Patient Access in the Context of Adaptive Pathways for Medicines: What Could Make It Work?

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KEY POINTS . . .

As no medicine has yet reached the stage of marketing authorization according to the adaptive pathways approach, the consequences for health technology assessment, pricing and reimbursement negotiations remain unclear.

Under adaptive pathways, early and continuous scientific dialogue becomes a central piece of the process.

Adaptive pricing and reimbursement models may be needed to account for the potential changes in the medicine's value proposition over time.

Adaptive Pathways

In 2014 the European Medicines Agency (EMA) launched a pilot project to explore "Adaptive Pathways," [1-2] an approach for the development of medicines and the generation of data with the goal of ensuring timely patient access to treatments that address high unmet medical needs.

In practice, this means that a promising medicine could be granted regulatory approval in an initial small and well-defined patient population based on compelling evidence of a positive benefit risk profile from a phase I and/or phase II study. In addition, a plan to generate evidence post approval would be proposed proactively by the medicine developer and delivered according to set timelines. Over time, product development would continue and the initial approval would expand potentially to wider patient populations [Figure 1].

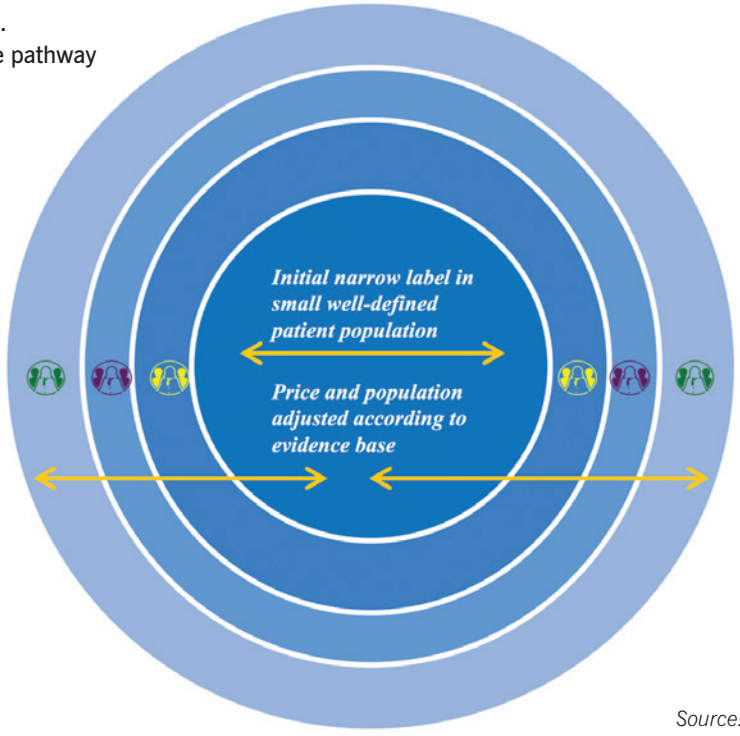
Acknowledging that in many collectively funded European health care systems patient access is delayed until after the medicine has gone through a health technology assessment (HTA), pricing, and reimbursement negotiations, the EMA foresaw the importance having early and continuous engagement of HTA bodies about the generation of evidence.

However, as no medicine has yet reached the stage of marketing authorization through the adaptive pathways approach, the consequences for national HTA, pricing, and reimbursement negotiations remain unclear to HTA bodies and payers as well as medicines developers.

The Challenge of Value Assessment

HTA bodies and payers frequently express concern about remaining levels of uncertainty of new medicines at the time of launch. They are concerned particularly about how to assess the value of products that have been approved based on less than a comprehensive data package. Under adaptive pathways, medicines developers are concerned that the evidence package submitted to regulators for the initial >

Figure 1.
Adaptive pathway concept



Source: EFPIA

approval subsequently will receive poor national HTA ratings, leading to challenged price and reimbursement negotiations. The concerns are very much related to past experiences and include examples of products such as Bosulif (bosutinib) and Erivedge (vismodegib), which were granted conditional approval based on single-arm phase I/II and II studies, respectively. These products subsequently received "no" (level V) and "minor" (level IV) ASMR ratings by the HAS [3] in France and "no quantifiable added benefit" and "minor added benefit" by the G-BA in Germany [4].

Could It Work Better Under Adaptive Pathways?

The adaptive pathways concept that is under current exploration in Europe aims at addressing these challenges proactively. By facilitating early and iterative interactions of the relevant stakeholders, including regulators, HTA bodies, medicines developers, and patients during the product life cycle, an adaptive pathway approach could help plan, manage evidence expectations, and inform decisions in a more coordinated and integrated manner compared to today's sequential approach.

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For all stakeholders involved, this would help establish a shared understanding of unmet medical needs and a shared willingness to accelerate access for selected medicines that have the potential to make important differences in the lives of the patients.

For example, it may be established up front that the initial regulatory approval will only be conditional and the stakeholders involved will jointly plan the most appropriate ways of obtaining additional evidence generation post-launch.

Scientific Advice: A Discussion Platform Centered on Evidence Generation

Over the past few years, early scientific dialogue involving joint meetings of medicine developer, EMA, and HTA agencies from different countries has been piloted (EunetHTA/EMA/SEED) and reported as valuable for all stakeholders involved [5-7]. Yet the process is not used systematically and, until now, has focused primarily on the evidence requirements to support the initial regulatory approval.

Under adaptive pathways, with the accelerated development timelines, early and continuous scientific dialogue becomes a central piece of the process.

For manufacturers, early dialogue opportunities provide a better and earlier understanding of the questions that HTA bodies may have at a later stage when assessing the value of a medicine and an early indication about the potential implications for pricing, reimbursement, and funding conditions. They also help identifying potential different expectations of regulators and HTA bodies in terms of evidence requirements, which the medicines developers can take into account when designing the medicine's clinical development plan.

At an early stage of product development, joint HTA and regulatory scientific advice processes will typically address questions related to biomarkers, study designs, subpopulations, hard and surrogate endpoints, or patient-reported outcomes. Under adaptive pathways iterative dialogues opportunities will be needed in order to gain stakeholders alignment about the additional evidence expected to be generated post approval based on randomized clinical trials and observational data from registries as well as the timing and sources of such data. The acceptability of data from outside of randomized, controlled trial settings will be an important topic for scientific advice, given frequently raised concerns about how observational data can be used to reduce remaining levels of uncertainty about the medicine's benefit and harm post launch [8].

In some cases, the opportunity to coordinate efforts for data collection across countries will need to be explored, as frequently it will not be possible to conduct a study in 28 different countries to address local payers' questions. Having all relevant stakeholders together to discuss tools, methods, and sources of data may increase the mutual understanding of the challenges related to the generation of the required evidence, help inform potential tradeoffs, and ultimately increase the confidence in future study results.

Identifying critical questions about a medicine's effectiveness, safety, or appropriate utilization early on in the development process and agreeing on the design of post-launch studies already prior to regulatory approval could be important measures to prepare and expedite national HTA appraisals and the design of managed-entry agreements at the national level.

Adaptive Pricing

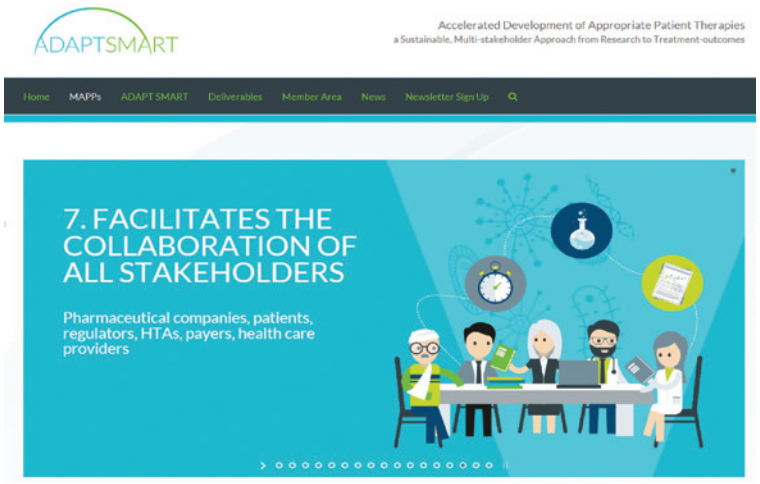
Under adaptive pathways, adaptive pricing and reimbursement models may be needed to account for the potential changes in the medicine's value proposition over time. Although most stakeholders agree on the concept, differences in opinion exist as to how this could actually be implemented.

In the context of a new medicine having received preliminary regulatory approval based on a more limited evidence package, payers raise the expectation that the initial price should be lower due to the greater initial uncertainty around the value proposition. This is of concern to medicines developers because, usually, in the current environment it is not possible to negotiate for higher price post-launch when additional evidence becomes available that further substantiates the value proposition.

Through discussions between stakeholders in the context of the IMI ADAPT-SMART initiative, an alternative model potentially acceptable to payers and medicines developers emerged. In this scenario, payers and the developer would negotiate a list price coupled with a discount reflecting the initial level of uncertainty at the time of launch. Both parties would agree on the conditions under which the level of discount would be modulated at set milestones in line with the evidence generated and the corresponding reduction of uncertainty.

Ultimately, payment models would have to be aligned with local processes as pricing and reimbursement is a member-state competence in the European Union. They would also need to be tailored to the product in question and the feasibility of implementing models that require data collection.

Figure 2. Multi-stakeholders dialogue



Managed Entry Agreements

Managed entry agreements, defined as an arrangement between a manufacturer and a payer that enables access to a medicine under specific conditions, are commonly used in EU member states. Financial-based agreements, such as confidential discounts, rebates, and price-volume agreements, are simple to implement and thus are most commonly used and favored by payers who are reluctant to engage in more complex payment schemes that require tracking outcomes data [9-12].

The main reasons for the reluctant use of outcomes-based managed-entry agreements include, but are not limited to, the lack of administrative infrastructure that would enable an easy implementation and the need to appropriately incentivize all stakeholders—especially prescribing centers—to enable high-quality data collection.

Under adaptive pathways, with evidence accumulating post approval, manufacturers and payers in the respective countries would have to identify flexible, mutually acceptable payment solutions. Hopefully, the early dialogue at European level on the post-approval data collection could help address this challenge.

Regardless of the type of managed-entry agreement ultimately selected, the alignment of a medicine developer and a payer on their respective expectations about the data and the financial outcomes associated with a new medicine is a critical component to ensure trust among the parties. This could be achieved by a prospective mapping of the potential result scenarios of the agreed post-approval evidence plan with the consequences on the price and reimbursement status of the medicine prior to its initial launch.

Conclusion

Through the public-private partnership initiative IMI ADAPT SMART [13] and other forums as well as the workshops organized by the EMA, stakeholders (regulators, HTA bodies, companies, payers, patients, health care professionals, academics, and policy makers) have the opportunity to better understand what adaptive pathways seek to achieve and to share their views and questions about the approach [Figure 2]. After a rather slow start, progress has been achieved in these multi-stakeholder initiatives. In parallel, the EMA pilot project has provided practical experience [14].

Adaptive pathways are critically important to provide patients with the best chance for timely access to treatments that have the potential to address high unmet medical needs. To be successful, it is imperative that stakeholders continue to engage in the design of adaptive pathways and, despite the challenges, maintain a willingness to identify ways forward.

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Additional information:

The preceding article is based on an issues panel given at the ISPOR 19th Annual European Congress.

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