Medicines Adaptive Pathways to Patients (MAPPs) – Opportunities and Challenges in Europe

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KEY POINTS . . .

Medicines Adaptive Pathways to Patients (MAPPs) aim to provide timely/early access to promising therapies that address a deep unmet medical need.

These pathways mean a shift in the way evidence is planned, generated and used, i.e. co-planned upfront and giving more weight to post-launch data.

Many challenges exist, including health technology assessment (HTA) and funding approaches and the results of the current MAPPs pilot will inform stakeholders about the way forward.

The following article is based on the Issue Panel, "Early Access to Therapies through Adaptive Licensing: How Do You Make It Work For All Key Stakeholders?" given at the ISPOR 17th Annual European Congress, 8-12 November 2014, Amsterdam, The Netherlands

Medicines Adaptive Pathways to Patients (MAPPs) is an EU-level initiative that seeks to provide timely and potential early access to promising medicines that address significant unmet medical needs. The MAPPs' scope covers regulatory approval and, critically, post-approval decisions associated with health technology assessment (HTA), pricing, reimbursement, and health care delivery. The general principle is that approval and reimbursement decisions are made using a more flexible framework, allowing launch of the therapy based on limited, yet clearly promising, evidence that can be expanded and assessed regularly post launch [1-2].

What are MAPPs?

Sometimes referred to as 'adaptive licensing' or 'staggered approval', MAPPs focus on therapies that address areas of high unmet medical need, i.e. life threatening or seriously debilitating conditions where therapeutic options either do not exist or are very unsatisfactory. Additionally, candidates for MAPPs should offer a convincing promise, based on preclinical or clinical evidence, of large treatment effect and change in standard care. MAPPs are not for 'me-too' drugs, nor for those with little or no convincing evidence.

From a regulatory perspective, the process is as follows: Initial licensing is granted in a limited, well-defined population on the back of promising clinical trial data, then broadening to a wider population based on iterations of evidence gathering. Crucially, the development plan across target populations and indications is agreed up-front with the EMA, which distinguishes the process from the conventional indication expansion approach. The MAPPs plan may include a range of studies, such as 'classic' randomised controlled trials (RCTs), single arm studies, pragmatic trials and other forms of real-world studies. Acceptance of studies beyond the conventional pre-approval RCTs, however, should not be interpreted as an attempt to lower evidentiary standards.

The reimbursement aspect is just as important as the regulatory one in the MAPPs proposal, to avoid a situation where the medicine gets marketing authorisation but no market access because payers do not have the evidence they need. Hence, the upfront agreement for the development plan is based on a joint consultation with HTA bodies/payers, the European Medicines Agency (EMA) and the drug developer. MAPPs build on existing processes on the regulatory side (e.g. early scientific advice, conditional marketing authorisation [MA], MA under exceptional circumstances, temporary authorisations [ATU]) and on the reimbursement side (e.g. conditional reimbursement, coverage with evidence development, managed entry agreements). The novelty is that the approach is meant to be planned over the compound's life cycle and co-ordinates the regulatory and HTA/payer sides.

Why MAPPs are Needed

Several trends are driving the MAPPs initiative. One is the long-standing societal pressure on regulators (EMA) to accelerate the market approval of innovative medicines for patients with severe conditions (i.e. life threatening or seriously debilitating) and none, or very few, therapeutic options. MAPPs are consistent with other EU initiatives to support innovation in the face of challenging development. For example, a regulatory framework exists since 2000 to incentivise development of orphan medicinal products (OMPs) where, typically, evidence at launch is scarce. Furthermore, the concept of MAPPs is underpinned by the idea that continuous, post-launch 'real-world' data (RWD) are increasingly relevant. EU regulators are particularly concerned with external validity, and do not want the gap between efficacy and effectiveness to increase. The EMA welcomes RWD early on to confirm results of conventional clinical trials; the move towards requesting post marketing studies for both safety and >

efficacy to continually assess the benefit-risk balance of medicines is testimony to this.

Pressure also exists on payers to grant rapid reimbursement for innovative, value-adding therapies in areas of high unmet need, especially in areas such as oncology and rare diseases. In a way that is parallel to the regulatory trend, some HTA bodies and payers have opened up to the idea of providing access to therapies based on limited evidence that will be confirmed post launch – this is reflected by the existence of early access programmes, conditional reimbursement and other types of managed entry agreements in several EU countries.

In this context, MAPPs constitute a flexible pathway within the current pharmaceutical legislation and reimbursement framework that would accelerate access to crucial therapies for patients in need. In addition, MAPPs would provide a framework to handle the eventual rise of personalised medicines that are likely to have large clinical benefits in subgroups but could potentially have value in larger groups.

MAPPs Could Benefit a Range of Stakeholders

Patients should be the primary focus when it comes to introducing novel therapies and MAPPs aim to increase opportunities for those with little or no therapy options (Table 1). Furthermore, if the process is inclusive enough, it could help integrate the patient view into the evidence planning (e.g. definition and selection of outcomes, acceptable benefit/risk, and definition of value). For both regulators and payers, MAPPs could provide a controlled environment to enable early access to therapy for patients while managing the clinical or financial risk. As to the drug developer, the new framework is expected to foster better interactions with regulators and HTA bodies, which should increase chances of success in 'risky' therapeutic areas; however, this incentive might be more helpful to the smaller companies that otherwise would have little opportunity to get to market.

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Current Status of MAPPs

The MAPPs pilot phase opened in March 2014 to candidates in early stages of development (normally during or prior to Phase II but considered on a case-by-case basis) [3]. The process has involved meetings between EMA, the sponsor companies, HTA bodies, organisations issuing clinical treatment guidelines, and patient organisations – discussions are held in a safe harbour (confidential) environment and are not binding. Since this is a pilot, it is not known at present what the impact will be on regulatory and payer approval pathways in future.

MAPPs Face Multiple Hurdles

An important consideration is that the MAPPs proposal is not about achieving earlier access at all costs, since regulators would not want to open the flood gates to therapies that might turn out to have an unacceptable benefit/risk ratio, for example if they are used in the wrong patient groups. More fundamentally, concerns from payers and HTA bodies must be considered. One major fear is that it may be difficult to withdraw a product if its performance proves disappointing post launch – high-profile examples have shown that pressure on politicians from patients can block delisting of therapies despite poor evidence of effectiveness and lack of cost effectiveness. Since the MAPPs are a combined regulator-HTA process, however, a joint motion to remove the product, backed by appropriate communications, would be expected to create less public push back because it would be supported by several institutions.

Figure 3. Net Health Gain from Using HTA to Promote Efficiency.

Stakeholders	Potential benefit
Patients	• Access to medicines that would otherwise only be available via a clinical trial (if at all) • Opportunity to get more involved in development
Regulators	• Controlled environment for assessment of benefit/risk
Payers	• Controlled environment to offer access to high-need patients
Pharma/biotech	• More fluid interactions between pharma, regulators and HTA bodies • More attractive for smaller or focused pharma companies?

Another risk is that, once in the market, physicians may be tempted to prescribe the new therapy outside the approved indication – this is not a new concern, but it will be exacerbated by the fact that the therapy will be indicated in quite a narrow group, possibly with expectations that it could be useful outside this indication. Hence, initial assumptions about the target population (size and expected benefits) made at time of initial pricing and reimbursement (P&R) negotiations could be incorrect.

MAPPs may also be a challenge for the relatively rigid HTA and P&R mechanisms currently in place. For example, these mechanisms might not cope fast enough with a rapid succession of expansions in the target groups and indications, combined with evolving post-launch evidence. HTA and P&R processes would need to be more agile and 'adaptive'. Establishing a fair price might be difficult: one could argue for a higher price in subpopulations where benefit is greatest, but at the same time one could make a case for a lower price to account for uncertainty. Increasing the price, if the evidence backs up the promise, may be logical but this has very rarely happened in the past; alternative proposals could be to maintain the price as the target population increases in size. Further difficulty in managing the international price is that HTA bodies and payers across Europe may have different views on pricing in the face of uncertainty, hence creating a problematic spread in price.

Success Factors for MAPPs

Drivers of Changes

Given the diversity of HTA and P&R approaches across EU member states, it is likely that a few countries will be the drivers and early adopters of MAPPs. Possibly, the smaller countries will be particularly incentivised to quickly join the initiative because, individually, they might struggle to cope with the funding of therapies approved through adaptive licensing. Organisations such

as EUNetHTA, which have been working closely with EMA, might be expected to be catalysts and co-ordinators. A note of caution, however, is warranted: politics will, at all levels, pay a key role in success, and this is hard to predict.

Dialogue and Co-operation
Dialogue and co-operations are pre-requisites for success. Alignment is needed between regulatory agencies, HTA bodies, health care systems, providers etc. Arguably, alignment within countries might need to precede alignments between countries. Patient organisations must also have a voice in MAPPs: these organisations are in principle consulted in the proposed process, but the question is whether patient involvement will occur throughout, ideally from the creation of the development plan to funding to delivery at the point of care.

Increased interactions between regulators, HTA bodies, payers, therapy developers, and patient organisations might in theory threaten the principle of independence. This view has been aired, in particular from the sides of payers and HTA bodies. Surely, evaluators and decision makers must be able to act rationally and in a balanced way to fulfil their mandates, but it is clear that regulators, industry, and patient groups have been able to work in partnership for some time, so why not payers and HTA bodies as well? Also, from the industry perspective, there might be a fear that creating the development plan for their compounds jointly with both payers and regulators would be somehow risky and too constraining – but mitigating consideration is that such dialogue will clearly boost credibility of the industry through generating a transparent, prospective view on development of therapies that fill an unmet need.

New Methodology and Tools
To support MAPPs implementation, new enabling methodologies and tools may need to be developed and tested. This development may, for example, focus on adaptive clinical trial designs, patient centric benefit/risk assessments, potential use of multi-criteria-decision analysis (MCDA), and tools to continuously evaluate the therapy as new evidence (including real world data) becomes available. Registries are likely to play an important role in confirming efficacy suggested by the pre-launch clinical trial(s), in addition to the generation of a larger range of outcomes around effectiveness and safety. A number of think-tank initiatives have been launched to address methodology, including IMI/ GetReal and NEWDIGS [4-5].

Managed Entry Agreements (MEAs)
MEAs have been used for more of a decade in Europe to address uncertainty at launch about the clinical value of new therapies, as well as limiting or making their budget impact more predictable. Since MAPPs will likely heighten these issues, MEAs are expected to be very useful, if not necessary, ad hoc approaches until consistent and sustainable solutions are found to address the P&R challenges highlighted above.

Conclusion
Time will tell whether the MAPPs approach is attractive to the various stakeholders or not. Current thinking based on modelling suggests that in a number of, but not all, cases a MAPPs scenario could improve revenues (as measured by net present value) for new compounds, and benefit patients and physicians (as approximated by the number of patients appropriately treated with the medicine) [6].

References
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Additional information:
To view Dr. Lucas' presentation, please visit the Released Presentations page for the 17th Annual European Congress at: http://www.ispor.org/Event/ReleasedPresentations/2014Amsterdam.

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