of any required follow-on RCTs after initial Marketing Authorisation ('loss of equipoise'; lack of willingness of patients to enrol in RCT); what possibility to draw inferences from observational (non-RCT) data that are sufficiently reliable to support decision-making for regulators, payers and prescribers?
- d. What is the level of confidence that the observational part of adaptive licensing can be implemented (adequate infrastructure for registry or e-health records)?
- e. What is the likelihood that other decision-makers (HTA bodies/payers, healthcare professionals, patients) will be willing to contribute to discussions of the pilot?

- f. What is the level of confidence that prescriber behaviour will be as anticipated? (risk of large share of off-label use, can this be mitigated by collaboration with payers?)
- g. Any other questions or points the sponsor wished to address

Please outline a vision and timeline for how regulatory, payer and other stakeholders' interactions might look, including indicative timelines for regulatory evaluation and decision making through the product lifecycle.

Annex II – Retrospective case studies

The following retrospective case studies, developed by an ad-hoc group at the Agency, are for illustrative purposes only, and are designed to give an indication of the existing regulatory flexibilities that could be used in the context of Adaptive Licensing. These cases focus solely on regulatory aspects and do not involve consultation with HTA bodies, which would be the intention in future discussions. Furthermore they do not replace guidance or advice or set regulatory policy, but are merely examples of possible scenarios that might be discussed in the context of AL.

Case 1

This is a drug to treat patients with certain types of mutations associated with malignant melanoma. The clinical development programme consists of the following:

Phase II. Single arm study in previously treated patients with a certain mutation and Stage IV disease. This study shows outstanding efficacy compared to historical controls.

Phase III: Previously untreated patients with the same mutation and unresectable stage IIIc/IV/melanoma: Randomised vs recognised standard of care.

Adaptive Licensing approach: regulators could discuss and consider conditional approval based on uncontrolled Phase II data given an outstanding efficacy, and high degree of unmet need, in previously treated patients with the identified mutation. At the time of approval there would be a specific obligation to conduct a Phase III study in untreated patients. This would need to be advanced in terms of recruitment at time of approval to avoid the risk of being unable to complete the study.

Post authorisation: Expand population to previously untreated patients based on phase III study. It is possible that registry type data could be used to expand the range of mutations approved once the principle of efficacy is established and provided that there is mechanistic information to support such an expansion.

Early and repeated dialogue with regulators advised during the development process, to agree possible basis for conditional approval (subject to results), likely commitments and their timings, and how to subsequently expand indication.

The issues not addressed include whether HTA bodies would accept the exceptional uncontrolled data in previously treated patients as basis for reimbursement initially?

Could registry / observational (NON-RCT) type data be used to expand range of mutations once the principle of efficacy in this indication with this molecule is established, assuming the mutations are sufficiently rare to preclude a RCT?

Case 2

This is a novel antibiotic - a new beta-lactam (carbapenem) plus a new beta-lactamase inhibitor.

The traditional approach would be to develop the product for a range of organ specific infections with or without concurrent bacteremia, perhaps with appropriate qualification *when proven or strongly suspected to be caused by carbapenem resistant Gram negative pathogens.*

For a novel antibacterial agent that is for intravenous administration the normal expectation to get an organ specific indication would be two randomised double-blind active controlled studies for each major indication sought.

Regulators could consider an alternative scenario given the high unmet need, with an initial 'niche' indication: *Treatment of bacterial infections due to aerobic Gram-negative pathogens in patients with very limited treatment options.*

The clinical development programme for this could be based on:

Pharmacokinetic(PK)/Pharmacodynamic(PD) data and modelling only (plus limited safety from PK study) OR

PK/PD plus underpowered open label uncontrolled enriched study OR

PK/PD plus one fully powered study in relevant population.

The choice would depend on the reliability of the PK/PD modelling and potential to address unmet medical need/urgency; the chosen approach would have to be justified from a scientific and regulatory perspective

Whilst it is not foreseen that variations to an initial pathogen-based indication to add standard body site based indications could be made based only on further PK/PD work and 'off-label' observational data, some safety data would be generated and it would be particularly important to monitor prescribing due to the potential for resistance to develop. Conventional RCTs could proceed in parallel to obtain organ based indications. A single pivotal trial in each indication may be sufficient since the product is licensed and real-world data are being accumulated.

Early and repeated dialogue with regulators advised during the development process, to agree possible basis for 'normal' or conditional marketing authorisation (MA; subject to studies done and results), likely 'condition/s to the MA' or 'specific obligations', as applicable, their timings, and how to subsequently expand the indication.

Early parallel scientific advice might address the likelihood that other decision-makers (HTA bodies/payers, healthcare professionals, patients) would be willing to accept the initial 'niche' development plan.

Case 3

The hypothetical product here is autologous chondroblast-like cells genetically modified to express growth factors that enhance cartilage healing and repair, planted on a matrix (combined ATMP).

This product offers potential patient benefits, namely the potential for shorter operation time as compared to conventional autologous chondrocyte implantation (ACI) due to the small "dose" given (matrix is a carrier for cells that can divide due to their chondroblast-like character (not chondrocytes), emigrate and fill joint defect) - it thus allows minimally invasive surgery.

Genetic modification: Vector system that does not integrate (an important safety factor) and that mediates transient expression of the growth factors [in order to promote repair in the first weeks after implantation, but not to pose a long-term safety risk after repair is accomplished] that result in a by far quicker repair of the cartilage lesions as compared to conventional ACI.

A possible scenario for an Adaptive Licensing strategy that regulators might discuss is as follows:

Early meeting with Innovation Task Force (ITF) in the margins of the Committee for Advanced Therapies in order to determine level of "risk" for this ATMP.

Early Scientific Advice on quality and non-clinical areas of the development in order to verify that the development plan provides appropriate evidence to assess that expression of genes is only transient and that there is a negligible risk of tumourigenicity and biodistribution and to agree whether the restricted patient population that is targeted for adaptive licensing is feasible (patients with large

cartilage lesions who require fast healing process and/or cannot tolerate long operation times), and how to clearly delineate this patient population. Also clinical Scientific Advice to agree on the study designs and post approval development, including future studies to broaden the treatment-eligible population.

Summary of evidence base on which regulators might consider basing an initial (normal) MA:

Comprehensive non-clinical database suggesting no elevated risk for tumourigenicity despite genetic modification and chondroblast-like character of the cells. Data on the lack of relevant biodistribution.

Open-label randomized superiority trial against a conventional autologous chondrocyte implantation [ACI] product.

Primary endpoint: Structural repair (magnetic resonance imaging at 6 and 12 months), histological analysis in a subgroup of patients.

Patient population: Patients with clinical conditions that make a shorter operation time necessary, and patients who are in need of fast recovery.

Outcomes for a marketing authorisation under this paradigm might include:

Significantly shorter operation time than for ACI (chondroblasts can still divide, therefore lower dose possible as for conventional ACI).

Structural superiority of time to cartilage repair (e.g. trend at 6 months, statistically superior at 12 months)

Lower number of treatment failures and operation-related complications.

Condition/s to the MA at time of approval: MAH to continue monitor tumourigenicity, biodistribution and other defined outcomes in patients treated outside of clinical trials, which could be used to complement additional RCT data to extend the patient population.

Issues not addressed include the likelihood that other decision-makers (HTA bodies/payers, healthcare professionals, patients) will be willing to accept this development plan - and the level of evidence they would require.