EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

EMA Adaptive licensing: a ~~tool~~ *concept* for accelerated access to innovative medicines?

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Slides largely re-produced from a previous EMA presentations to (DIA, Paris; STAMP, Brussels).

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- What is adaptive licensing; what is adaptive pathways?
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Implementing the European Medicines Agency's Road map to 2015: The Agency's contribution to Science, Medicines, Health

"From Vision to Reality"

Exploring the balance between early approval with limited data and later approval with more extensive data package

Considering the merits and mechanics of an optional approach to early authorisation of medicines in a restricted population e.g. based on early information from good responders. Exploring the broader applicability of 'staggered' approvals and preparing guidance on the applicability of such approaches.

Adaptive Licensing; (One) Definition

Adaptive Licensing 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.**

Problem statement – regulatory context

One concern was to reduce the ‘big bang’ at the point of licensing; transitioning from clinical trials to use in clinical practice that was not well controlled and not well monitored. A ‘**regulatory**’ problem.

Where uncertainties exist, start in a small(er), well-defined group of patients to control use and monitor outcomes. Expand use in a stepwise manner based on real-world data in addition to further clinical trial work, i.e. ‘adaptive’ **licensing**

More generally, is the available regulatory toolset fit for purpose? Does the potential of real world data change the licensing paradigm?

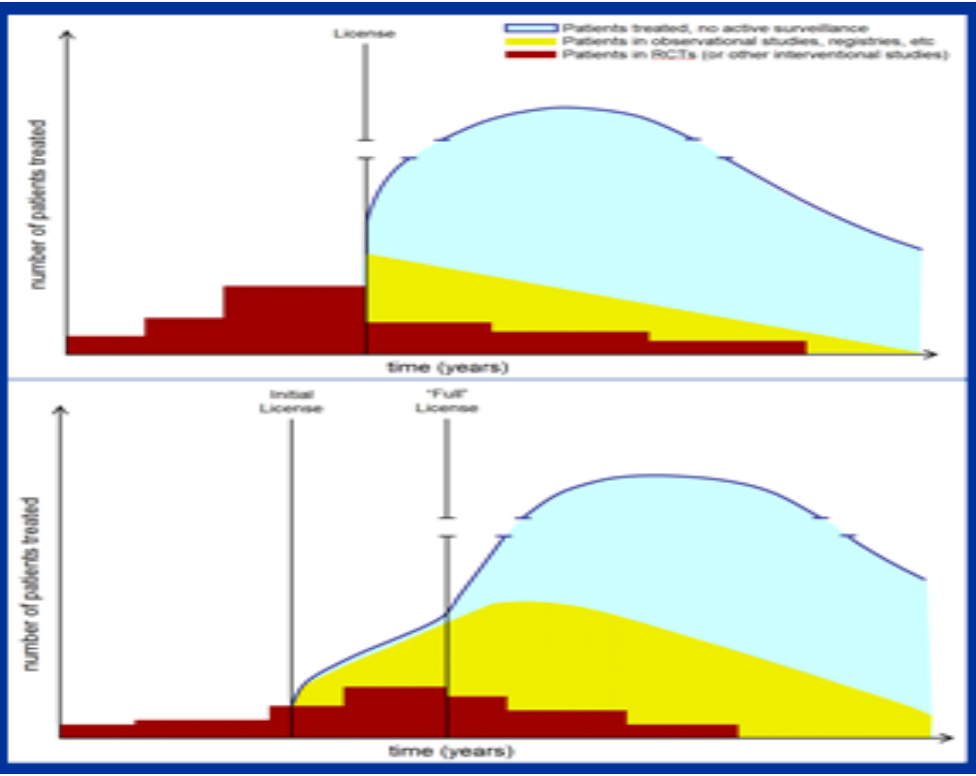
Problem statement – wider context

Post a (**centralised**) MA, the benefits in terms of patient access can only be realised **nationally**

Recognition that other stakeholders would need to be involved, for planning and implementation

No benefit to a 'regulator-only' advancement. A '**public health**' problem involving multiple parties i.e. '**Medicines Adaptive Pathways to Patients (MAPPs)' or Adaptive Pathways.**

Problem statement – a way to handle increased uncertainty?



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Current scenario:

Post-licensing, treatment population grows rapidly; treatment experience does not contribute to evidence generation

Adaptive Licensing:

after initial license, number of treated patients grows more slowly, due to restrictions; patient experience is captured to contribute to real-world information

Early access tools: Overview

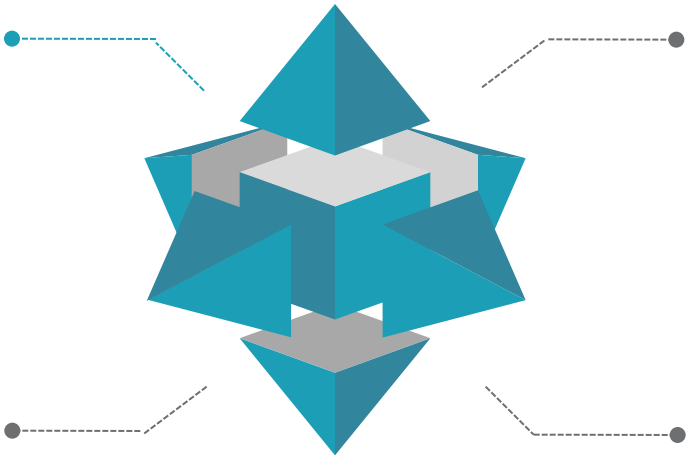
PRIME

Major public health interest, unmet medical need.

Dedicated and reinforced support.

Enable accelerated assessment.

Better use of existing regulatory & procedural tools.



Adaptive Pathways

Scientific concept of development and data generation.

Iterative development with use of real-life data.

Engagement with other healthcare-decision makers.

Accelerated Assessment

Major public health interest, unmet medical need.

Reduce assessment time to 150 days.

Conditional MA

Unmet medical need, seriously debilitating or life-threatening disease, a rare disease or use in emergency situations.

Early approval of a medicine on the basis of less complete clinical data.

Status Quo

Regulation permits:

- Initial Marketing Authorisation and subsequent variations
- Conditional Marketing Authorisation
- Post-authorisation studies, including observational research

- Scientific Advice (including patient representatives)
- Parallel Scientific Advice with Health Technology Appraisal

CHMP Scientific Advice

Voluntary, chargeable. Run by Scientific Advice Working Party o.b.o CHMP (EMA)

SAWP – chair, 29 members plus alternates ('co-ordinators') plus national experts. EMA scientific and administrative secretariat. Extensive, well-established machinery.

Quality, Non-clinical, Clinical (all therapeutic areas), Stats, PK etc.

'Joint members'; CHMP, COMP, PDCO, CAT and PRAC. Some patient reps.

What changes?

AL uses **existing** regulatory tools and processes - e.g. 'Cond' MA. Demonstration of positive Benefit/Risk is – as usual - required for approval. AL **is not a new type of MA, or a designation for medicines of particular potential public health impact.**

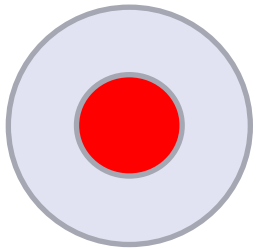
The novel aspects of an adaptive licensing from the perspective of the regulator relate to increased dialogue with downstream stakeholders and increased collection and utilisation of (real world) post-authorisation data.

Early access = greater uncertainty or smaller target population

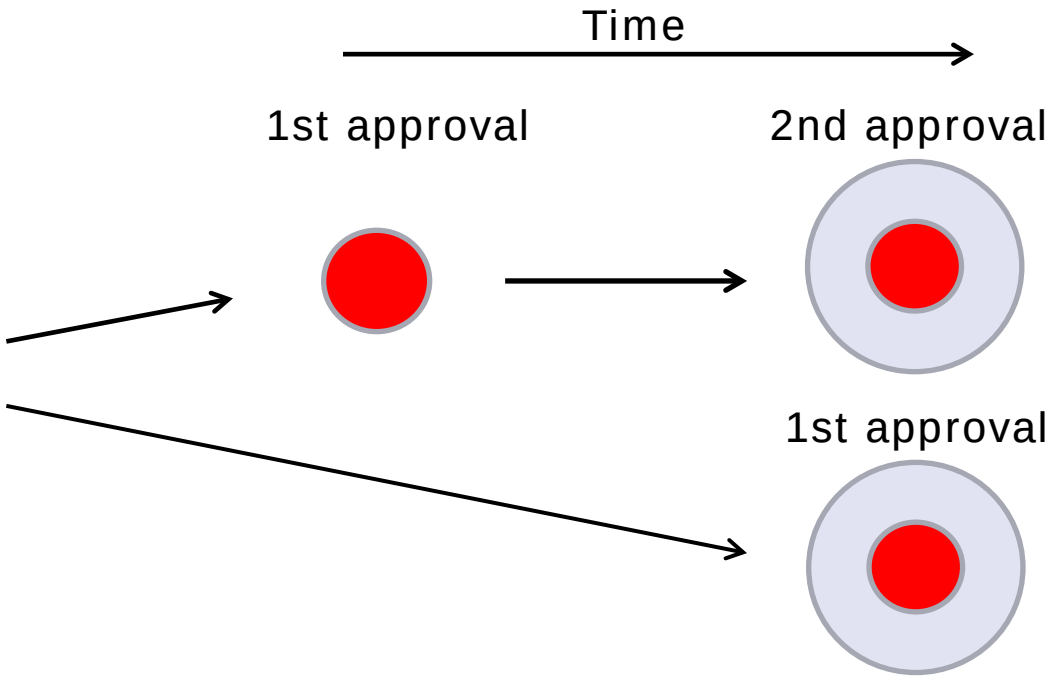
How can different stakeholders address the uncertainty?

Adaptive pathways concept ("**expansion of the indication**")

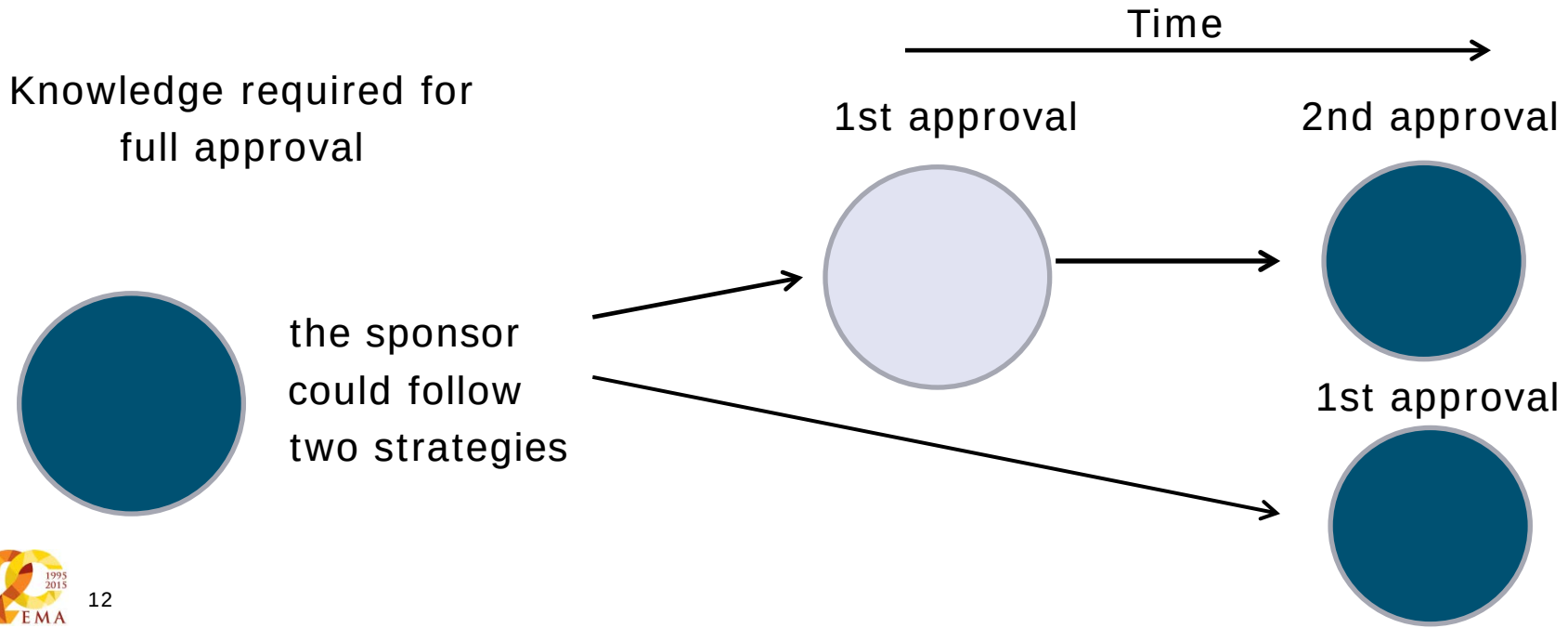
Final target indication in grey, patient group with highest need in red



the sponsor could follow two strategies



Adaptive pathways concept ("**conditional approval**")



The EMA pilot; experience to date

Support the definition of pathway of product development and (potential) earlier access to medicines through early dialogue involving all stakeholders (regulators, HTAs, payers, patients…).

Criteria for candidate selection

1. An **iterative** development plan (start in a well-defined subpopulation and **expand**, or have a Conditional Marketing Authorisation, maybe surrogate endpoints and **confirm**), **or both**.

2. **Real World Data** (safety and efficacy) can be acquired to supplement Clinical Trials

3. Input of all **stakeholders**, particularly HTAs, is fundamental

Unmet medical need is an important feature that allows full use of regulatory tools

The EMA pilot; experience to date

Safe-harbour discussions:

Why? To promote free-thinking and open dialogue at a concept level.
"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."

Can act as a 'pre-submission' for a formal procedure, alternatively go direct to a formal procedure!

Initial experience

- 59 products submitted as candidates
- 20 selected for in-depth discussion with company (Stage I)
  - 4 SMEs
  - 5 are Orphan drugs
  - 4 are ATMP (Advanced Therapy Medicinal Products)
  - 5 Anticancer
- 15 Stage I discussions have taken place
- 11 proposals selected for Stage II (in-depth meeting after Stage I) (1 ATMP, 5 Orphan, 3 SME; 3 anticancer)

Iterations in AP applications

Some proposals included both expansion of the indication and confirmation after CMA.

- Expansion of indication (to either less severe patients or other indications): 15/19
- Specified CMA route: 11/19 (maybe more)
- Early/surrogate endpoints proposed: 11/19

RWE examples in AP applications (1)

- Use of existing disease registries to identify natural history of the disease, current SoC, resource utilisation, adherence to treatment;
- Single arm studies for rare diseases compared with outcomes inferred from disease registries;
- Open label salvage studies in patients with no therapeutic options remaining, with the purpose of obtaining an expansion of the indication;
- Collection of efficacy and safety data from early access/compassionate use programs to supplement RCTs in small populations;
- **Post-authorisation drug registries for effectiveness, long-term outcomes, drug utilisation, PROs, time to treatment failure, diagnosis confirmation**;

RWE examples in AP applications (2)

- Linking drug registries to risk-sharing schemes for reimbursement (pay per performance, annuity payments…)
- **Expansion of the indication based on a mixture of disease registries and compassionate use data (for rare, severe diseases, where RCT data were available for less severe forms of the disease**);
- Post authorisation studies to investigate biomarker (or other subpopulation selection criterion) status of an all-comer population;
- Investigation of non-serological outcomes for vaccines.

Who participated?

Involved in at least one procedure were HTAs from:

UK, NL, SE, DE, IT, FR, AT, NO, FI

EUNetHTA as observer

Other bodies have been involved for vaccines.

Payers participated in one case to provide high-level comments on risk sharing plan.

What are we learning?

Companies provided generally a sketchy elaboration of value proposition (early stage? Risk aversion?). SMEs so far have been more creative.

Recognised divide in perception of risk from medical/market access division of companies (Questionnaire in ADAPT SMART)

Resource intensive procedure: felt particularly by HTAs. Challenge to bring right stakeholders with right expertise into the discussion

As compared to parallel SA/HTA, payers input is missed (acceptability of reduced package)

Procedures that progressed to parallel SA/HTA had more detailed discussion.

ATMP issues

CMC evolves continuously, pre and post-authorisation.

2 selected products wanted to discuss CMC, and both were ATMPs

Upscaling as a paradigm for adaptive licensing. Comparability considerations with manufacturing changes/extension to further sites.

Potential adaptive proposals:

1) initially license small scale production, scale up later

2) aim for restricted use in centres of excellence from the outset.

- License initially for production and use in one centre.
- Submit a variation to scale up after licensing when the investment is safer

Dedicated quality discussion are possible within AP, involving CAT and BWP

The pilot continues

Well developed proposals sought in terms of iteration, RWD use and HTA / payer involvement.

Need better developed proposals to really test the concept.

- What questions can be answered by which RWD sources using which trial designs?
- Different ‘models’ for appraisal and re-imbursement.
- ‘What if’ scenarios would be usefully discussed.

Prepare for (or go direct to!) formal procedures

2nd interim report under development

Conclusions

AP thinking tests how to use the tools and flexibilities optimally, with agreement of multiple stakeholders.

Current regulatory framework enables a flexible approach.

Some useful discussions, but more detailed proposals are required to fully examine the concept.