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Initiatives driving accelerated access to medicines in Europe: Review of recent concepts and developments

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Abstract

Improving timely patient access to new medicines, particularly in areas with high unmet need, has been a healthcare priority during the past 5–10 years, with several new regulatory initiatives from the European Medicines Agency, as well as on national level within the European Union. Nevertheless, evidence suggests that medicines going through these regulatory initiatives experience variable reimbursement outcomes due to uncertainties in the clinical or economic evidence base. New initiatives, including the adaptive pathways concept, have therefore been introduced that embrace a holistic view of a medicine's route to patient access. These involve expanded clusters of stakeholders working together to prospectively influence and design evidence generation strategies, including use of real-world evidence, to ensure that development plans meet the needs of multiple stakeholders including regulatory agencies and health technology assessment bodies. Multi-stakeholder dialogues, provided through scientific advice, are already available for medicines in Europe in various forms and are important tools for regulators, health technology assessment bodies and pharmaceutical companies to develop evidence generation plans optimised to support decision-making on marketing authorisation and reimbursement of new medicines. Multiple stakeholder groups have been actively engaged in advancing developments of initiatives driving timely access and it is likely to continue due to the need to balance this with affordability. The aim of this article is to provide a review of the latest, as well as a future perspective on, developments with respect to accelerated access of medicines in the European Union with a particular focus on procedures for formal scientific advice.

Keywords

Health Care Economics and Organizations (MeSH), reimbursement, access to medicines, adaptive pathways, scientific advice

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Background on initiatives aimed at accelerating access

In the past 5–10 years, there have been an increased number of initiatives and schemes put into place with the aim of improving timely patient access to new medicines in Europe. This includes a number of regulatory initiatives from the European Medicines Agency (EMA) aimed at improving patient access for medicines targeting indications with high unmet medical needs. These EMA-led regulatory initiatives include conditional marketing authorisation (CMA)[1] and accelerated assessment (AA).[2] In both of these initiatives, the marketing authorisation (MA) process is adjusted to allow for quicker access to medicines through either allowing for authorisations based on less comprehensive data (in the case of CMA) or through accelerated review of the MA application (in the case of AA). A recent (March 2016) addition by the EMA is the PRIority MEdicines (PRIME) scheme which builds on existing frameworks, such as the AA, but aims to provide companies with enhanced support around the clinical development plan to optimise the data generated for regulatory purposes. On a European Union (EU) member

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state level, compassionate use programmes (CUPs)[3] are available in most countries where certain medicines can be made available to patients with life-threatening or seriously debilitating conditions and with a clear unmet medical need without having an MA for the particular condition.[4] In the United Kingdom, the national regulatory body, the Medicines and Healthcare Products Regulatory (MHRA) can, through the Early Access to Medicines Scheme (EAMS), grant access to medicines that do not yet have an MA when there is a clear unmet medical need.[5]

During the past 5 years, there has been an increased recognition that faster access for patients to new medicines also requires facilitation for reimbursement and funding for the new medicines following a successful MA which involves decisions taken on a national level by health technology assessment (HTA) bodies and payers. Indeed, some evidence suggests that medicines going through the CMA route experience variable outcomes from HTA and reimbursement appraisals, due to uncertainties in either the clinical or the economic evidence base, and hence does not necessarily lead to improved patient access.[6] It is therefore evident that what is satisfactory from a regulatory perspective might not be from a reimbursement perspective. In addition, the CMA route has been suggested as sometimes being used as a second resort by pharmaceutical companies, and not purposely planned, when it is evident that a standard MA would not be granted.[7] In a report developed by the EMA on the 10-year experience of CMA, it was highlighted that the conditional MA had been granted to 30 medicines; however, the report called for a number of improvements, including wider use of an early dialogue between the EMA and the pharmaceutical companies, and engagement of further stakeholder groups in these discussions, including HTA bodies.[8]

In recognition of the shortcomings of the current pathways for patient access to medicines, there has been an effort towards development of initiatives which takes a more holistic view of a medicine's route to patient access. These initiatives build on the need to involve an expanded cluster of stakeholders at relevant stages of the development plan to overcome potential future hurdles concerning evidence generation and use. The efforts to date have been primarily focused on disease areas with a high unmet need.

From a European perspective, the adaptive pathways (AP) (formerly known as 'adaptive licensing' or 'Medicines Adaptive Pathways to Patients (MAPP)') was launched through a pilot project in March 2014. The AP is defined as a 'scientific concept for medicine development and data generation which allows for early and progressive patient access to a medicine'[9] and is integrated into the existing regulatory framework (including CUP, CMA and regular scientific advice) for medicines in the EU. On a national EU member state level, an initiative similar to the AP concept has recently been launched in the United Kingdom, the accelerated access pathway (AAP), which will be introduced from April 2018.[10] The AAP offers a new route to market for breakthrough technologies and treatments which aims to align and coordinate regulatory, HTA, reimbursement, evaluation and diffusion processes to bring these new technologies to patients quicker. The ambition, set by the UK Government, is to make these treatments available for use up to 4 years earlier than through the previous pathway to patient access.

The aim of this article is to provide a review of the latest developments with respect to accelerated access of medicines in the EU, namely, the AP concept, including a review of the three principles underpinning the concept in terms of what they entail and the recent developments. A particular focus is placed on a review of procedures for formal scientific advice that support enhanced multi-stakeholder dialogue. Finally, the article will provide a perspective on the future of accelerated access initiatives.

The AP concept and the three principles

The AP concept is primarily focused on medicines in areas with a high unmet medical need and where it may be difficult to generate clinical data via regular route. To be suitable for the AP approach, the medicine must also meet criteria associated with three key principles.[9]

The first key element is the use of an iterative development plan of the medicine whereby evidence can be collected stepwise and an approval can be sought in a restricted patient population with the highest unmet need and thereafter be expanded to a wider patient population or through the expansion from conditional MA (based on early clinical data with surrogate endpoints) to general MA by further confirmation of the benefit–risk ratio.[9] The second key element involves the use of real-world evidence (RWE) as a complement to clinical trial data in order to facilitate in situations where a CMA is granted but a decision on reimbursement cannot be made without collecting additional data.[11] There must be evidence of a coherent prospective plan for the collection of RWE. The final key element is vital for the AP concept and involves multi-stakeholder dialogue in all aspects of the development plan for the medicine as a part of the AP approach. There is a need for integrated involvement of regulators, HTA bodies, patients, payers, healthcare professionals and the company in the discussion of the product development programme, control of the prescription and risk management, in order for the company to prospectively plan how the demands of these stakeholders can be met.

For the AP pilot, the EMA received 62 applications for participation and 18 of these were selected as suitable to explore further in in-depth, face-to-face meetings with the EMA and other stakeholders. At the end of the pilot, seven of these applications were deemed suitable to include in the process and had progressed through to scientific advice

(six of those in parallel regulatory–HTA scientific advice).[12] For those applications that were not selected, the majority were advised to pursue traditional development routes as they did not fulfil the pilot criteria including having a development plan that did not allow for scope expansion and iteration, including areas without unmet need and a product in late-stage development without the possibility to amend the development plan.[12]

An iterative development plan for medicines (Principle 1)

Principle 1 involves the iterative and prospectively planned drug development plan with stepwise data collection to expand the approval population or to reduce uncertainty.[12] Due to the stepwise concept, it allows pharmaceutical companies and stakeholders to have discussions at checkpoints along the development plan for the medicine and for any adjustments of the product development plan if required, based on the data and advice obtained from discussions with the key stakeholders.[13]

In the AP pilot, for the discussions around the drug development plan, an emphasis was put on assessing the feasibility of the study design methodology proposed in delivering the required data.[13] Some of the specific items discussed were the robustness of data sources, whether the endpoints suggested were clear-cut, actionable and methodologically reliable and whether the methodology proposed would allow for reliable treatment comparisons to quantify therapeutic efficacy.

The stepwise approach is also an important aspect in order to facilitate the management of uncertainty around key data points that may exist at the initial MA. An aspect of the concept of a stepwise approach to managing uncertainty is currently seen to some degree in managed access agreements that are available in a number of countries including Belgium, the Czech Republic, France, Italy, the Netherlands, Sweden and the United Kingdom.[14–16] Managed access agreements are typically agreements between a healthcare payer and the pharmaceutical company and may take different types including those simply involving the provision of a medicine discount by the companies, those that include payment-by-performance and those that include a condition of additional evidence generation.[14] For the latter two forms, and hence particularly for the last one, the pharmaceutical company is required to collect additional data to confirm any uncertainties of the clinical profile or to collect real-world effectiveness through, for example, registries during a limited time period. It is anticipated that managed access agreements will be important tools for the post-authorisation evidence generation element of the AP concept, although details on the type and content of these are yet to be seen. Concerns have also been raised by payers that some of the existing managed access agreements are associated with a high administrative burden.[17–19] However, current and future developments in digital technology is likely to facilitate the adoption of more innovative and outcome-based managed access agreements through, for example, the integration of healthcare data and increased availability of large-scale data analytic tools.

The use of RWE as a complement to randomised controlled trials data (Principle 2)

This principle requires pharmaceutical companies having a prospective plan for collecting RWE, as a complement to randomised controlled trial (RCT) data, with high-quality data to further refine the benefit–risk profile, the therapeutic value and the price of a medicine. RWE is obtained from analysing real-world data (RWD), which has been defined by the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) as 'data used for decision-making that are not collected in conventional controlled randomised trials'.[20] This includes data from retrospective or prospective observational studies and observational registries. The use of RWE is currently utilised by the EMA in a number of ways including safety assessments and in support for decisions on restricting indications, making labelling changes and in withdrawals of MAs.[7] For HTA bodies, RWE is commonly used for descriptive analyses on, for example, burden of illness or treatment patterns and also to some extent to assess safety of a medicine; however, its use for treatment effectiveness is less widely accepted and level of acceptability varies by country to country.[21] However, due to acknowledgement of limitations with RCT, and potential benefits of RWE, a number of national and international collaborations between various stakeholders exist, including the Innovative Medicines Initiative GetReal Consortium (IMI-GetReal).[22] The IMI-GetReal is a 3-year project set up to investigate methodologies for the collection and synthesis of RWE and its use in drug development and assessment. The outputs provided in the IMI-GetReal project are collected and summarised in the RWE Navigator tool.[23] In addition, ISPOR together with the International Society for Pharmacoepidemiology (ISPE) has set up a task force with the objective to develop recommendations regarding good procedural practices that would 'enhance decision makers' confidence in evidence derived from RWD studies'.[24] The task force also has representation from the EMA.

In the AP pilot, RWE was suggested, by the applicants, to be applied in a number of ways. This included in identification of natural history of the disease, current standard of care, resource utilisation and adherence to treatment from existing disease registries; single-arm studies for rare diseases compared with outcomes inferred from disease registries; collection of efficacy and safety data from early access/compassionate use programmes to supplement

RCTs in small populations; post-authorisation drug registries for, for example, effectiveness and long-term outcomes; and linking of drug registries to risk-sharing schemes for reimbursement.[25]

Enhanced early multi-stakeholder dialogue (Principle 3)

Principle 3 involves a more enhanced dialogue with various stakeholders including regulators, HTA bodies, payers and patients.

Multi-stakeholder dialogues, through scientific advice, are already available for medicines in Europe in various forms. This section will first provide an overview of the various forms of scientific advice currently available and then focus on the advice process which is most relevant for timely patient access and the AP concept, namely, the regulatory and HTA bodies' parallel consultation.

Scientific advice, in Europe, is currently provided in three different forms: with regulatory agencies only, with HTA bodies only and through integrated parallel advice with both regulatory agencies and HTA bodies.

European regulatory scientific advice is provided either on a national level with regulatory agencies, such as the Federal Institute for Drugs and Medical Devices (Bundesinstitut für Arzneimittel und Medizinprodukte, BfArM) in Germany, the MHRA in the United Kingdom (such as EAMS) and the Medical Products Agency (MPA) in Sweden, or on a European level by the EMA (through the Scientific Advice Working Party (SAWP)). The advice procedure, aimed at facilitating the MA procedure by reducing potential areas for objections by the EMA during the approval process, is regarded by the agency as the key instrument in supporting the development of effective and safe medicines.[26] This is further evident from the addition of PRIME, where iterative scientific advice is an important tool. An EMA report from 2015 concluded that pharmaceutical companies who amended their clinical development programme in accordance with the EMA recommendations were more likely to be granted an MA.[27]

Scientific advice from HTA bodies can be provided as a single-country HTA scientific advice or as a multi-country engagement. The overall aim of seeking HTA scientific advice is to support pharmaceutical companies in designing an evidence generation plan which satisfies the requirements of an HTA reimbursement submission in order to reduce likelihood of any delays in patient access. Rather than focusing on the benefits and risks of a medicine and usually within a highly controlled setting, as in regulatory advice, HTA bodies look at the clinical and economic value within a real-life setting of current treatments and service pathways. Although there may be many issues of interest across national HTA bodies, local requirements or deviations on opinions are likely to exist which are of high importance to capture when seeking single-country HTA advice.

Integrated regulatory and HTA body scientific advice can be provided on a national level (by, for example, the National Institute of Health and Care Excellence (NICE) and MHRA in England (such as EAMS or joint regulatory HTA advice), Tandvårds- och läkemedelsförmånsverket (TLV) and the MPA in Sweden and G-BA and BfArM in Germany) or as a parallel consultation between the EMA and the HTA bodies.

The parallel regulatory HTA scientific advice was initiated by the EMA in 2010. This early form of parallel scientific advice required pharmaceutical companies to invite HTA bodies individually to participate in the scientific advice process. In July 2017, a new process (termed parallel consultation) was initiated by the EMA and the European network for Health Technology Assessment (EUnetHTA) which replaces the previous parallel regulatory HTA scientific advice process.[28] Parallel consultation aims to support pharmaceutical companies to obtain feedback from regulators and HTA bodies on their evidence generation plans to support decision-making on MA and reimbursement of new medicines at the same time.[29] The parallel consultation procedure may take two possible pathways: consolidated and individual (see Table 1). The consolidated pathway is only available for medicines that meet three criteria, namely, responding to an unmet need, has a new mode of action for the indication and targets a life-threatening or chronically debilitating disease. The decision on which pathway a medicine would take is done by the Early Dialogue Working Party (EDWP). The EDWP is a standing committee established by EUnetHTA to ensure robust high-quality HTA outputs and members include HTA bodies from France (Haute Autorité de Santé (HAS)), Germany (G-BA), the United Kingdom (NICE), Italy (Agenzia Italiana del Farmaco (AIFA)), Hungary (National Health Insurance Fund Administration (NHIFA)) and the shared seat of the Netherlands (Zorginstituut Nederland (ZIN)) and Belgium (Belgium Health Care Knowledge Centre (KCE)).

A recent analysis of meeting minutes from parallel advice sessions between EMA and HTA bodies shows that the level of agreement between the two stakeholder groups was high across all topic domains studied including patient population (77% agreement), study endpoints (60%) and other study design characteristics (60%).[30] The article authors recognised that it would be important to discuss how to deal with any critical disagreements between the EMA and the HTA bodies in upcoming discussions on the parallel advice process. The EMA and EUnetHTA have highlighted several key achievements with parallel scientific advice including the introduction of a more streamlined and potentially less resource-consuming process through a joint advice process, modifications to the EMA assessment reports to fit the needs of HTA bodies and earlier information sharing between the EMA and the HTA bodies to facilitate a more timely reimbursement review.[31]

Table 1. Summary of the consolidated and the individual pathways for parallel consultation.[28]

	Consolidated	Individual
Responsibility for HTA body recruitment	Centrally via EUnetHTA ED Secretariat	Centrally via EUnetHTA ED Secretariat
Selection criteria	Only applications which meet all the following criteria: A new mode of action for the indication AND targeting a life-threatening or chronically debilitating disease AND responding to unmet need (no treatment or only unsatisfactory treatment available)	Not applicable
Level of participation of HTA	Full participation of the EDWP (FR, DE, IT, HU, UK and a shared membership between NL/BE) and up to three additional HTA bodies[a]	Voluntary HTA bodies[a], coordinated by EUnetHTA
Outcome	A written report with consolidated HTA advice on shared positions, plus individual answers when consensus has not been achieved	Individual HTA bodies provide written individual answers to the questions directly to the applicant
Timeframe	Final answers will be sent to the applicant after approximately 75 days	The answers will be sent to the applicant within 15 working days of the face-to-face meeting
Participation from other stakeholders	Clinical experts and patient representatives are invited to attend meetings	Clinical experts and patient representatives are invited to attend meetings

BE: Belgium; DE: Germany; ED: Early Dialogue; EDWP: Early Dialogue Working Party; EUnetHTA: European network for Health Technology Assessment; FR: France; HTA: Health Technology Assessment; HU: Hungary; IT: Italy; NL: the Netherlands; UK: United Kingdom.
[a]Preferences of applicants are taken into account but participation is not guaranteed.

The importance of an early dialogue between EMA and HTA bodies has also been recognised in a recent white paper where scientific advice (multi-HTA or parallel) was highlighted as one, out of eight, aspects with particular importance for policymakers to consider for future adjustments in HTA decision frameworks.[32]

The pilot AP project included the option of AP parallel consultation between regulators and HTA bodies. Similar to the regular parallel consultation procedure, contact points consist of a pre-submission meeting (two for small to midsize pharmaceutical companies) and a face-to-face meeting. In addition, the pilot provided a framework for informal dialogue between key stakeholders called 'safe harbour' discussions where the companies are able to explore different scenarios and options for the technical and scientific questions based on previous examples in a confidential forum. The range of stakeholders engaged in commenting on the AP concept and the pilot has been extensive and include representatives of regulators, clinical organisations, patient associations, pharmaceutical companies, HTA bodies and payers.[7] However, in the pilot AP scientific advice sessions, involvement has been limited to regulators and HTA bodies, as well as clinical and patient representation in some instances. A stakeholder group which has voiced some concerns about the AP concept, and who has labelled their current level of involvement as insufficient, is the payer community.[33] During the AP pilot, payers participated in one case where they provided high-level comments on a risk-sharing plan.[25] The payer community has highlighted a number of weaknesses with the AP concept including potentially experiencing the same difficulties as medicines approved through the CMA route in that immature or incomplete data will be used and concern around who should take the financial burden around post-authorisation monitoring. Question marks from payers also exist around certain points, for example, how to deal with possible MA suspension/withdrawal/restrictions, increase/decrease in reimbursement level and communication of AP process to patients (and doctors).[33,34] In recognition of the emerging important role of payers, the EMA and EU payers held a first meeting in September 2017 with the aim to 'explore synergies and foster mutual understanding and cooperation to help improve timely and affordable access of patients to new medicinal products'.[35] A report from the meeting is pending publication (November 2017).

Future for accelerated access initiatives in Europe

Recent new initiatives aimed at driving timely access of medicines put multi-stakeholder engagements in a central position through the enhanced dialogue as part of the iterative development plan included in the AP concept and the addition of the safe harbour discussions. It is likely that these developments with respect to iterative early dialogue across multiple stakeholders are set to increase even further and gain expanded prominence also in regular EMA

MA and parallel scientific advice routes but expectedly even more important for certain types of products in areas with a particularly high unmet need. For these products, a dialogue across a larger group of stakeholders will be required, rather than a 'one-shot' approach to scientific advice. For multi-stakeholder engagements, a further discussion is required on how to deal with any critical disagreements between parties involved in the scientific advice process, such as regulators and HTA bodies. It is also of great importance that all stakeholders involved are fully engaged in and committed to the process. Although it is to be expected that these engagements will require additional resources and efforts from all stakeholders involved, the experience from EMA regulatory scientific advice in terms of increasing the likelihoods of obtaining an MA after having altered development programmes accordingly may mean less resources required in dealing with objections or complications at a later stage. The difficulty of ensuring that people with relevant expertise can provide input into the engagements has, however, been highlighted[11] and will need to be monitored. From a company perspective, the asset owners will need to ensure that they are fully prepared for meetings with clear strategic objectives and have a well-developed value proposition with relevant questions targeted to the right audience, as well as have a credible and realistic RWE plan.

It is expected that the payer community will have an even more prominent role in the multi-stakeholder scientific advice procedures of the future, particularly due to the aspect of post-authorisation monitoring and RWE collection. In addition, the introduction of new breakthrough medicines can be challenging for payers with fixed short-term budgets and therefore payers will need to develop new innovative flexible pricing models for managed access agreements and require an early dialogue between company and payers. The trend of involving payers in dialogues at earlier stages of patient access to medicines is already seen in initiatives on a national level through TLV's 'trepartsöverläggningar' which invites payers to participate in discussions around a reimbursement application, should both company and payers wish to.[36]

There are also signs that multi-stakeholder scientific advice processes in the future may offer more flexibility in terms of process timelines. The Scientific Advice Program offered by the Canadian Agency for Drugs and Technologies in Health (CADTH) provides greater flexibility in terms of process timelines, more timely advice for smaller requests and engagement at multiple time points if required.[37]

Finally, as the majority of the focus and efforts around accelerated access is put on those medicines addressing an unmet need, the concept of a 'high unmet need' must be further defined, as raised by both AP stakeholders and at the ISPOR Annual European Congress 2017.[7,38,39]

In conclusion, early and enhanced dialogue with extended stakeholder groups is a crucial element in supporting the introduction of breakthrough medicines responding to an unmet need with sufficient evidence to ensure accelerated access while balancing this with affordability for payers in the European health systems.

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