

Executive Briefing #4

EMA Adaptive Pathways Workshop Summary from an Industry Perspective

David Schwicker, January 2017

Adaptive Pathways (AP) is an initiative developed by the European Medicines Agency (EMA) focussed on medicines expected to have a **significant clinical impact** in patient populations with **high unmet needs**.

The EMA has hosted an Adaptive Pathways **workshop** in December 2016 to discuss **stakeholder** input and questions. This ORPHA Strategy briefing summarizes the workshop from the perspective of the pharmaceutical and biotechnology **industry**.

Key Takeaway Points

- Adaptive Pathways is a prospectively planned, iterative scientific development concept in areas where collection of data via traditional routes is difficult, e.g. in rare diseases.
- It permits a stepwise approval in tightly defined patient populations with a gradual extension of the target population as more data become available. The standards of regulatory approval remain unchanged.
- AP involves collaborating with all relevant stakeholders very early in the development process, particularly with HTA bodies and patients.
- For industry, AP is a “safe harbour”, informal, non-committal entry to explore alternative development routes.
- Key to success will be changing the culture of stakeholder interactions and building trust.
- The potential for several years of earlier marketing authorisation and market access are highly attractive, in the right indications and for selected transformative medicines.
- This benefit is balanced against the risks inherent in generating sufficient evidence for conditional marketing authorisation earlier in the development process, as well as the feasibility and cost of commitments post-authorisation.
- A key caveat lies in the commitment of HTA bodies in conducting value appraisals based on the more limited evidence available at the time of early market entry, enabling rapid national market access and reimbursement in step with early marketing authorisation.
- The convincing demonstration of value based on less complete early evidence presents a significant challenge and should be an integral part of any early access strategy.
- AP makes use of real-world evidence to complement RCTs. Before initiating pivotal real-world studies, industry should seek joint scientific / HTA advice to ensure that the study design and endpoints are actionable for early regulatory and HTA decision-making.

European Medicines Agency (EMA)

Hans Georg Eichler, Senior Medical Officer at EMA, characterized the traditional regulatory process as mainly geared towards approving the next blockbuster drug, and emphasised the increased need to focus on non-conventional, transformative products. Adaptive Pathways is an attempt to successfully address **inevitable uncertainties** and the '**access versus evidence**' conundrum through adequate pre-planning, the collaboration of stakeholders, and enlarging the toolbox for evidence generation.

Existing data **quality standards** and the **risk/benefit basis** remain **unchanged**. AP is intended only where the benefit to public health of the immediate availability on the market outweighs the risk inherent in the fact that additional data are still required. Every regulatory decision bears uncertainty, the question is: **is early access worth it?** The focus is on unmet need in life-shortening and debilitating conditions with a major impact on quality of life, and on medicines with a credible promise of relevant improvements in patient-relevant outcome(s). Not just providing HOPE but real HELP for patients, clearly „moving the needle“.

The **life-cycle** perspective in generating data is a key element of AP. Knowledge generation is a continuum: pre-and post licensing evidence are not two different lives, it's one continuous life. **Pre-planning** of research across the life span of a medicine is key (including post-marketing).

Francesca Cerreta, Senior Scientific Officer at EMA, pointed out that the AP approach is **not a new regulatory route** but about harnessing the use of existing legislative and regulatory tools in a more efficient way.

A key learning from the pilot has been that AP applies only to a **limited** number of medicines. A number of product candidates for the pilot were not plausible and needed to revert to the traditional regulatory route. **Criteria** for successful AP pilot applications were:

- Right product, with a potential to provide significant benefits in patient outcomes
- Right endpoint(s), clearly actionable for early regulatory and HTA decision-making
- Right treatment population, clearly defined and with an unmet medical need
- Right company, with competence and building trust that the agreed development plan can be carried out

The next step for AP will be the **integration into scientific advice**, to make the process sustainable. Future submissions will be treated as parallel scientific / HTA advice requests, granting an additional pre-submission meeting.

Patients /Patient Organisations

The **patient representatives** emphasised that a key issue for patients in Europe is not only addressing unmet medical needs, but also the **limited access** to treatments. A further concern is that the availability, prices and utilization of transformative medicines continue to differ markedly between EU member states, mainly due to divergent reimbursement systems.

A challenge was addressed to the HTA bodies present to harmonise, better coordinate and **accelerate value appraisals**, pricing and reimbursement across Europe. Patients should have a key voice in HTA procedures, not only at central level during EMA/HTA parallel scientific advice meetings, but at national levels when early access is considered.

The need for communication of benefit/risk to physicians and patients was emphasised. The ultimate decision on medicine use should be left to the patient and her or his physician. **Let the patient decide** to accept or decline higher risk of treatment.

Providers

Healthcare professionals cautioned against a decrease in data quality in the interest of **patient safety**: nearly half of all investigational drugs that successfully complete phase II studies fail in phase III, mostly because of lack of safety or efficacy. If new drugs are approved on the basis of phase II trials there is a 50:50 chance that they are unsafe, ineffective, or both. There was a degree of doubt expressed that additional RWE generated post-authorisation can reliably mitigate risks for patients.

Industry

The **pharmaceutical and biotechnology industry** has expressed interest and is ready to collaborate, as evidenced by 63 product applications for the Adaptive Pathways pilot in 2016. Most of the representatives at the workshop were companies participating in the AP pilot. The **safe harbour approach**, informally and openly discussing innovative pathways and input on the entire evidence generation plan with regulators, HTAs, and patients, is particularly welcome.

Conditional marketing approvals are still often seen as a **"last chance" regulatory route** by industry. It is a challenge for regulatory bodies to make CMA into an attractive proposition.

Industry supported the need for increased HTA commitments for more **rapid market access decisions**, at the same time as the early regulatory approval, and suggested that the EMA issue joint scientific and HTA **guidance on RWE**. Particularly, added clarity on decision-making **relevant endpoints** "that payers will pay for" was requested.

Real-World Evidence (RWE)

Most participants agreed that there is a potential for an **increased use of RWE** in the evaluation of medicines. However, opinions on RWE remain **diverse**. Questions raised concern the methodology, reliability and the usefulness of RWE in decision-making, particularly regarding treatment effects.

Hans-Georg Eichler interjected that the Randomised Clinical Trials (RCTs) vs. real-world evidence (RWE) debate appears quasi-religious. While RCTs have the highest internal validity, in some cases they cannot answer the questions. The efficient increase of knowledge of benefits, risks and value should embrace the **full evidence spectrum** (RCTs, pragmatic trials, observational studies). RWE **complements** rather than replaces RCTs. The right study type for the right question, where feasible, should be utilised.

Rob Hemmings, MHRA, proposed an ethical and scientific mandate to investigate what is possible with RWE. Given the methodological challenges, **the dialogue on RWE is not trivial** and requires competence, capacity and experience. The key is: **will the study deliver?** Observational studies must be underpinned by sound methodology, i.e. without important bias, and deliver **endpoints and results actionable for decision-making**.

Based on the workshop discussion, it is apparent that RWE still has a long way to go before becoming established as a universally accepted mainstay of benefit/risk and value evaluations. While real-world and patient-centred data is undoubtedly a crucial component of an early access strategy, care must be given that studies address the **right questions**. Consequently, industry should consider seeking **early joint scientific and HTA advice** before committing significant resources. Observational studies that do not provide a design and endpoint(s) that are relevant and actionable for regulatory and HTA decision-making ineffectively bind valuable resources and time on the pathway to early access.

Health Technology Assessment Agencies (HTAs)

While a number of national bodies are open to collaborating, as seen in the increase in early joint scientific / HTA advice, others are more guarded. Viewpoints, experience, resources and legal frameworks differ considerably between the HTA agencies.

The representatives of AIFA (Italy) and HAS (France) made positive statements, early dialogues and adaptive routes are well regarded. Both countries have longstanding and good experience with **compassionate use** programs before market authorisation (Italy Fondo 5%, France ATU), in clearly defined and well-controlled patient populations or for individual patients.

UK NICE's Prof. Sarah Garner stated that the new collaborative process is challenging and resource intensive for all stakeholders. Progress will be made for NICE by discussing specific products. In order to succeed, **Managed Entry Agreements (MEAs)** need to get their selection criteria right: only considered for transformative medicines, and down stream evidence requirements must be specified in risk management plans.

For Ad Schuurman, MEDEV and ZIN (Netherlands), payers want control on volume (indication, dose, start-stop). From a payer viewpoint, when a drug enters the market it is "lost", i.e. goes from third to first line treatment, to off label use, etc. There is scepticism that commitments regarding limited utilisation and small patient populations can be well regulated in the present system. Adaptive pathways thus require **adaptive reimbursement** and guarantees. The reimbursement level should be decreased and increased according to mutually agreed outcomes, the medicine can be suspended or withdrawn, the population or indication can be restricted.

Some HTA bodies and payers feel that shifting the evidence generation to after marketing authorisation and market access may not be the best approach. A number of **critical issues** were raised, including the limited experience with MEAs, particularly with outcomes-based agreements, which are rare due to the high administrative burden and complexity, as well as the lack of national legal frameworks for adaptive pricing and reimbursement and exit strategies, should an initial promise of a high effect size not be confirmed. Further concerns surrounded the feasibility, availability, and reliability of the additional evidence generated post-authorisation. The EMA has begun to address the concerns raised by HTAs in the follow-up to the workshop.

Given the diversity of HTA opinions regarding early access, for industry, it will continue to be a challenge to convincingly **demonstrate product value** based on **less complete data at early market entry**. The risk remains that very different value judgements across the EU member states are achieved for the same – nationally adapted – early HTA dossier; from full reimbursement to outright rejection. Whether the increasing international cooperation in value

appraisals and price negotiations (e.g. the Benelux initiative for orphan drugs) will alleviate or accentuate this situation remains to be seen. Therefore, addressing HTA and value should be **integrally pre-planned as part of an early access strategy**.

The general consensus was, however, that **progress in early access** must be made in order to ensure that patients in the EU have access to safe, effective and affordable medicines.

“**Collaboration is key**, solutions can be found by changing the culture of interactions and building trust.”

Further Information

A documentation of the workshop, including a summary statement and the presentations given, is provided on the EMA website: www.ema.europa.eu > search for Adaptive Pathways Workshop.

Further information on current early access tools, programs, and initiatives is available at: <https://www.orphastrategy.com/early-access/>

About ORPHA Strategy Consulting

In rare diseases and for transformative medicines, **early access strategies, benefit/risk and value demonstrations** are often **uncharted terrain**, requiring highly specific expertise and experience.

ORPHA Strategy’s principal, David Schwicker (<https://www.orphastrategy.com/biography/>), has industry consulting expertise spanning more than 25 years, and has gained a unique understanding of how early access programs, initiatives, and rare disease and orphan drug incentives can benefit a client’s transformative medicine to **prospectively accelerate marketing authorization and market access**. To this is added a focus on **innovative development pathways** that emphasise the use of **real-world evidence**.

Thank you for your interest. To start a strategic discussion on early access, please contact:

David Schwicker
Principal, ORPHA Strategy Consulting
Basle, Switzerland
+43 664 7345 25 14
david@orphastrategy.com
www.orphastrategy.com

Copyright ORPHA Strategy Consulting, 2017. ORPHA Strategy regularly publishes Executive Briefings, which focus on news and current trends in early access, adaptive development pathways, transformative medicines, orphan drugs and designations, rare diseases, and real-world patient-centered evidence. They are available for download here:

<https://www.orphastrategy.com/orpha-executive-briefings/>