HOW THE REGULATORY FRAMEWORK IS EVOLVING FOR INNOVATIVE PRODUCTS

Adaptive Pathways Workshop
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Timely authorisation of products expected to cover unmet or high-impact medical needs is vital to support innovation and to improve patient access. The introduction of adaptive pathways is challenging but initiatives such as the EMA adaptive licensing project and recognition of the issues around HTA approval for conditionally approved products in the EU are helping shape the regulatory framework.

This workshop considered how the regulatory hurdles to bringing such products to market could be overcome in order to improve patient access to vital new treatments.

The discussions outlined in this reflection paper are intended to stimulate further debate, and do not represent the views of TOPRA, DIA or any single corporate entity or individual named in this document.

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ADAPTIVE PATHWAYS WORKSHOP

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ACRONYMS & ABBREVIATIONS

AA Accelerated Assessment
AP Adaptive Pathway
ATMP Advanced Therapy Medicinal Product
ATU Authorisation for Temporary Use
CHMP Committee for Medicinal Products for Human Use
CMA Conditional Marketing Authorisation
DCP Decentralised Procedure
EC European Commission
EFPIA European Federation of Pharmaceutical Industries and Associations
EMA European Medicines Agency
EUnetHTA European Network for Health Technology Assessment
HAS Haute Autorité de Santé
HMA Heads of Medicines Agencies
HTA Health Technology Assessment
IMI Innovative Medicines Initiative
MA Marketing Authorisation
MAA Marketing Authorisation Application
MAPPs Medicines Adaptive Pathways to Patients
MRP Mutual Recognition Procedure
NDA New Drug Application
P&R Pricing and Reimbursement
PAES Post Authorisation Efficacy Study
PASS Post Authorisation Safety Study
QoL Quality of Life
R&D Research and Development
RCT Randomised Controlled Trial
SEED Shaping European Early Dialogues
SMEs Small and Medium-Sized Enterprises
SO Specific Obligation
STAMP Safe and Timely Access to Medicines for Patients

INTRODUCTION

Why the workshop was set up

This second joint venture between TOPRA and DIA brought together 65 delegates and keynote speakers in Brussels on 30 June 2015 to discuss adaptive pathways (AP) and in particular the implications from multiple stakeholder perspectives, including regulators, industry representatives and health technology assessment (HTA) bodies.

The programme followed the successful 2014 TOPRA/DIA joint workshop on the Escher Project where the conditional marketing authorisation (CMA) breakout session generated numerous questions and fruitful discussions. This subsequent TOPRA/DIA 2015 workshop aimed to focus on AP, incorporating CMA and to look into both the regulatory hurdles as well as discuss improvements in market access based on recent experience in the EU.

Fundamentally the workshop aimed to bring together insights from both regulatory and market access experts, thus connecting stakeholders. Session 1 aimed to define AP, introduce the concept from both regulatory and market access perspectives and discuss the differences between the European and US systems. The European Medicines Agency (EMA) Pilot status and learnings were also presented to provide a comprehensive view, which served as a basis for the whole workshop; Session 2 focused on learnings from the systems in place, both from the industry and HTA body viewpoints. In advance of the workshop a survey was conducted by the working party to analyse the products that are currently EU-approved through CMA and looking into the outcomes of HTA assessment at EU member state level. Additional products initially marketed on a CMA, but for which the conditions have been fulfilled and the MA converted to a ‘normal’/full MA, were not part of the survey. The survey results were presented, followed by interactive roundtable discussion sessions further assessing the current AP findings and proposals for future actions.
BACKGROUND

Adaptive Pathways

The ‘adaptive pathway’ has been identified by many interchangeable terms including ‘staggered approval’, ‘progressive licensing’, ‘adaptive licensing’ and more recently the ‘Medicines Adaptive Pathways to Patients’ (MAPPs). This varied terminology could be seen as indicating a lack of clarity regarding the scope and definition of the topic, or the fact that it is an innovative topic with multiple aspects that requires flexibility.

The EMA defined the AP approach as being based on a prospectively designed development plan which is the subject of an early dialogue with stakeholders (regulatory authorities, patients’ organisations, HTA bodies). The development plan would generally foresee an initial authorisation of a medicine, granted on the basis of the demonstration of a positive benefit–risk balance at the time of authorisation, most likely in a restricted patient population, possibly on the basis of surrogate endpoints. This would be followed by iterative phases of evidence gathering, including real-world data, and the adaptation of the marketing authorisation to extend access to the medicine to broader patient populations while gradually refining the knowledge of the benefit–risk balance during the post-authorisation phase.

Consequently the EMA criteria for inclusion in the AP Pilot project included:

1. An iterative development plan (eg, either by gradual expansion of the target population, perhaps starting from a population with high(est) medical need, or progressive reduction of uncertainty after initial authorisation based on surrogate endpoints)
2. Ability to engage HTAs and other downstream stakeholders, with proposals for how the demands of these stakeholders can be met
3. Proposals for the monitoring, collection and use of real-world data, post-authorisation, as a complement to randomised controlled trial (RCT) data, to inform updates to the regulatory label and to the positions of other stakeholders.

HTA Research

While it may be possible to agree on processes and procedures from a regulatory viewpoint via these adaptive development pathways, ultimate access in the market is dependent on pricing and reimbursement decisions that are based on national legislation and practices. A survey was therefore designed by the TOPRA/DIA Working Group to investigate these national market access activities and associated progress by looking specifically at conditionally approved products (which is one of the mechanisms for AP). This survey was distributed by the European Network for Health Technology Assessment (EUneHTA) with Haute Autorité de Santé (HAS) endorsement to 37 national organisations (29 countries) and completed by: Portugal (INFARMED), Finland (FMA), Sweden (TLV), UK (Scottish Medicines Consortium), Luxembourg (CMS), Germany (GBA) and France (HAS). Partial responses were provided by Malta (Pharmaceutical Affairs Directorate) and Cyprus (PharmServices, Ministry of Health). Findings of the survey were presented during Session 2 of the workshop.
THE WORKSHOP

Session 1: The historical scene and current perspective

Susan Forda, Eli Lilly, opened this session with a comparison between the EU and US expedited and alternate pathways. In addition to succinctly setting the scene for the workshop, Susan highlighted that none of the expedited pathways can work efficiently without agency resources, and in particular the US can often require additional, not simply earlier, resources. A number of desired commonalities were identified: alignment and clarity of qualifying criteria and definitions for pathway; supportive engagement of adequately resourced regulatory officials; meaningful, achievable advantages fundamental to pathway; regulatory flexibilities needed given development uncertainties and accommodation for global development considerations.

Current analysis indicates that, in the US, more products undergo some accelerated mechanism – 73 new drug applications (NDAs) have been approved through accelerated, priority, fast-track and/or breakthrough therapy designation from 2010–2013. Meanwhile, only 19 EU marketing authorisation applications (MAAs) have benefited from accelerated mechanisms – conditional marketing authorisations (CMAs), accelerated, exceptional circumstances or advanced therapy medicinal products (ATMPs), often receiving additive ‘special treatments’ in the US. However, particularly in the EU, there is a marked contrast between the high burden of disease (eg, diabetes) and those products which are approved via accelerated assessment (AA) and CMA (eg, infection indications). Malignant disease is, however, adequately addressed by alternative pathways.

Hugo Hurts, MEB, the Netherlands, focused on timely access and identified that although policies have well-defined goals, we may not be achieving these yet. The role of the national member state regulatory agencies was also highlighted, particularly in relation to assisting with the resource-stretched EMA scientific advice meetings and also in ‘drug rediscovery’, ie, national conditional approvals, which although not innovative, enable patient access at an affordable level. Cooperation with HTA bodies is deemed to be improving; however, the limiting factor in the success of AP is currently perceived as pricing and reimbursement (P&R) agencies. The EU agencies and the European Medicines Agency (EMA) are considered to be collaborative and particularly open to dialogue. Future evolution requires a balancing act between all stakeholders, with further alignment and voluntary collaboration where possible. The pharmaceutical industry must play a role in stimulating this alignment by recognising that budget impact will be more dominant over the value of products.

The concept of value was further explored by Leeza Osipenko, National Institute for Health and Care Excellence (NICE), UK, who encouraged industry to discuss requirements for data collection with HTA agencies early in the process to maximise the usefulness of evidence generation for reimbursement within the AP scheme. For example, companies should start considering quality of life (QoL) data collection in earlier trials if they plan to bring their products to the market prior to the completion of pivotal studies. The limitations associated with the lack of funding in the European HTA agencies to cope with the resource demands of AP were also highlighted.

Insights into the current EMA AP Pilot were shared by Anne-Virginie Eggimann, bluebird bio Inc. In relation to LentiGlobin gene therapy development, the EMA discussions were considered very active and also thought-provoking, and gave reassurance and support to the SME at all stages. These ‘safe-harbour’ discussions were deemed to be the most valuable element of the AP process, and the procedure was more flexible and informal than similar FDA interactions.

Paul McCleverty, Janssen Pharmaceutical Company, presented a ‘big pharma’ experience of the Pilot with early stage biological and small molecules. He likewise agreed that the safe harbour had lived up to its promised potential; however, better attendance by HTA bodies would be useful. Internal company buy-in and agreement is perceived to be a challenge, particularly in relation to planning for consolidated global oncology clinical trial design.
THE WORKSHOP
Session 2: Current developments – where we are today

Magda Chlebus, EFPIA, engaged the audience with the concept that evolution is driven by science, and success is not when we have product on the shelf, but when it is available to patients. If we design the right pathways, we will prosper, but only when developed with the right mind-set; we should not consider a ‘smaller set of data’ but instead a relevant and insightful ‘different data set’. AP encompasses more than the EMA Pilot and incorporates other safe-harbour forums such as the Innovative Medicines Initiative (IMI). The importance of the ADAPT-SMART consortium (an IMI proposal submitted in response to the ‘coordination and support action’ call topic on MAPPs (Medicines Adaptive Pathways to Patients)) was noted. Despite initial fears, industry has embraced AP (58 applications), but to continue evolving we must all work together in a safe-harbour environment and address the remaining gaps of ‘RealData’, managing uncertainties and ‘BigData’ for health outcomes.

Francois Meyer, Haute Autorité de Santé (HAS), conveyed that adaptation is essential for survival, and France has embraced the concept of AP for medical devices (French 2010 law); adaptive access via the authorisation for temporary use (ATU) named patient and cohort procedures; and also post-approval French studies with HAS-approved protocol. Early dialogue has been successful whatever the pathway, and is key for AP; however, France has struggled to participate in HTA AP discussions due to resource constraints and a focus on SEED (Shaping European Early Dialogues) Consortium activities (report due Q3 2015). To the HTA bodies, the AP meetings have appeared to be ‘normal’ scientific advice. A request was therefore made for ‘traditional’ development pathways to be presented during Early dialogue interactions alongside more creative accelerated strategies to allow a more informed decision to be made.

Olga Solomon, European Commission, focused on the problem of translation of scientific advances into innovative medicines and the question of whether our current legal framework is delivering. The Commission expert group STAMP (Safe and Timely Access to Medicines for Patients) was not set to deal with a revision of the legal framework or to focus on the complex areas of HTA and P&R, but rather to identify weaknesses and solutions that will enable a better use of current regulatory tools. STAMP discussions have been intense, dynamic and fruitful, using the Escher conditional findings as one of the elements for further discussion and analysis. The STAMP minutes and documents are publicly available on the Commission’s website. The Commission recognises that CMA is perceived negatively by many parties. Prospectively planned CMA applications could improve its use, accelerate assessment and may aid in a better design, feasibility and completion of the Specific Obligation (SO) studies. Current experience shows that SOs are completed on average in three years, and that for 50% of CMA approvals, completion of the last SO was extended by an average of 1.2 years. The EMA’s Pilot project AP and accelerated assessment have been also discussed at the STAMP.

The continuum of research and development (R&D) was highlighted by Yann Le Cam, EURORDIS, who stressed that even with a CMA, a company has no viable product without HTA approval and P&R. Current discussion emphasises data and assessment, but with no consideration of healthcare systems. In order to succeed, we need to be willing to take more risk and also to engage patient groups, and payers, in the more challenging assessments. All parties need to focus on access and sustainability to ensure patient outcomes are paramount, rather than the traditional approach of access versus sustainability and licensing outcomes.

Mira Pavlovic-Ganascia, HAS, and Steffen Thirstrup, NDA, presented the HTA survey results. There was deemed to be no difference in HTA decisions for centralised and other products and CMA is not necessarily an obstacle for HTA evaluation. The same methodology and criteria are applied, with cost-effectiveness and limited data cited as the primary reasons for declining reimbursement. However, CMA is seldom followed by a ‘tailored’ HTA approach such as conditional reimbursement or managed entry agreements.

References
1. Innovative Medicines Initiative. Available at: www.imi.europa.eu/content/home
The multi-sector audience divided into four groups to discuss topics which had emerged from the earlier sessions. A common theme included the lack of clarity on AP and the need for a better definition, to the extent that a glossary of terms was thought to be beneficial. Furthermore, this clarification would also allow for Regulatory and Market Access professionals to conduct internal education within industry and therefore encourage cross-functional dialogue and early uptake of AP concepts and mechanisms. This reflects the new paradigm for industry and the current lack of company infrastructure to ask the right questions of the right people and gather enthusiasm and action.

There was a common appreciation that the tools and mechanisms exist, but significant further discussion between all stakeholders is required, recognising that patients are now much more knowledgeable about their disease, and particularly those with high-impact unmet medical needs such as those implicated in AP. Stakeholders were urged to remember that the AP is more than getting a licence; it is fundamentally about getting product to patient in the timeliest manner through the consideration of payers’ requirements. The following topics emerged as perceived current challenges and potential recommendations and solutions.

**Perceived current challenges (not necessarily in priority order):**

- Challenging the current mind-set both across companies and agency stakeholders – we are often not creative enough to successfully apply adaptive thinking and methodologies, and are established in non-traditional lower risk approaches.
- Regulators, HTA and payers ‘speak different languages’ – we need to break the existing silos between key stakeholders.
- Lack of clarity about the different instruments and tools which are available for AP.
- Misconceptions and misrepresentations of expectations involved in AP and the scope of the products which should be considered.
- It is tempting to compare the unclear EU AP to recognised EU or US methodologies and regulatory pathways; however, this limits the creativity and application of the specific AP route.
- The initial AP Pilot was affected by under-funding and lack of resource for engaging with stakeholders, particularly from HTA/payer perspective.
- Data exclusivity – as the clock starts on CMA grant it may lead to a significant time-lag until the product is fully commercially available to patients.

**Proposed recommendations to address the gaps:**

- Early multi-party dialogue, eg, engagement between all parties regarding the best way to measure outcomes, such as endpoints and comparators.
- Earlier engagement of epidemiology and biostatistics to shape appropriate and robust data generation.
- Learning from the safe-harbour discussions (not only in relation to the AP Pilot, but to wider initiatives).
- Proactive and smart use of the existing regulatory tools by companies, eg, conditional S0s, post-authorisation efficacy studies (PAES), post-authorisation safety studies (PASS), and compassionate use.
- Consider developing reimbursement risk-sharing schemes. Likewise, formulation of an exit strategy for payers and HTA agencies, if the AP product fails to generate real-world data or if the conditions set up by regulators at the time of licensing cannot be met.
- Conduct of HTA data assessment in parallel with the CHMP MAA assessment rather than post-marketing authorisation (MA) grant; in addition to removal/adaptation of the EC administrative closure steps to allow rapid access of approved products to patients.

An adaptive pathway is more than getting a licence; it is about getting product to patient in the timeliest manner.
SUMMARY OF DISCUSSIONS

Questions focused initially on the practical aspects of AP and the Pilot; compatibility with both paediatric development and orphan products was questioned and felt not to be an obstacle or an additional challenge for products undergoing the AP Pilot. However, it was noted that for products currently in the AP Pilot, MAAs will likely not be submitted for a few years following the currently proposed and discussed development plans.

Panel discussions and questioning then turned to the philosophy and framework of the AP. The MA and the price are deemed to be the critical elements and although we have advanced the MA with the possibilities for mechanisms such as CMA and AA, and early engagement between industry and HTA via parallel scientific advice, we still have a significant gap with no communication between industry and payers. This point raised an interesting and energised discussion of what separates payers from HTA and indeed what distinct requirements HTA agencies have in comparison to regulatory agencies. Money and politics were, somewhat controversially, pitched as the answers. The more serious explanation was a shift in focus between these factors: regulators look to the benefit–risk ratio for that individual new product, not necessarily in relation to other prior approvals; HTA bodies look to the new product ‘health gain above and beyond existing options’.

From a political viewpoint, we have evolved in the right direction with centralised regulatory assessments, however, the national member state divergence is still evident within mutual recognition/decentralised procedures (MRPs/DCPs); from an HTA perspective this variance is more noted with a desire to focus on the national level priorities and the need to cater for individual member state capita. The fundamental message however was that product cost does not equate to product value; to succeed and reach the patient rapidly, it is vital to robustly demonstrate cost-effectiveness and value in relation to the specific patient population.
CONCLUSION

This interactive joint workshop provided an ideal forum to identify the challenges brought forward by AP, such as additional evidence generation and the barriers in global registration programmes.

The roundtable discussions also provided a more holistic view across the product lifecycle from clinical early development to payer negotiations, and therefore generated recommendations which will be passed to the multiple different stakeholders.

Our aim is to further engage stakeholders in 2016 with further expansion to include payers and patients in addition to industry, regulators and HTA bodies.

RECOMMENDATIONS AND KEY POINTS

The consolidated list of the following recommendations will be shared with the key stakeholders (EMA; HMA; EUnetHTA; EFPIA) to encourage further action and evolution.

EMA specific:
- Clarification on which products should be included in the AP
- Suggestion to adapt current scientific advice or early dialogue to fit the concept and specific issues raised by AP
- Improved methodology to achieve success with limited data requirements (including safety issues)
- Enabling involvement of patients and payers in safe-harbour discussions, and establishing a platform to capture all stakeholders’ views from these discussions.

EMA and HTA bodies:
- Conduct early dialogue meetings on adequate evidence generation
- Develop methodology on how best to collect and use real-world data (including observational data)
- Be clear on instruments and tools to use.

Payers and HTA bodies:
- Develop suitable platforms to involve payers
- Develop risk-sharing/managed entry schemes
- Develop rules for stopping reimbursement if products are not successful in the real-world setting.

European Commission
- Use better existing tools; involve member states
- Appropriate funding/resourcing for AP.

RESOURCES
Further information is available from:
- Innovative Medicines Initiative (IMI): www.imi.europa.eu/content/home
- EUnetHTA: http://www.eunethta.eu/