ADAPTIVE LICENSING AND REAL WORLD EVIDENCE

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INTRODUCTION

- Traditional drug licensing approaches are based on binary decisions, i.e. to go and not to go, when an experimental therapy is presumptively transformed into a fully vetted, safe and efficacious therapy.[1]
- On the other hand, adaptive licensing (AL) is an ambitious and evolving new initiative of drug licensing based on the adaptive pathway (AP) that incorporates Real World Evidence (RWE)[2] (Fig. 1).[1]
- AP is based on step-by-step learning under the conditions of acknowledged "uncertainty" with iterative phases of data collection and regulatory evaluation.[3]
- The AP approach allows patient-specific approvals for timely access to new technologies and generates near real-time data for appropriate medical decisions.[1]
- Adaptive approaches connect decision-making to an emerging evidence base, rather than a conventional single-point-in-time evaluation.[3]
- It promotes patient access to innovation, reduces clinical uncertainty, ensures effectiveness, and improves the health technology development process.[4]
- Nowadays, the collection programs of observational information are speeding up at much higher rates than ever, creating a huge volume of data. However, the accessibility of the healthcare evidence from the real-world experiences is limited. In such a scenario, the generation and collection of RWE become a necessity.
- The aim of AP approach is to introduce flexibility in the decision-making by the regulators through enforcement of AL and emphasizing on generation of RWE.

Traditional Licensing

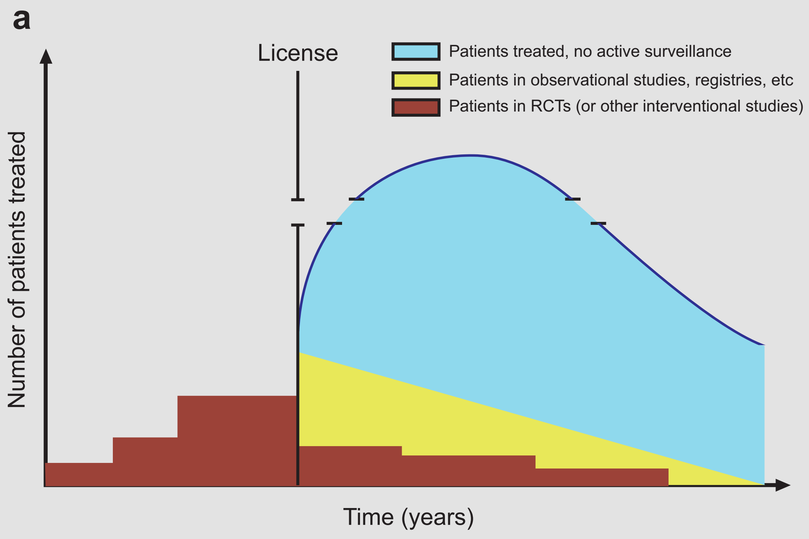

Fig. 1 (a) The treatment population grows rapidly post-licensing and treatment experience does not contribute to evidence generation

Adaptive Licensing

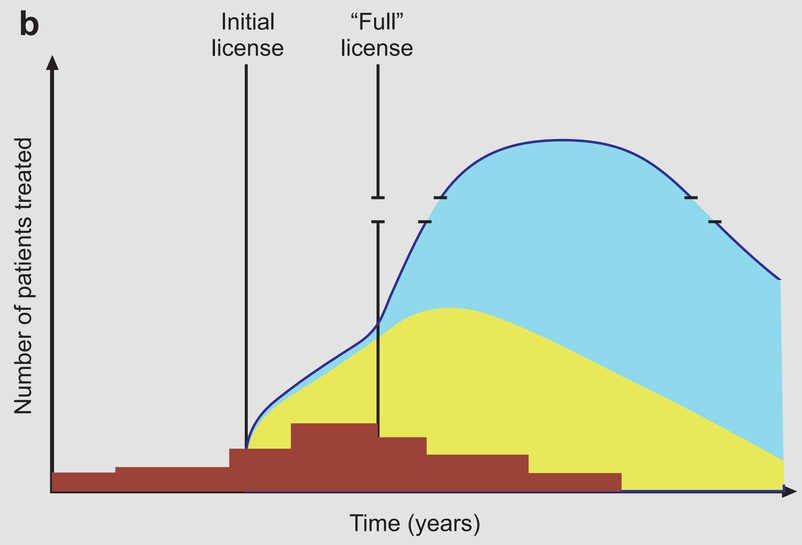

Fig. 1 (b) After an initial license, number of treated patients grow slowly due to restrictions and patient experience is captured to contribute to real-world information

Implementation of RWE in AL

- RWE is the planned and systematic recollection of clinical data generated outside a conventional RCT.[2]
- It derives results from a larger dataset gathered through the analyses of observational data from various sources such as electronic medical records, registries or administrative databases, and medical claims databases.[5]
- The healthcare evidence minimize the time for a drug to reach a market, and reduce the costs and time of clinical trials.
- A growing number of regulators, payers and Healthcare Technology Assessment (HTA) organizations involves patients in their decision-making processes. This generates the patient-specific RWE to support the licensing authorities to take appropriate decisions on marketing of an intervention.
- Additionally, the regulators have just begun to explicitly address and communicate "uncertainty" in their benefit-risk assessment models that would lead to step-wise iterative learning before full licensing.
- RWE data collection within AL has the potential to improve the understanding of disease processes and epidemiological factors, which, in turn, would allow RCTs to become more efficient.
- National Institute for Health and Care Excellence (NICE), UK is on the way to setting up and standardizing the guidelines for evidence generation.

Drivers of AL[3]

- **Patient expectations**
  - Demand for timely access of new technology with emphasis on unmet medical need
- **Emerging science**
  - Fragmentation of treatment populations and early disease interception
- **Healthcare systems under pressure**
  - Rise of payer influence
- **Pharma investors under pressure**
  - Sustainability of drug development

Enablers of AL[3]

- Improved understanding of diseases and medical conditions
- Better knowledge management
- Innovative clinical trial designs
- Rapid learning systems in the healthcare environment
- Feedback from patients: understanding acceptability and uncertainty
- Prediction, monitoring and targeted prescribing

Pilot project on APs approach

- European Medicines Agencies (EMA) launched a pilot project to explore the APs approach in 2014.[6]
- This project explored a scientific concept of medicines development and data generation intended for medicines that address patient unmet medical needs.
- Under the programme, EMA invited companies to submit ongoing medicine development programmes (MDPs) that met the pre-defined criteria (Fig. 2).

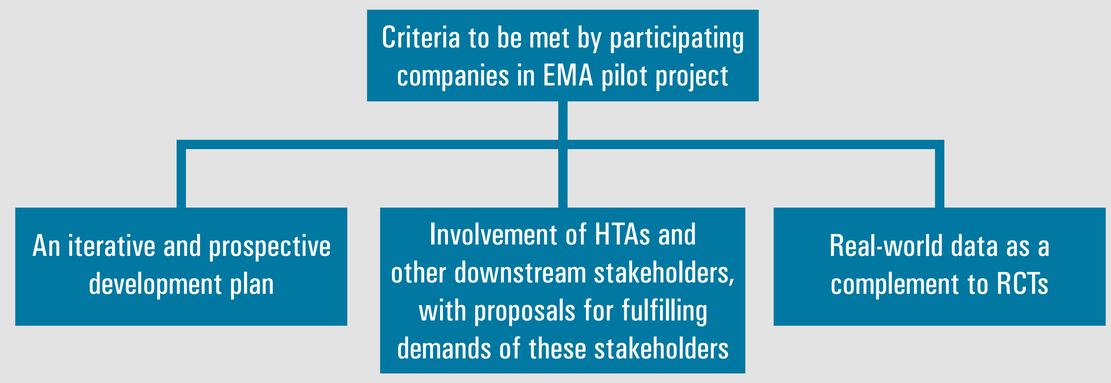

Fig. 2 EMA's pre-defined criteria for selection of participating companies for ongoing MDPs

Outcomes of AP pilot project

- The AP pilot project focused on a flexible life-cycle development of medicines that can plausibly address an unmet medical need in a defined population.
- AP would encourage the multi-stakeholder dialogue, regulators, interested HTAs, healthcare professionals and patients to discuss a product development strategy for such medicines.
- An agreement between stakeholders can be reached on a prospective approach to evidence generation throughout the lifespan of those medicines, with a view to optimise and align their requirements as much as possible.
- AP can support MDPs in therapeutic areas where evidence generation is challenging, such as infectious diseases, Alzheimer's disease, degenerative diseases, and rare cancers.
- The project suggests the creation of common evidence base to address both regulators and HTA needs while consulting all the concerned decision-makers on their respective requirements.
- An appropriate and perspective planning incorporates the intended multiple stakeholder's requirements to avoid the need for additional studies later in the development stage.
- AL based regulatory framework would offer robust mechanisms to ensure close monitoring of a medicine's benefits and risks, once it is on the market, and a prompt regulatory reassessment and action can be taken if needed.
- AP concept is not applicable to all the medicines but applies to the medicines that would possibly be useful to a patient population with an unmet medical need and where the criteria for AP fits in (Fig. 3).

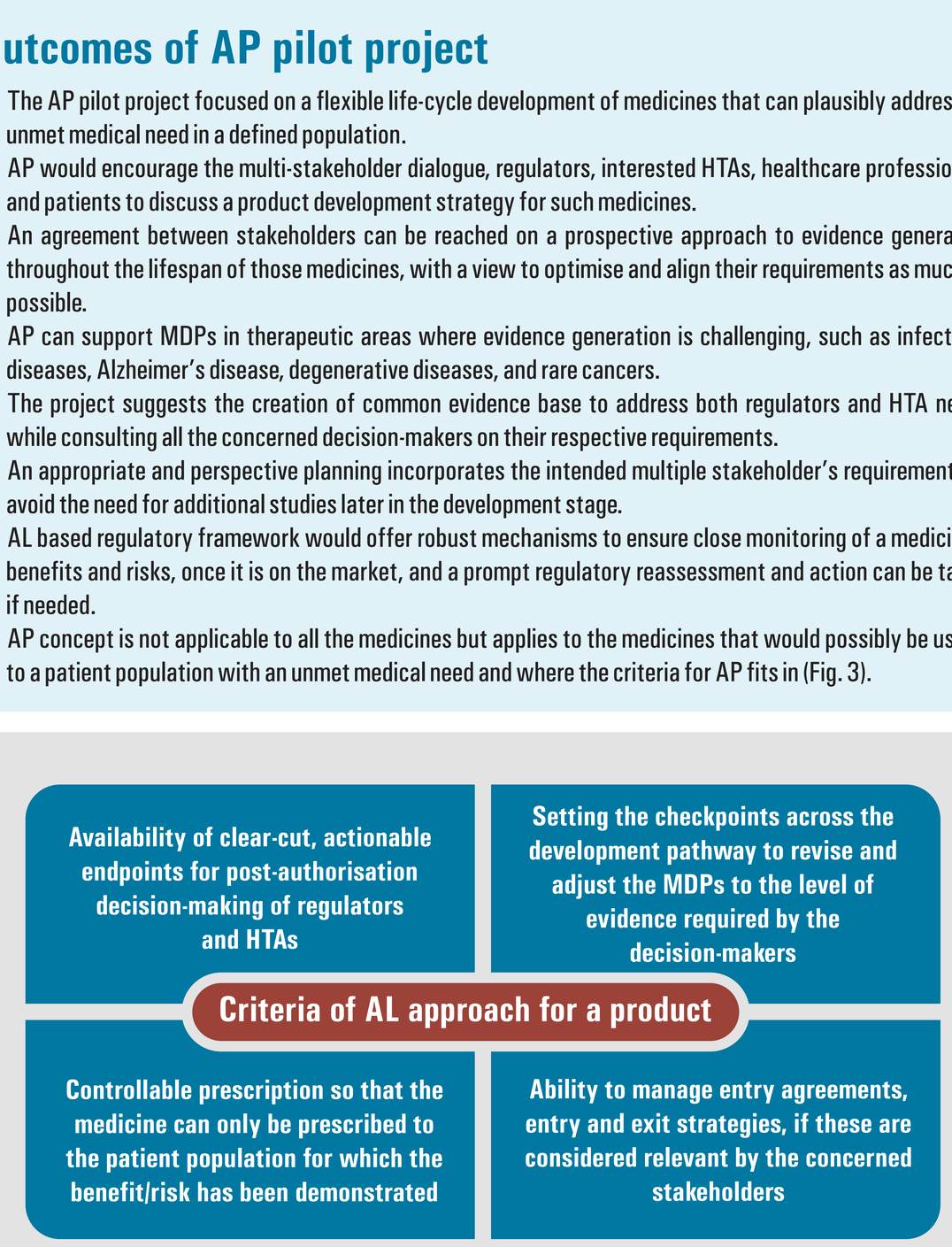

Fig. 3 Criteria of AL approach for a product

CHALLENGES AND FUTURE ASPECTS

- The participation of patients needs to be increased to accelerate the APs, support enrolment in trials and registries and provide insights on feasibility and ethical aspects.
- Inputs from healthcare professionals should be sought on the feasibility of implementing patient registries in clinical practice by having controls on prescription.
- The lack of commonly accepted and methodologically sound strategies of RWE generation and collection remains a challenge to support the successful implementation of AP approaches.
- The participation of decision-making organizations that are responsible for pricing and reimbursement on the basis of HTA recommendations is essential.
- The decision-makers input on design, acceptability and feasibility of adaptive pricing strategies, and payers input on the principles and feasibility of such schemes would be important.
- The lifespan approach to licensing, coverage and learning from real-world experience as supported by APs.

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