ADAPTIVE PATHWAYS AND PATIENT ACCESS – a perspective from Europe

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Adaptive Pathways in regulation

- 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 seeks *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

Source: EMA The adaptive pathways pilot www.ema.europa.eu/

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

Source: EMA The adaptive pathways pilot www.ema.europa.eu/

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

Source: EMA The adaptive pathways pilot www.ema.europa.eu/

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

Source: EMA The adaptive pathways pilot www.ema.europa.eu/

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

Source: EMA The adaptive pathways pilot www.ema.europa.eu/

Transitions needed to move to an AP scenario (1)

Conventional scenario	Adaptive licensing scenario
Single gated licensing decision The life span of a technology is clearly divided into a pre- and a post licensing phase by the moment of marketing authorization.[6]	**Life span management** AL acknowledges that knowledge continues to accumulate after a license is granted and that access is best addressed by repeat cycles of "learning-confirming-(re)licensing." Early engagement of decision makers enables integrated planning of drug development, licensing, reimbursement (coverage), utilization in clinical practice, and monitoring of treatment outcome. The life-span management is expected to lead to lower realized risks for patients compared to the current approach—in spite of smaller data packages early on.

Source: Eichler et al.
Clinical Pharmacol Ther 2015;97:234-246

Transitions needed to move to an AP scenario (2)

Prediction
Historically, once a drug was authorized, regulators had limited power to monitor performance or influence real-life use of the drug. This was a responsible justification for demanding high evidence standards in order to predict a drug's performance in the market place. Analogous considerations applied to coverage decisions.

Monitoring
Regulators in several jurisdictions have been granted substantial new authorities in postlicensing surveillance and risk mitigation; the tools for monitoring real-world performance (e.g., registries, e-medical records, postauthorization efficacy studies, methodology to address confounding) are improving, effectively providing a basis for a life-span approach to marketing authorization. Analogous considerations apply to coverage decisions.

Source: Eichler et al.
Clinical Pharmacol Ther 2015;97:234-246

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 nonrandomized 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.

Source: Eichler et al.
Clinical Pharmacol Ther 2015;97:234-246

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.

Source: Eichler et al.
Clinical Pharmacol Ther 2015;97:234-246

Transitions needed to move to an AP scenario (5)

Focus on licensing
Obtaining a marketing authorization is the primary goal of sponsors, considerations of (payer) access follow later.

Focus on patient access
The information needs of all decision makers (including regulators, payers, providers, and patients) are considered from the start and, where possible, are aligned to enable efficient drug development and timely access; patients are increasingly involved in decision making.

Source: Eichler et al.
Clinical Pharmacol Ther 2015;97:234-246

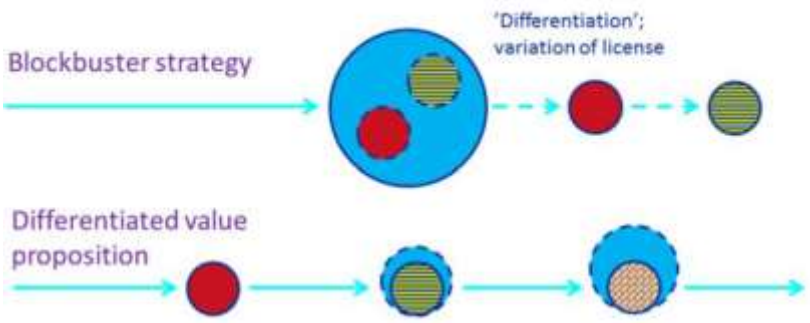
Transitions needed to move to an AP scenario (6)

Open utilization
Physicians have near-complete freedom of prescribing drugs off-label, without evidence generation.

Targeted utilization
Greater emphasis by regulators, payers, and industry on targeted drug utilization in the marketplace and on mitigating off-label use; with a view to ensure safe use, continued learning, and cost-effectiveness.

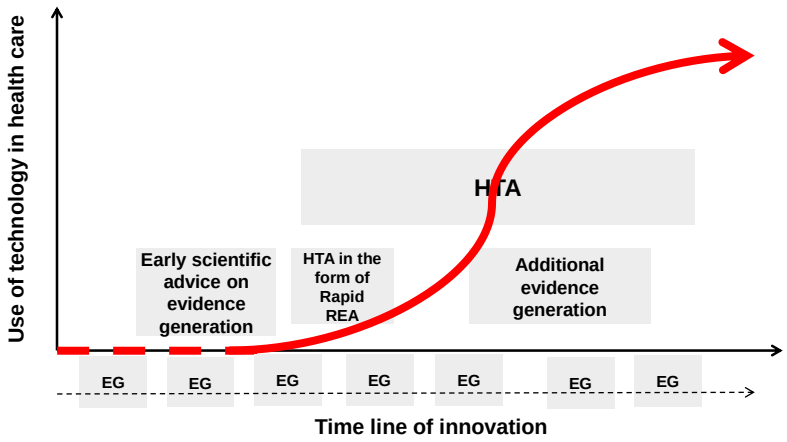
Source: Eichler et al.
Clinical Pharmacol Ther 2015;97:234-246

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



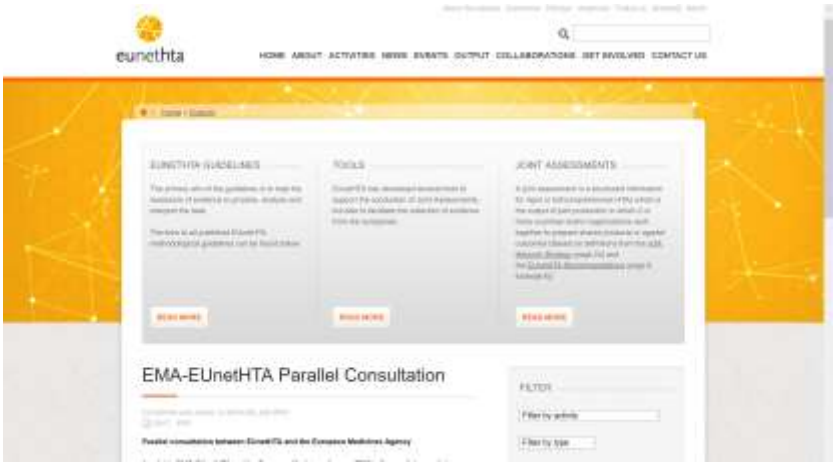
Source: Eichler et al.
Clinical Pharmacol Ther 2015;97:234-246

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



Source: EUnetHTA
www.eunethta.eu

Early dialogue on evidence generation



Source: EUnetHTA
www.eunethta.eu

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

SCOPE	HTA Core Model DOMAINS	
Rapid REA	1. Health problem and current use of technology	Reliable, timely, transparent, information
Rapid REA	2. Description and technical characteristics	Reliable, timely, transparent, information
Rapid REA	3. Safety	Reliable, timely, transparent, information
Rapid REA	4. Clinical effectiveness	Reliable, timely, transparent, information
Comprehensive/ Full HTA	5. Costs and economic evaluation	Reliable, timely, transparent, information
Comprehensive/ Full HTA	6. Ethical analysis	Reliable, timely, transparent, information
Comprehensive/ Full HTA	7. Organisational aspects	Reliable, timely, transparent, information
Comprehensive/ Full HTA	8. Patient and social aspects	Reliable, timely, transparent, information
Comprehensive/ Full HTA	9. Legal aspects	Reliable, timely, transparent, information

Source: EUnetHTA
www.eunethta.eu

Thank you!

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