

Executive Briefing #3

Early Access – The State of Play in Europe 2017

David Schwicker, January 2017

Long established paradigms of medical innovation are being increasingly challenged. The rising **influence of patients** emphasises the demand for timely access to innovative therapies. The increased **fragmentation of treatment populations** due to better disease stratification and **transformative therapies** challenges established clinical development pathways and puts pressure on a regulatory process, which is geared towards blockbusters.

Transformative **orphan, speciality and advanced medicines** offer a major therapeutic advantage over existing treatments, or benefit patients with no treatment options and clear unmet medical needs. There is a growing realization with regulators and HTA bodies that transformative medicines often **defy traditional routes** of authorization and access. This provides new opportunities for **adaptive development pathways** and **early market authorisation and market access**, employing a broader set of data and an iterative, **life-cycle** approach to evidence generation, including **real-world and patient-centred evidence**.

The European Medicines Agency (EMA) hosted an **Adaptive Pathways workshop** in December 2016. All major **stakeholders** attended. This executive summary can thus be regarded as a **current “state of play” for early access** in Europe from an industry perspective.

- 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 data presents a significant challenge and should be an integral part of any early access strategy.
- 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.

The **EMA**, and particularly key scientific proponents at the EMA, are seriously dedicated to early access. They are leading the charge in Europe with early access tools and initiatives, including Adaptive Pathways. The EMA's aim is 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.

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. The **safe harbour approach**, informally and openly discussing innovative pathways for development with regulators, HTAs, and patients, is particularly welcome.

Patient representatives are enthusiastic, embracing their increased involvement very early in the development process. They emphasised that access is as important to patients as addressing unmet needs, given that the availability, prices and utilization of transformative medicines continue to differ markedly between EU member states.

Healthcare providers are equally interested, but caution against softening of benefit/risk criteria in the interest of patient safety. The EMA affirmed that standards of regulatory approval remain **unchanged**. Early access 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 post-authorisation.

Last to the party are the **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. This applies to early access and related issues such as compassionate use, managed entry agreements, and adaptive pricing and reimbursement.

The general consensus is 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."

For **developers** of transformative medicines, the potential offered by early access for several years of earlier marketing authorisation and market access could be highly attractive, in the right indications and for selected transformative medicines, for example those eligible for an **orphan designation in rare diseases**.

This **benefit** is balanced against the **risks** inherent in generating sufficient evidence of relevant improvements in patient-relevant outcome(s) and/or of a relevant effect size in surrogate endpoints for **conditional marketing authorisation** earlier in the development process (e.g. in Phase II), as well as the feasibility and cost of binding commitments to generate further (real-world) evidence post-authorisation.

Additionally, the convincing **demonstration of value** based on less complete data at the time of early market entry represents a significant challenge that should be **pre-planned** as part of each **early access strategy**. A key caveat lies in the commitment of HTA bodies in conducting value appraisals based on the more limited evidence available, enabling rapid national market access and reimbursement in step with early conditional marketing authorisation.

Stakeholders agree that there is a potential for an **increased use of real-world evidence (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.

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. Real-world and patient-centred data is undoubtedly a crucial component of an early access strategy, however, care must be given that studies address the **right questions**. Industry should consider seeking **early joint scientific and HTA advice** before committing significant resources and initiating pivotal research. 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.

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:

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