



Legal constraints with regard to MAPPs

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1. Abbreviations

ADAPT-SMART	Accelerated Development of Appropriate Patients Therapies, a Sustainable, Multi-stakeholder Approach from Research to Treatment-outcomes
CMA	Conditional Marketing Authorisation
CUP	Compassionate Use Program
DE	Data Exclusivity
IP	Intellectual Property
MA	Marketing Authorisation
MAH	Market Authorisation Holder
MAPPs	Medicines Adaptive Pathway to Patients
MP	Market Protection
NPS	Named patient supply
Orphan Regulation	Regulation (EC) No 141/2000
OME	Orphan Market Exclusivity
Paediatric Regulation	Regulation (EC) No 1901/2006
RDP	Regulatory Data Protection
SPC	Supplementary Protection Certificate

2. Executive summary

The conceptual framework of Medicines Adaptive Pathways to Patients (MAPPs) has its basis in fostering access to novel beneficial treatments for the right patient groups at the earliest appropriate time in the product lifespan in a sustainable fashion. Embedded in the MAPPs concept are key facets of products getting to the market earlier and in initially small defined (sub) population, with an emerging evidence base supporting a positive benefit-risk and indication expansion. This creates uncertainty for medicine developers and authorities as to whether there are any legal constraints or even blocks. Activities of the D2.08 working group as part of Work Package 2, have been to map the general regulatory landscape with regard to both the centralised approval and the market access, in particular pricing and reimbursement, of medicinal products applicable for the intended MAPPs concept.

A broad review of the main legal areas governing medicinal product development, approval and market access, in the context of MAPPs, was undertaken - except any potential impact of MAPPs on Intellectual Property and Regulatory Exclusivity Rights that will be analysed by D3.06 working group, within Work Package 3. The two documents should be read and understood together.

The result of the conducted review is that the current legal framework does not include any legal constraints in implementing MAPPs at both European and national level or prevent the implementation of an adaptive approach to medicines development. MAPPs can work well within the existing legal framework.

3. Introduction

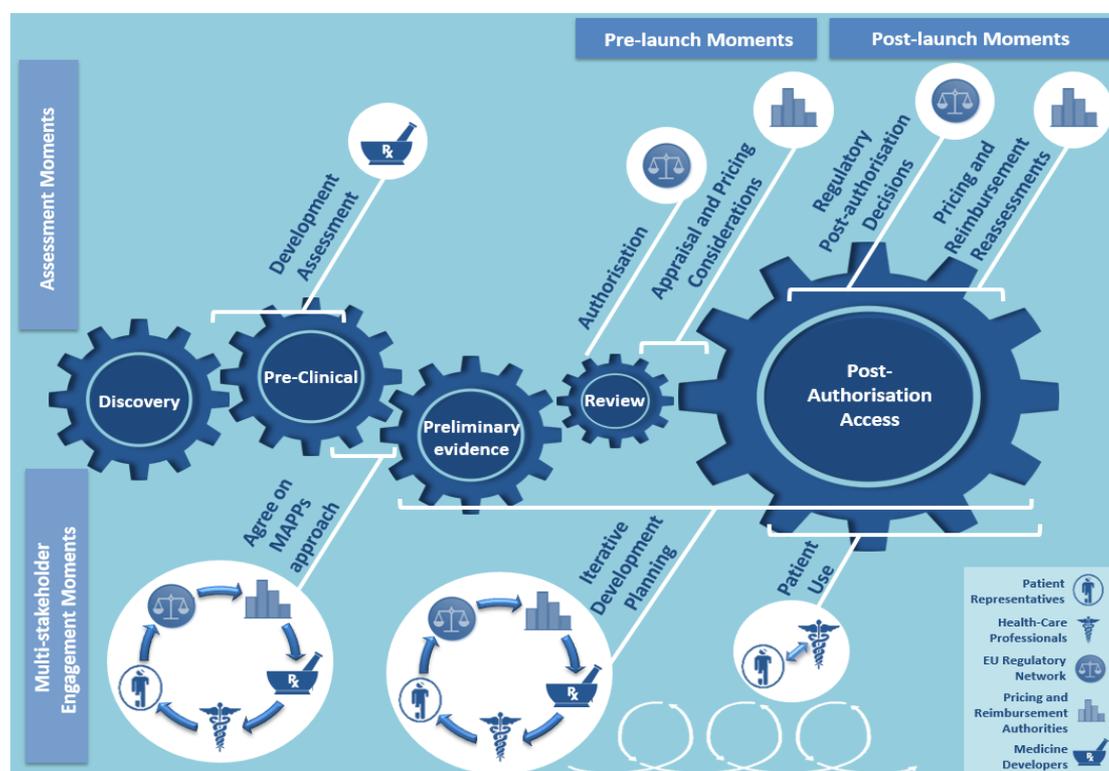
3.1. Scope of MAPPs

Medicines Adaptive Pathways to Patients (MAPPs) activities seek to foster access to beneficial treatments for the right patient groups at the earliest appropriate time in the product life-span in a sustainable fashion in order to improve the position of both the patients in need of genuinely transformative treatments and the research-based pharmaceutical industry. The scope of MAPPs covers regulatory approval, health technology assessment (HTA), pricing, reimbursement, and health care delivery. MAPPs aim to be applicable within the current EU regulatory and legal framework.¹ It does not foresee a new designation or a change in the existing regulation, but a better use of the existing regulatory tools and procedures (such as conditional marketing authorisation - CMA) to achieve earlier approval and reimbursement decisions of products demonstrating a positive benefit-risk balance. Additional evidence generated post-launch aims to support progressive reduction of

¹ For more information about the Innovative Medicines Initiative (IMI) ADAPTSMART project and MAPPs please see <http://adaptsmart.eu/>

uncertainty about benefits and risks and may lead to adjustments in utilisation (e.g. an expanded indication) and price.

The MAPPs conceptual framework with its multi-stakeholder engagement and assessment moments is depicted in the below diagram, where each product life-cycle phase is symbolised by a blue cog. The cogs are sized to represent the characteristic duration of the phase during the lifespan of a typical medicine. The top half of the figure includes the assessment or decision moments by the stakeholders represented. Although these moments may be informed by multi-stakeholder inputs, in the end, the designated stakeholder, eg regulator or HTA, makes an assessment and an ultimate decision based on their respective remits. Within the bottom portion of the diagram, moments of multi-stakeholder engagement are illustrated.



3.2. Scope of WP 2.08

Activities of the D2.08 working group have been to scan the current European legislative framework to detect and assess any current or future legal obstacles or constraints to the acceptance and implementation of an effective and flexible adaptive pathway. This has been explored in a series of teleconferences. This work is complementary to the activities of the D3.06 working group that has assessed the impact of MAPPs on intellectual property and regulatory exclusivity right periods.² The two documents should be read and understood together.

² ADAPT SMART report D3.06 “Impact of adaptive licencing and adaptive access on Intellectual property and regulatory exclusivity right periods” (October 2017)

4. Current Legal Framework

4.1 General Legal Framework

The general legal framework for placing medicinal products on the market within the EU is harmonized and laid down in Directive 2001/83/EC³ ("Directive 2001/83") and Regulation (EC) No 726/2004⁴ ("Regulation 726/2004"). The essential aim of this EU legislation is to safeguard public health. For this reason, as a rule, medicines can only be placed on the market in the EU after they have been authorised by a competent authority – and to be authorised, they must undergo strict testing and an assessment of their quality, safety and efficacy. The relevant provisions are primarily laid down in Directive 2001/83/EC and Regulation (EC) No 726/2004. .

- Directive 2001/83 provides for general rules on MAs as well as for procedures for nationally authorised medicinal products including those authorised through the Mutual Recognition Procedure or the Decentralised procedure. In this situation, MA is granted by the national competent authorities and valid only in the Member States where the MA is granted.
- Regulation 726/2004 lays down a centralised Community procedure for the authorisation of medicinal products, for which there is a single application, a single evaluation and a single authorisation allowing direct access to the single market of the Community. It also defines the scope and eligibility of applications for evaluation under the centralised procedure through which medicinal products must ("mandatory scope") or may ("optional scope") be authorised by the Community.

4.2. Various Kinds of Market Authorisations

In order to achieve timely access for patients to potentially beneficial treatments, the MAPPs concept foresees utilizing existing regulatory approval pathways in stages without changing the current regulatory standards for evaluation. This means that the requirements to demonstrate a positive benefit:risk balance, as defined in Article 1(28a) of Directive 2001/83, will be no different from medicinal products being authorised via today's 'standard' authorisation process (for example either full or conditional MA). The applicant will have to provide a full dossier containing all required quality, non-clinical and clinical data in order to provide the required evidence for the quality, safety and efficacy of the product.

Due to the nature of the products being considered in the scope of MAPPs (i.e., novel promising treatments in the area of unmet medical need for the patients in the EU), the earlier grant of a centralised MA granted by the European Commission with the scientific support of the EMA is the ultimate goal, so that the centralised approval pathway and its innovative assessment possibilities can be leveraged.

³ Directive 2001/83/EC of 6 November 2001 on the Community code relating to medicinal products for human use, OJ L 311 of 28.22.2001, p. 67, as amended.

⁴ Regulation (EC) No 726/2004 of 31 March 2004 laying down Community procedures for the authorization and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency, OJ L of 30.4.2004, p. 1, as amended.

As such promising medicinal product will be assessed through the centralised process in the following ways⁵:

a) *Standard 'full' MA*

For a standard '**full** MA, all required quality, non-clinical and clinical data have been provided⁶, and the assessment of these data has led to the conclusion that the benefit:risk profile of this product is positive⁷ and that its quality, safety and efficacy are established. Irrespective of that, the MA for the medicinal product may be granted subject to specific conditions (e.g., to conduct post-authorisation safety and/or efficacy studies or the existence of an adequate pharmaco-vigilance system⁸). Such a full MA is valid for five years and may then be renewed on the basis of a re-evaluation of the benefit:risk balance by the Commission as responsible authority⁹. Such an approval may be achieved in a well defined sub-population.

b) *MA under exceptional circumstances*

Regulation 726/2004 foresees the possibility of a MA under exceptional circumstances in its Article 14(8).¹⁰ Such an authorisation under exceptional circumstances may be used for products for which the applicant submits that they will be unable to provide comprehensive data on the efficacy and safety under normal conditions of use. The reasons might be:

- The indications for which the specific product is intended are encountered so rarely that the applicant cannot reasonably be expected to provide comprehensive evidence;
- In the present state of scientific knowledge, comprehensive information cannot be provided; or
- It would be contrary to generally accepted principles of medical ethics to collect such information.

Consequently, the authorisation under exceptional circumstances is granted subject to a requirement for the applicant to introduce specific procedures, in particular concerning the safety of the medicinal product, notification to the

⁵ As laid out above, MAPPs will take place under the centralised pathway so that in this and the following sections will only discuss the centralised approval pathways and authorisation possibilities.

⁶ See Articles 6(1) of Regulation 726/2004 in conjunction with 8(3) of Directive 2001/83.

⁷ The risk-benefit balance is positive if the therapeutic effects of the medicinal product do outweigh its potential risks.

⁸ The MAH may be obliged to conduct a post-authorisation efficacy study (PAES), imposed in accordance with Regulation (EC) No 357/2014, or a post-authorisation safety study (PASS) in accordance with Article 1(15) of Directive 2001/83.

⁹ See Article 14(1) and (2) of Regulation 726/2004.

¹⁰ The relevant documentation for applications in exceptional circumstances are laid down in Part II of Annex I of Directive 2001/83/EC, as amended.

competent authorities of any incident relating to its use, and action to be taken¹¹.

c) *Conditional MA*

Article 14(7) of Regulation 726/2004 contains the legal basis for a so-called conditional MA (CMA). A CMA will be valid for one year, on a renewable basis, and the MAH will be required to complete ongoing studies or to conduct new studies (specific obligations) with a view to confirming that the benefit:risk balance is positive. In addition, specific obligations may be imposed in relation to the collection of pharmacovigilance data¹².

The reason for the possibility of a CMA is that for certain categories of medicinal products, in order to meet unmet medical needs of patients and in the interest of public health, it may be necessary to grant MAs on the basis of *less complete data* than normally required. In such cases, it is possible for the CHMP¹³ to recommend the granting of a MA subject to specific obligations to be reviewed annually. This may apply to medicinal products for human use that are eligible for centralised approval by the Commission and which:

- Aim at the treatment, the prevention or the medical diagnosis of seriously debilitating diseases or life-threatening diseases; or
- Are to be used in emergency situations, in response to public threats duly recognised either by the WHO or by the Community in the framework of Decision No. 1082/2013/EU; or
- Are designated as orphan medicinal products in accordance with the Orphan Regulation.

A CMA may be granted where the CHMP comes to the conclusion that, although comprehensive clinical data referring to the safety and efficacy of the medicinal product have not been supplied, all of the following requirements are met:

- The benefit:risk balance of the medicinal product, as defined in Article 1(28a) of Directive 2001/83, is positive;
- It is likely that the applicant will be in a position to provide the comprehensive clinical data;
- Unmet medical needs will be fulfilled; and
- The benefit to public health of the immediate availability on the market of the medicinal product concerned outweighs the risk inherent in the fact that additional data are still required¹⁴.

¹¹ See EMA pre-authorisation procedural advice for users of the centralised procedure of 30 August 2017 (EMA/821278/2015) under 1.10.

¹² The provisions for the granting such an authorisation are laid down in Regulation (EC) No 507/2006.

¹³ Committee for Human Medicinal Products (CHMP), one of EMA's committees.

¹⁴ See EMA pre-authorisation procedural advice for users of the centralised procedure of 30 August 2017 (EMA/821278/2015) under 1.9.

d) *MAs and other authorisations for access to medicinal products*

The term “MA” includes more than just the full approval, but all kinds of MAs, (i.e., also the CMA and the MA under exceptional circumstances). However, necessary regulatory approvals for making available a medicinal product in the context of a compassionate use program (CUP) or named patient supply (NPS) is not equal to and/or cannot be considered a MA.:

The rule is that a medicine can be marketed in the European Union (EU) only after it has been authorised. Sometimes, it is in the interest of patients to have access to medicines prior to MA grant. In order to do so, the EU legislator provided the possibility for Member States to set up compassionate use programmes to make these medicines available to groups of patients who have a disease with no satisfactory authorised therapies and who cannot enter a clinical trial. Such programme is set up under strict defined conditions, while MAA submission is foreseen in a near future. Even if an approval by a national competent authority (NCA) is needed, such an approval is different and not equal to a full MA (eg the UK EAMS Scheme, or the French ATU system). In addition, with regard to Advanced Therapy Medicinal Products (ATMPs), Article 28 of Regulation (EC) No 1394/2007¹⁵ (the ATMP Regulation) introduced the so-called hospital exemption by inserting Article 3(7) into Directive 2001/83. According to this amendment, any ATMP, as defined in the ATMP Regulation, which is prepared on a non-routine basis according to specific quality standards, and used within the same Member State in a hospital under the exclusive professional responsibility of a medical practitioner, in order to comply with an individual medical prescription for a custom-made product for an individual patient, does not fall within the scope of Directive 2001/83 and is not governed by the EU pharmaceutical law. The aim is to enable patients to receive an ATMP under controlled conditions at an early stage of the development.

4.3. Various Kinds of Authorisation procedures

As per regulation, the normal timeframe for the evaluation of a MA application under the Centralised procedure is 210 days, excluding clock stops to allow the sponsor to address issues raised by the CHMP during the procedure.¹⁶

However, Article 14(9) of Regulation (EC) No 726/2004 foresees the possibility to request an accelerated assessment procedure in order to meet in particular the legitimate expectations of patients and to take account of the increasingly rapid progress of science and therapies, for medicinal products of major interest from the point of view of public health and therapeutic innovation. If the request is accepted by the EMA, the procedure will be reduced to 150 days.

¹⁵ Regulation (EC) No 1394/2007 of the European Parliament and of the Council of 13 November 2007 on advanced therapy medicinal products and amending Directive 2001/83/EC and Regulation (EC) No. 726/2004, OJ L 324 of 10.12.2007, p. 121.

¹⁶ Articles 6(3) and 7c of Regulation (EC) No 726/2004

In 2016 the EMA has implemented the PRIME ("PRiority MEDicines") scheme to enhance support for the development of medicines that target an unmet medical need. This voluntary scheme is based on enhanced interaction and early dialogue with developers of promising medicines, to optimise development plans and speed up evaluation so these medicines can reach patients earlier. Once a candidate medicine has been selected for PRIME, the EMA will amongst others not only organise a kick-off meeting with the CHMP/CAT rapporteur and a multidisciplinary group of experts to provide guidance on the overall development plan and regulatory strategy and scientific advice at key development milestones, but also confirm the potential for an accelerated assessment at the time of an application for a MA.¹⁷

Since 2014, the EMA has also explored further the practical implications of the adaptive pathways concept¹⁸ with medicines under development, in the context of parallel scientific advice with HTA bodies, and with additional stakeholders, such as patients and payer organisations.

4.4 Specific rules for orphan medicinal products under the Orphan Regulation

The Regulation 141/2000¹⁹ ("Orphan Regulation") introduced specific rules and incentives to stimulate research, development and authorisation of medicinal products for the treatment of patients suffering from rare conditions, which are in particular "life-threatening or chronically debilitating condition affecting not more than five in 10 thousand persons in the community".²⁰

Upon authorisation of a medicinal product as an orphan designated medicinal product, it benefits from the orphan market exclusivity ("OME") right as a reward for the respective investments made. The OME right provides that the Commission, the EMA and any competent authorities at Member State level "*shall not, for a period of 10 years upon approval, accept another application for an MA or grant an MA or accept an application to extend an existing MA, for the same therapeutic indication, in respect of a similar medicinal product*".²¹

Not only "standard" MAs, but also CMAs and MAs under exceptional circumstances may benefit from OME. With this regard, the Commission recently stressed in its Notice on the application of Articles 3, 5 and 7 of the Orphan Regulation 141/2000 that in order to maintain orphan designation at the point of MA grant the submitted data package has to provide evidence with regard to the required significant benefit

¹⁷ See more details under www.ema.europa.eu under "Human Regulatory" / "Research and Development" / "PRIME: priority medicines".

¹⁸ See more details under www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000601.jsp&mid=WC0b01ac05807d58ce

¹⁹ Regulation (EC) No 141/2000 of 16 December 1999 on orphan medicinal products, OJ L 18 of 22.1.2000, p. 1.

²⁰ See Article 3(1) of Regulation 141/2000.

²¹ Article 8(1) of the Orphan Regulation.

over existing treatments, and that this applies irrespective of whether it is a full MA or a conditional MA²².

4.5 Specific rules under the Paediatric Regulation

The Regulation 1901/2006²³ ("Paediatric Regulation") introduced specific rules in order to ensure that medicines for use in children are of high quality, ethically researched and authorised appropriately, as well as the the availability of information on the use of medicines for children is improved. The main impact of the Regulation was the establishment of the Paediatric Committee (PDCO), which is responsible for coordinating the work of the EMA on medicines for children, as well as to determine the studies that companies must carry out on children as part of paediatric investigation plans (PIPs). 4.6. Market Access, in particular Pricing and Reimbursement

Directive 89/105/EEC (so-called "Transparency Directive")²⁴ provides for a common procedural framework to ensure that national pricing and reimbursement decisions are made in a transparent manner and that these decisions do not disrupt the operation of the Internal Market. The background is that within the EU, Member State authorities are free to set the prices of medicinal products and to decide on their reimbursement under their social security systems.

The national pricing and reimbursement systems for medicinal products established in the EU Member States differ very much from country to country, dependent on its own economic and health needs. Different schemes and policies are used as a consequence.

5. Methodology

As part of Work Package 2, work stream D2.08 was led by consortium members of Lygature and Novartis. Consortium members that volunteered to support these deliverables included people from AstraZeneca, GSK, MSD, Roche, Servier and EFPIA.

With respect to the development, authorisation and market access of medicinal products under MAPPs, the question arose whether there are any current or future legal obstacles or constraints to the acceptance and implementation of an effective and flexible MAPPs pathway²⁵.

²² Commission notice on the application of Articles 3, 5 and 7 of Regulation (EC) No 141/2000 on orphan medicinal products, OJ C 424 of 18.11.2016, p. 3.

²³ Regulation (EC) No 1901/2006 of 12 December 2006 on medicinal products for paediatric use and amending Regulation (EEC) No 1768/92, Directive 2001/20/EC, Directive 2001/83/EC and Regulation (EC) No 726/2004, OJ L 378 of 27.12.2006, p. 1.

²⁴ Council Directive of 21 December 1988 relating to the transparency of measures regulating the pricing of medicinal products for human use and their inclusion in the scope of national health insurance systems (89/105/EEC), OJ L 40 of 11.2.1989, p. 8.

²⁵ The question on the impact of MAPPs on Intellectual Property (IP) and regulatory exclusivity rights was dealt with in work package D3.06 and therefore exempted from the activities of this work stream.

In order to assess the potential legal constraints in implementing MAPPs at both European and national level, the work has been distributed between the Group members who were also requested to reach out to colleagues, partners, and collaborators within their organisations with relevant experience in legal, regulatory affairs and other research & development functions. The outcome of the assessment was then discussed and agreed by the workstream members.

6. Results

The current legal framework does not include any legal constraints or obstacles at both European and national level that could prevent the implementation of an adaptive/MAPPs approach to medicines development.

6.1 General Legal Framework

The general EU legal framework²⁶ accommodates the implementation of the MAPPs principles and not provide for any constraints or even "road blocks" in this regard. However, the timing and timelines for some requirements which are laid down in non-legislative acts have been identified as potential issues (e.g., the timing of the submission of the paediatric investigational plan in accordance with the Paediatric Regulation. With this regard, it is suggested to model the timing and timelines of all requirements set in the EU legal framework, while waiting for the further improvement of the implementation of both Regulations as announced by the European Commission as a result of the publication of its 10 year Report on the Paediatric Regulation which just got published on 26 October 2017²⁷.

6.2 Provisions on Conditional Marketing Authorisation and PRIME

A dedicated review of the provisions concerning CMAs, MAs under exceptional circumstances and the PRIME regime was conducted. These tools and procedures were considered key to lead to obtaining earlier authorisation for medicinal products addressing an unmet medical need. In addition, it was not observed that the fact that a MA was "*only*" granted conditionally or under exceptional circumstances did as such have an impact on health technology assessment and/or pricing of the medicinal product in scope. However, taking into account the level of uncertainties at the time of appraisal, in the framework of MAPPs the envisaged early dialogue would help understanding and addressing the HTA/payers need and a plan to reduce uncertainty as evidence base evolves

²⁶ The review of the general EU Legal Framework covered all legislative acts being included in Volume 1 of EUDRALEX: EU Pharmaceutical legislation for medicinal products, with the exemption of the provision for orphan medicinal products (which were reviewed separately) as well as the IP and regulatory exclusivity rights (which are covered by the activities of work package D3.06).

²⁷ Report from the Commission to the European Parliament and the Council, State of Paediatric Medicines in the EU - 10 years of the EU Paediatric Regulation, Brussels, 26.10.2017, COM(2017) 626 final.

6.3 Provisions on Orphan Medicinal Products

In addition, a dedicated review of the provision for orphan medicinal products was conducted. The outcome was that the Orphan Regulation does not contain any constraints. However, with regard to the Commission's "Guideline on the format and content of applications for designation as orphan medicinal products and on the transfer of designations from one sponsor to another" dated 27.03.2014²⁸, certain statements concerning the ability (or not) of sponsors to define orphan subsets of recognised conditions based on linking patient sub-population characteristics with the pharmacological action and the effectiveness of that medicine (i.e., 'medical plausibility'), may need to be clarified in order to enable the ever finer levels of patient stratification envisaged with adaptive pathways.²⁹

The same applies to the respective sections of the recent "Commission notice on the application of Articles 3, 5 and 7 of Regulation (EC) No 141/2000 on orphan medicinal products"³⁰, in particular with regard to the following statement:

"There is an increasing shift towards personalised medicine, leading to the stratification of the patient population. Nevertheless, 'sub-setting' a condition with the use of biomarkers will not be acceptable unless the sponsor provides solid scientific evidence that the activity of the product would not be shown on the larger population."

This statement may need updating/further qualification to fully enable adaptive pathways for medicinal products with orphan designation. In addition, surrogate endpoints may need to be taken into account stronger as as with MAPPs there may be greater reliance on surrogate endpoints in rare diseases where hard clinical end points are not (yet) possible.

6.4 Provisions on Market Access, in particular Pricing & Reimbursement

A scan of the market access related framework was performed, with particular consideration of the access schemes in several central European countries, i.e. Bulgaria, Czech Republic, Hungary, Poland and Romania.

No legal hurdles with regard to market access were observed relating to products that were approved on a conditional basis or under exceptional circumstances. As stated above, all products must have obtained a valid MA pursuant to Article 6 of Directive 2001/83 in a first step in order to then be able to be included in the national pricing and reimbursement regime in a second step. Each medicinal product will then be evaluated by its own merits in accordance with the national procedure and requirements. Some countries also foresee additional access tools (e.g., so-

²⁸ European Commission, ENTR/6283/00 Rev 4.

²⁹ The orphan medicinal product Kalydeco (active substance: ivacaftor) is often cited as being an example of an adaptive pathways approach to product development. Patient stratification and the approved therapeutic indication of Kalydeco are based on the presence of specific mutations in the CFTR gene. The present legal framework did not pose a barrier to the development of this medicine.

³⁰ European Commission, OJ C 424 of 18.11.2016, p. 3.

called managed entry agreements)³¹, which facilitate market entry, and by this do not constitute specific market entry hurdles.

7. Conclusion

The current legal framework applies to products under MAPPs, and products approved under MAPPs are not different compared to any other medicinal products. This is in particular true with regard to the authorisation tools and procedures.

Within the current EU framework, the currently available authorisation tools and procedures are generally supportive of MAPPs, although some uncertainties remain, but only with regard to some non-legislative provisions, e.g. with regard to the timing of the submission of the paediatric investigational plan in accordance with Regulation 1901/2006. Both with regard to the framework governing the approval of medicinal product and with regard to Market Access rules, no legal hurdles were identified.

³¹ ADAPT SMART report D3.05/D3.07 “Managed entry agreements in the context of adaptive pathways”