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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.**

If we look at these criteria….AP is already here even if we do not call it so.

Lemtrada (Multiple sclerosis)

Expensive ($160K) drug with difficult safety profile. 2 courses of treatment at month 0 and 12.

5-yr open label follow up results: 60-68% of patients did not require retreatment (remission, relapse, disability, MRI..)

Follow-up may continue to 10-15 yr. Biomarkers?

Would these results have been obtainable in an RCT?

How will these findings affect the B/R and value proposition?

Aim of AP pilot is to support development, not institute new procedures or a "qualification"

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.

Is the available regulatory toolset fit for purpose? Does the potential of real world data change the licensing paradigm?

To realise the benefit and smooth the road to access, other stakeholders need to be involved, for planning and implementation

No benefit to a 'regulator-only' advancement.

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.**

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

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.**

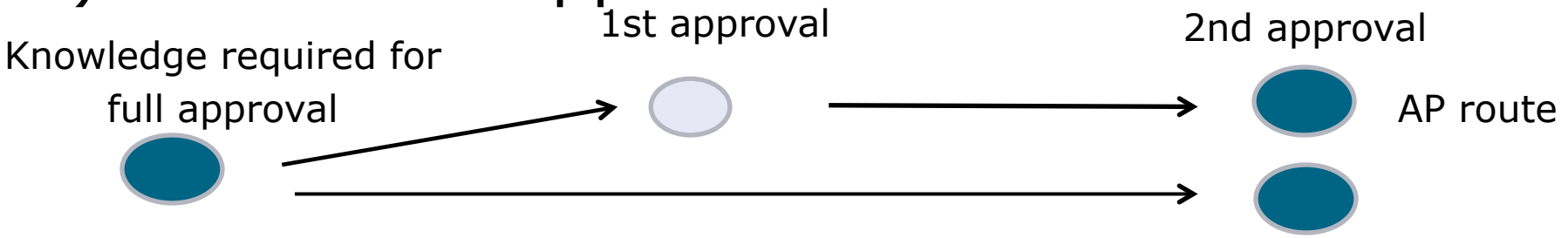
The novel aspects of an adaptive licensing from the perspective of the regulator relate to increased dialogue with downstream stakeholders and increased collection and utilisation of (real world) post-authorisation data.

Early access = greater uncertainty or smaller target population

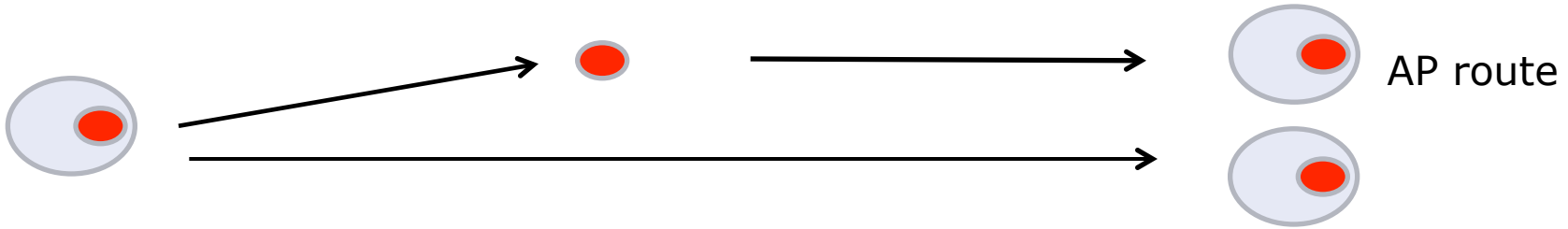
How can different stakeholders address the uncertainty?

The Adaptive Pathways concept

1) Conditional approval scenario



2) Expansion of indication scenario



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
- 21 selected for in-depth discussion with company (Stage I)
  - 4 SMEs
  - 5 are Orphan drugs
  - 4 are ATMP (Advanced Therapy Medicinal Products)
  - 5 Anticancer
- 17 Stage I discussions have taken place
- 14 proposals selected for Stage II (in-depth meeting after Stage I) (3 ATMP, 6 Orphan, 4 SME; 4 anticancer)

Iterations in AP applications (as of October 2015)

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

Case study

Potentially curative ATMP

Surrogate endpoint available (CMA based on surrogate)

Proposal for alternative pricing and reimbursement models (e.g. annuity payments, performance-based, risk-sharing)

Registry to follow up on hard clinical endpoints/performance/ reimbursement

Patients' input on endpoint relevance has been sought

Dedicated BWP/CAT discussion on CMC and stopgaps to clinical development (separate from clinical discussion)

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 is a **lifecycle** approach, involve PRAC, PDCO, COMP, CAT, BWP.
- AP thinking tests how to use the tools and flexibilities optimally, with agreement of multiple stakeholders. Understanding of **payers**' reaction to actual proposals or hypothetical scenarios would help.
- CMC poses **specific challenges for ATMPs**.
- Current regulatory framework enables a flexible approach.
- Some useful discussions, but more detailed proposals are required to fully examine the concept.