In March 2014 European Medicines Agency (EMA) launched a pilot project to explore the adaptive pathways approach, a scientific concept of medicines development and data generation intended for medicines that address patients’ unmet medical needs.

Adaptive pathways seek to balance timely access for patients who are likely to benefit most from the medicine with the need to provide adequate evolving information on the benefits and risks of the medicine itself.

Adaptive Pathways in regulation

- Adaptive pathways is not a new route of approval for medicines. It makes use of existing approval tools, in particular conditional marketing authorization.
- The adaptive pathways concept is not meant to be applicable to all medicines, but only to medicines that are likely to offer help for a patient population with an unmet medical need.


Adaptive Pathways in regulation

- Adaptive pathways can be defined as a prospectively planned, iterative approach to bringing medicines to market. The iterative development plan will initially target the development to a well-defined group of patients that is likely to benefit most from the treatment.
- This is followed by iterative phases of evidence gathering and progressive licensing adaptations, concerning both the authorised indication and the potential further therapeutic uses of the medicine, to expand its use to a wider patient population as more data become available.

APs in regulation, HTA, Access

• A key aspect of adaptive pathways is the involvement of all relevant decision-makers in the process across the life span of the medicine, including those who decide about patient access in the Member States: To help determine which medicines could be appropriate for adaptive (iterative) development; to jointly agree a data generation plan to meet the needs of regulators and health technology assessment bodies (HTAs) and to ensure that the use of the medicine is well monitored and managed.


Plan for evidence generation

• All involved stakeholders agree upfront on a plan of post-licensing knowledge generation for a medicine, before it is authorised, and the marketing authorisation holder commits to carrying out this plan.

• The cooperation between stakeholders and a strong pharmacovigilance system are the basis for the systematic monitoring of the safety and the overall performance of a medicine in clinical practice.

Transitions needed to move to an AP scenario (1)

![Diagram showing conventional and adaptive licensing scenarios]


Transitions needed to move to an AP scenario (2)

![Diagram showing prediction and monitoring]

Transitions needed to move to an AP scenario (3)

RCT only
In many therapeutic areas, information from RCTs is almost exclusively the basis for regulatory decisions; information from non-randomized studies is often not considered robust enough by regulators and sometimes by payers (exceptions may be orphan medicines and postlicensing safety studies).

Toolkit for evidence generation
The entire toolbox of knowledge generation is used to underpin regulatory and coverage decisions, including conventional RCTs, real-world (pragmatic) RCTs, and all variations of (nonrandomized) observational studies. Real-world evidence gains importance to inform postinitial rounds of licensing and coverage. Key is identifying prospectively situations where non-RCT studies can be convincing.


Transitions needed to move to an AP scenario (4)

Broad populations
Sponsors often aim to obtain as broad as possible an initial license. Effects in identifiable subgroups that are nested within the broad population may (if at all) be addressed subsequently, often for purposes of differentiation against incoming competitor products.

Targeted populations
An adaptive approach would initially aim to show positive benefit-risk and added value in a defined subpopulation, followed by additional clinical trials and studies in other subpopulations that would lead to gradual widening (or restricting) of the label and the covered populations, as supported by new data.

Transitions needed to move to an AP scenario (5)


Transitions needed to move to an AP scenario (6)

The transition from "big to small" to "small to big" with AP


HTA along the Health Technology Life-cycle
- Evidence generation along the time-line

Source: EUnetHTA www.eunethta.eu
Early dialogue on evidence generation

The Domains of the HTA Core Model® - assessing dimensions of value

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<th>HTA Core Model DOMAINS</th>
<th>SCOPE</th>
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<td>Rapid REA</td>
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<td>2. Description and technical characteristics</td>
<td>Comprehensive/Full HTA</td>
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<td>3. Safety</td>
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<td>4. Clinical effectiveness</td>
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<td>5. Costs and economic evaluation</td>
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<td>9. Legal aspects</td>
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Source: EUnetHTA
www.eunethta.eu
Thank you!