



Impact of adaptive licencing and adaptive access on Intellectual property and regulatory exclusivity right periods

October 2017

The work leading to these results was conducted as part of the ADAPT SMART consortium (Accelerated Development of Appropriate Patient Therapies: a Sustainable, Multi-stakeholder Approach from Research to Treatment-outcomes). For further information please refer to www.adaptsmart.eu. This paper is the result of the collective input from working group D3.06 and only reflects the views of the authors.

This project has received funding from the Innovative Medicines Initiative 2 Joint Undertaking under grant agreement No 115890. This Joint Undertaking receives support from the European Union's Horizon 2020 research and innovation programme and EFPIA.



Contents

1. Abbreviations	3
2. Executive summary	4
3. Introduction	5
3.1. Scope of MAPPs	5
3.2. Role of Exclusivity Rights.....	6
4. Current Landscape of IP and Regulatory Exclusivity Rights in the EU	7
4.1. Patents	7
4.2. Supplementary Protection Certificates (SPCs)	7
4.3. Regulatory Data Protection (RDP)	7
4.4. Orphan Market Exclusivity (OME)	8
4.5. A Paediatric Reward	10
4.6. Relevance of the Exclusivity Rights	10
5. Role of the Marketing Authorisation for these Exclusivity Rights	11
6. Methodology.....	11
6.1. Selection of methodology	11
6.2. Semi-structured interviews.....	11
6.3. Scenarios.....	12
7. Results	12
7.1. Various Kinds of Market Authorisations	12
7.2. Role of the “Global Marketing Authorisation”	15
7.3. Assessment of the identified scenarios and the impact of MAPPs.....	16
7.4. Undermining of exclusivity rights by off-label or cross-label use	19
a) Off-label use	19
b) Cross-label use	20
c) Impact of off-label and cross-label use on MAPPs.....	21
8. Perceptual Issues and Considerations of the impact of MAPPs.....	21
9. Discussion.....	25
10. Recommendations.....	26

1. Abbreviations

ADAPT-SMART	Accelerated Development of Appropriate Patients Therapies, a Sustainable, Multi-stakeholder Approach from Research to Treatment-outcomes
AP	Adaptive Pathway
CMA	Conditional Marketing authorisation
CUP	Compassionate Use Program
EPAR	European public assessment reports
GMA	Global Marketing Authorisation
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
PIP	Paediatric investigation plan
Paediatric Regulation	Regulation (EC) No 1901/2006
RDP	Regulatory Data Protection
RER	Regulatory Exclusivity Rights
SmPC	Summary of Medicinal Product Characteristics
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 life-span 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 as to how this adaptive development and access impacts on intellectual property (“IP”) and regulatory exclusivity right (“RER”) periods. Activities of the D3.06 working group have been to map both the key *legal* impacts and additional key *perceptual* impacts that adaptive pathways and adaptive access has on IP and RER periods. The term RER encompasses regulatory data protection (“RDP”) and orphan market exclusivity (“OME”).

A broad review of the rules governing IP and RER as they are today, and with respect to MAPPs, was undertaken in the context of the following 4 scenarios deemed likely to occur with MAPPs: (i) Stand-alone MA (i.e. single indication only); (ii) MA with subsequent indications with the same compound, i.e. indication 1, subsequently followed by indication 2; (iii) MA under exceptional circumstances or conditional approval that subsequently gets approved for ‘full’ MA; and (iv) MA (full, conditional, or exceptional MA) that subsequently is revoked / suspended from a regulatory perspective. Any direct legal impact of MAPPs were assessed along with an exploration of several perceptual issues pertaining to the incentives of adopting and using MAPPs from an IP and RDP perspective.

No legal blocks were found for the 4 above scenarios. Within the current EU framework, current incentives are generally supportive of MAPPs, yet uncertainty remains as to how to best protect exclusivity periods from erosion (particularly in subsequent indications) and how a definitive economic case for MAPPs could be realized and accepted. For example, earlier to market (<5 years after the patent filing) will mean that there can be no supplementary protection certificate (SPC), thus the benefit of earlier to market might be offset by the loss of incentive in development of other indications. With regard to orphan market exclusivity (OME) protection, the OME is an indication specific exclusivity right, and a medicinal product can obtain multiple orphan designations, provided that these designations concern different orphan conditions. Thus the incentives for OME (and other incentives) will require ever more nuanced consideration under MAPPs.

The current review of EU incentives/exclusivity rights and the practical economics of so-called cross label use (i.e. generic products being approved with a reduced label compared to their reference product due to specific patent protection (or RER) of certain indications whereas these generic products nevertheless are prescribed and reimbursed for this protected indication) could negatively impact MAPPs. Cross label use across Member States could also be exacerbated under MAPPs.

There was a strong desire to maintain the current EU legal frameworks for IP and RER – MAPPs could operate effectively within in it. However, if in the future, the EU

legislative framework is re-opened for amendments it is vital that MAPPs concept is considered adequately alongside other existing instruments (e.g. conditional marketing authorisation).

3. Introduction

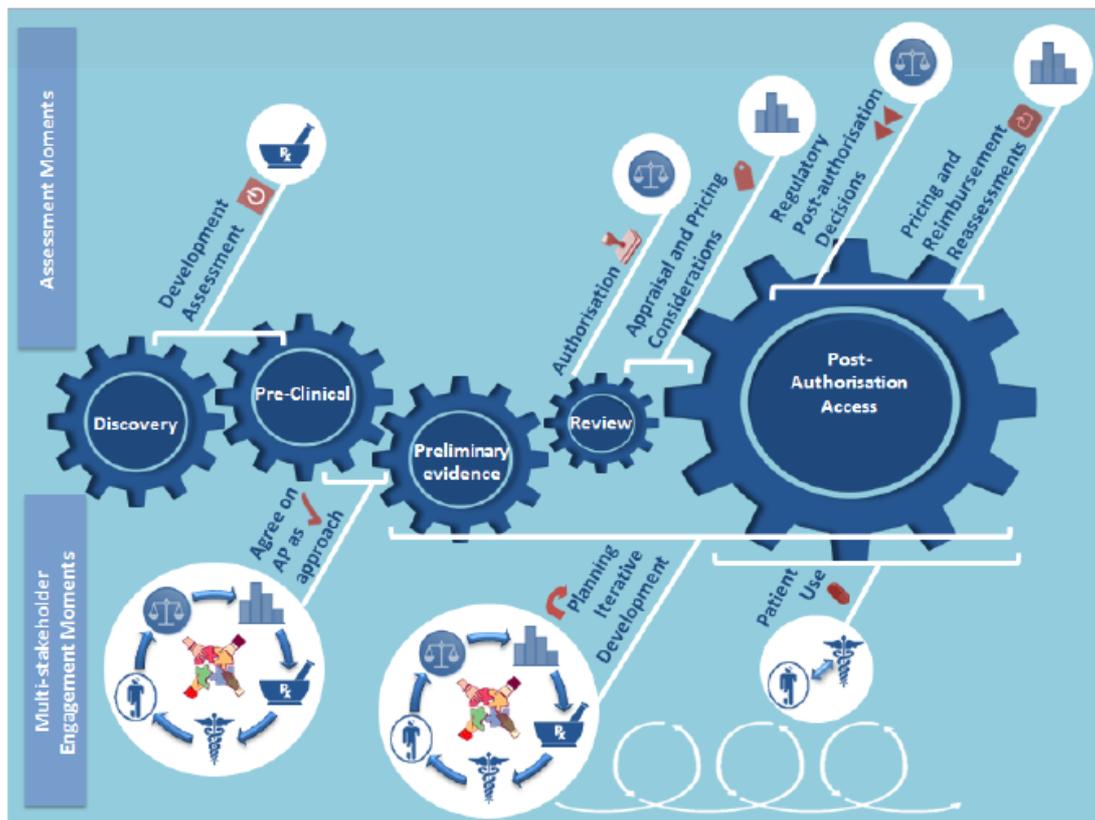
3.1. Scope of MAPPs

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 novel 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 aims to be applicable within the current EU regulatory and legal framework¹. It does not foresee a new designation but an optimal use of the existing tools and procedures (such as conditional marketing authorisation) to achieve earlier approval and reimbursement decisions of products that demonstrate a positive benefit: risk balance thus supporting an earlier launch of the medicinal product based on initial evidence. Additional data generated post-launch aims to support progressive reduction of uncertainty about benefits and risks and may lead to adjustments in utilisation and price in response.

The MAPPs conceptual proposal for the core multi-stakeholder engagement and assessment moments enabling an adaptive pathway is set out in the below diagram. There, each product life-cycle phase is symbolised by a blue cog. The separate cogs are comparatively 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 stakeholder represented. Although these moments may be informed by multi-stakeholder inputs, in the end, the designated stakeholder makes an assessment and ultimate decision based on their respective remits. Within the bottom portion of the diagram, moments of multi-stakeholder engagement are illustrated².

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

² http://adaptsmart.eu/wp-content/uploads/2017/06/ADAPT-SMART-seamless-pathway_final_website.pdf



Activities of the D3.06 working group have been to map both the key *legal* impacts and the key *perceptual* impacts that adaptive pathways may have on intellectual property (IP) and regulatory exclusivity right (RER) periods. While we did not set out to undertake a detailed analysis of the legal landscape. We present a review of the rules governing IP and RER as they are today, in the context of MAPPs, and any impacts that affect predominantly medicine developers and regulators have been explored in a series of group workings and extended interviews. This work is complementary to other work streams in assessing any current or future legal obstacles or blocks to the acceptance and implementation of MAPPs.

3.2 Role of Exclusivity Rights

The research and development of new medicines is a long, costly and risky process as out of thousands of compounds being tested only very few will finally obtain approval and be placed on the market. Adequate protection of these compounds by exclusivity rights for a defined period of time is therefore critical in order to allow for adequate return on the investment and to counterbalance the risk pharmaceutical companies take. Exclusivity rights are considered to be the key incentive for the innovator industry as they allow the industry to continue to invest in the development of new medicines, while generic or biosimilar products are made available for the “old” medicines after expiry of the exclusivity rights. Of key relevance are:

- ‘Intellectual property rights’ which are generally defined and understood as “protections granted to the creators of IP, and include trademarks, copyright,

patents, industrial design rights, and in some jurisdictions trade secrets".³ In the context of MAPPs, only patents and Supplementary Protection Certificates (SPCs) were considered to be of relevance.

- 'Regulatory exclusivity rights' (RER) which are understood as those exclusivity rights that are granted to a marketing authorisation holder (MAH) for their efforts of developing a compound and conducting the necessary studies in order to obtain a marketing authorisation (MA). In the EU, those rights are regulatory data protection (RDP) and orphan market exclusivity (OME).

4. Current Landscape of IP and Regulatory Exclusivity Rights in the EU

The current landscape of IP and RER in the EU is as follows (see **Figure 1**):

4.1. Patents

Patents are exclusive, nationally restricted rights in exchange for detailed public disclosure of an invention. On the basis of a granted patent, the owner of the patent is allowed to prevent others from making, using, selling, importing, or distributing a patented invention without permission of the patent holder for the duration of 20 years after filing of the patent application. The protection may in particular refer to the compound itself, its pharmaceutical forms, the manufacturing process as well as its uses (so-called "medical use patents").

4.2. Supplementary Protection Certificates (SPCs)

SPCs are patent-like rights that prolong the duration of a basic patent protection by a maximum of 5 years, whereas the total combined duration of exclusivity of such a basic patent and SPC cannot exceed 15 years starting with initial approval of the medicinal product. The objective of the SPC right is to compensate for loss of effective patent protection due to long period of testing and trials and the regulatory approval procedure.

4.3. Regulatory Data Protection (RDP)

RDP provides protection of non-clinical and clinical data being part of the dossier supporting the application for marketing authorisation of a medicinal product (the reference medicinal product) in situations where a second applicant wishes to refer to these data for the purpose of obtaining a respective generic or bio similar MA. In the EU, RDP protection is independent from any IP protection ("no patent linkage").

The current RDP rules in the EU⁴ provide for the following protection:

³ World Trade Organization, What are intellectual property rights? World Trade Organization. Retrieved 2016-05-23.

⁴ Article 14(11) of Regulation 726/2004 for medicinal products being approved centrally by the European Commission and Article 10(1) of Directive 2001/83/EC for medicinal products being approved nationally.

- An 8 year period of **data exclusivity (DE)** starting with initial MA grant during which a medicinal product may not be used as a reference medicinal product for the purposes of an abridged application procedure, and
- An additional 2 year of **market protection (MP)** period during which medicinal products authorised under these abridged procedure may not be placed on the market.

This 10 year RDP period can be prolonged by one additional year of market protection to a total period of 11 years (so-called "8+2+1 rule") under the condition that during the first 8 year period after initial MA grant a new therapeutic indication is authorised for this medicinal product which is held to bring a significant clinical benefit in comparison with existing therapies.

It is important to note that the 8 years of data exclusivity and the additional 2 years of market protection start upon the initial approval and are granted by law "automatically". The additional "+1" year of market protection requires (1) additional conditions to be fulfilled (i.e., approval of an additional indication of significant clinical benefit within the first 8 years after initial approval) and (2) pursuant to the Commission's Notice to Applicants a request to EMA to confirm the significant clinical benefit of this additional indication.⁵ Irrespective of that, the granting of the +1 year of market protection is generally rare, in particular with regard to conditional marketing authorisations (CMAs).

4.4. Orphan Market Exclusivity (OME)

OME was introduced in 2000 to stimulate research, development and authorisation of medicinal products for the treatment of patients suffering from rare conditions via Regulation (EC) No 141/2000 ("Orphan Regulation"). Where a medicinal product fulfils the criteria laid down in Article 3 of the Orphan Regulation for being designated as an orphan medicinal product, Article 8(1) provides that upon obtaining authorisation the designated orphan product is entitled to a ten year period of OME during which competent authorities shall not accept a MA application or grant a MA for a similar medicinal product for the same therapeutic indication. As it is the case for RDP, OME is independent of any IP protection and runs concurrently.

⁵ European Commission, Notice to Applicants, Volume 2A, Procedures for marketing authorisation, Chapter 1 Marketing Authorisation (Revision 6), December 2016, Section 6.2.

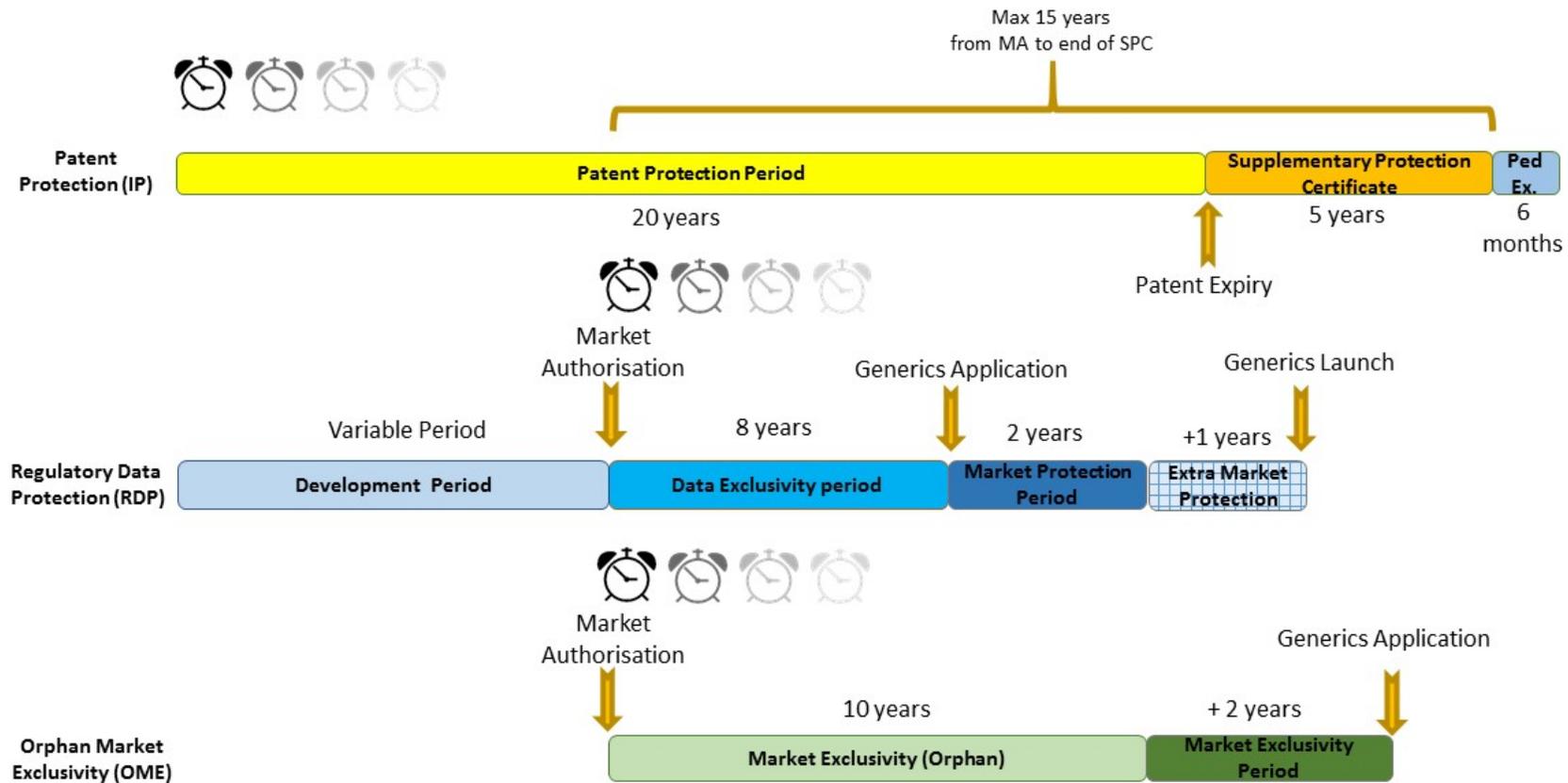


Figure 1. Schematic of the Patent protection periods, Regulatory Data Protection periods and Orphan Market Exclusivity

Patent exclusivity period is for a maximum of 20 years with up to an additional 5 years via a supplementary protection period (SPC). Once market authorisation (MA) of a reference product has been triggered the maximum patent exclusivity period possible is 15 years from the point of MA to the end of the SPC. A 6 month Paediatric Extension added to the end of all marketing exclusivities and patient protections is possible, with non-orphan products

Regulatory exclusivity periods follow the 8+2(+1) rule. The extra (+1) of exclusivity is only possible if a new indication with significant clinical benefit is authorised within the first 8 years

Orphan market exclusivity offers 10 years protection in an orphan indication. Authorisation of an orphan indication in a new orphan designation triggers its own market exclusivity period. Up to an additional 2 years of protection is possible for completion of a Paediatric investigation plan (PIP) for an orphan medicinal product

With regard to the scope, the OME is therefore an indication specific exclusivity right, and a medicinal product can obtain multiple orphan designations, provided that these designations concern different orphan conditions. If a medicinal product is authorised in different indications corresponding to different orphan designations, it is entitled to an independent OME right and period for each indication.⁶ However, according to the Commission Notice of 18 November 2016 (2016/C 424/03) under D.1, the addition of new indications within the same orphan condition does not give entitlement to additional periods of OME rights. If the same sponsor subsequently applies for the authorization of an additional indication being a subset of the condition in which the product got initially authorised, this indication will not benefit from any additional period of OME (i.e. the second indication will be covered by the OME granted to the initial authorization).

4.5. A Paediatric Reward

A paediatric reward is offered by the Paediatric Regulation in the form of a prolongation of an existing non-expired exclusivity right for the fulfilment of obligations being subject of a paediatric investigation plan (“PIP”) agreed with the EMA, depending on the nature of the product:

- For a non-orphan product, a reward in the form of a six month extension of an existing, not yet expired SPC is provided; and
- For an orphan designated medicinal product, a reward in the form of a two-year extension of the OME period is provided.

4.6. Relevance of the Exclusivity Rights

The IP Rights and the RERs are completely different in nature and independent exclusivity rights, designed to protect different things and to incentivise biopharmaceutical research and development in different ways. Each of these exclusivity rights has its own scope of protection:

- Patents protect inventions regardless of whether they are ever commercialised.
- RDP protects the extensive body of regulatory data generated by originators from being relied upon or referred to unfairly by others during a specific period of time.
- OME provides protection with regard to a rare indication against similar medicinal products.

Because these rights protect different things and operate and run independently of one another, they work together in a complementary, non-duplicative

⁶ See in this respect the EMA guidance note for sponsors: “Post-orphan medicinal product designation procedure”, version of 1 December 2015 which states in paragraph 2.3: *“Each orphan designation carries the potential for one ten-year market exclusivity for a particular indication. A medicine that has received several separate orphan designations for different indications can obtain more than one market exclusivities if these refer to separate designated conditions.”*

manner to encourage the development of new medicines. As a result, it depends on the concrete situation of the product in scope how relevant each of these rights (if applicable) is for its protection.

5. Role of the Marketing Authorisation for these Exclusivity Rights

The MA is of utmost importance for most of the above-mentioned exclusivity rights as the time of the (first) MA being granted in the European economic area (EEA) defines the start of the duration of the respective exclusivity right, and by this is the trigger point for the “exclusivity clock”.

- With respect to the IP rights, the point in time of initial MA grant is decisive for the duration of a SPC protection, and by this also for a potential 6 months SPC extension as a paediatric reward for non-orphan products.
- The same concept also applies with regard to the RER in the EU. The point in time of initial MA grant in the EU defines the start of the 10 year RDP period, and with regard to orphan medicinal products it also defines the start of the 10 year OME protection for the initially approved orphan indication(s).

6. Methodology

6.1. Selection of methodology

The deliverable D3.06 was led by consortium members of CASMI and Novartis. Consortium members that were involved within D3.06 included representatives from Novartis, Merck Group, Pfizer, EFPIA, Sanofi Genzyme, and MSD. In addition, input from all stakeholders was obtained during several workshops, in particular in the framework of a dedicated 1 day multi-stakeholder workshop including representatives from the Commission, payers, patient organisations, industry and external counsels.

With respect to MAPPs and adaptive pathways, questions arose how products authorised under MAPPs are protected, whether the early authorisation of a narrow initial indication does lead to a premature loss of exclusivity - if not counterbalanced by other incentives – and whether this becomes problematic for sponsors and for overall sector competitiveness.

6.2. Semi-structured interviews

Group members were requested to reach out to colleagues, partners, and collaborators within their organisations with relevant experience in legal, IP, Regulatory Affairs and other research & development functions. They were also requested to conduct semi-structured informal interviews, as one-to-one or as a group of 2-3 (max) to explore legal and perceptual issues of IP and RER around MAPPs. Outputs from the interviews were anonymised and recorded in the structured tables provided.

A presentation was shared with interviewees prior to interview. This included a brief background about ADAPT-SMART/ IMI, an introduction to the concept of MAPPs, and an illustration of how that would differ from the current traditional drug development pathway.

6.3. Scenarios

The following 4 scenarios were identified under which a MA would likely occur under MAPPs in order to be explored further and based on that to be able to fully assess any potential impact of MAPPs on IP and RER periods:

- i. Stand-alone MA (i.e. single indication only);
- ii. A MA with subsequent indications with the same compound, i.e. indication 1, subsequently followed by indication 2;
- iii. MA under exceptional circumstances or conditional approval that subsequently gets approved for 'full' MA;
- iv. MA (full, conditional, or exceptional MA) that subsequently is revoked/ suspended from a regulatory perspective.

The respondents were asked to comment on these scenarios for correctness and to explore if there were likely legal issues within the current EU framework arising under MAPPs. The same scenarios were explored under the question of whether there were any perceptual issues arising from MAPPs relating to IP and RER (i.e., there was no direct legal issue, however perceptions exist that MAPPs would be unappealing or could cause uncertainty for a variety of reasons).

Interview data were consolidated and the results are elaborated below. These outcomes were used as a basis for further consensus building in a workshop in April 2017.

7. Results

7.1. 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, are not different for products being authorised under MAPPs than for products being authorised via the 'standard' authorisation process. 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 nature of the products being considered in the scope of MAPPs (i.e. novel 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.

A centralised authorisation of a product under MAPPs could be achieved in the following ways⁷:

a) *Standard 'full' MA*

For a standard '**full**' **MA**, all required quality, non-clinical and clinical data have been provided⁸, and the assessment of these data has led to the conclusion, that the benefit: risk profile of this product is positive⁹, and that its quality, safety and efficacy are established.

Such a full MA is granted “unconditionally” (i.e., its validity follows the normal rules according to which the MA is valid for five years and may be renewed after 5 years for an indefinite period of time on the basis of a re-evaluation of the risk-benefit balance by the Commission as responsible authority¹⁰). 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 pharmacovigilance system¹¹).

b) *MA under exceptional circumstances*

The legal basis for the MA under exceptional circumstances is Article 14(8) of Regulation 726/2004.¹² Such an authorisation under exceptional circumstances is valid for one year, on a renewable basis, and may be used for products for which the applicant in his application is 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.

⁷ 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.

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

⁹ The risk-benefit balance is positive if the therapeutic effects of the medicinal product do outweigh its potential risks.

¹⁰ See Article 14(1) and (2) of Regulation 726/2004.

¹¹ 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.

¹² The relevant documentation for applications in exceptional circumstances are laid down in Part II of Annex I of Directive 2001/83/EC, as amended.

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 competent authorities of any incident relating to its use, and action to be taken¹³.

c) *Conditional MA*

The legal basis for a so-called conditional MA (CMA) is Article 14(7) of Regulation 726/2004. CMAs 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 data¹⁴.

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 initially to grant MAs on the basis of *less complete data* than is normally required. In such cases, it is possible for the CHMP¹⁵ to recommend the granting of a MA subject to certain 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

¹³ See EMA pre-authorisation procedural advice for users of the centralised procedure of 30 August 2017 (EMA/821278/2015) under 1.10.

¹⁴ The provisions for the granting of such an authorisation are laid down in Regulation (EC) No 507/2006.

¹⁵ Committee for Human Medicinal Products (CHMP), one of EMA's committees.

- 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 required¹⁶.

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). As a consequence, CMAs and MAs under exceptional circumstances also benefit from RDP and possibly OME. In 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 over existing treatments, and that this applies irrespective of whether it is a full MA or a conditional MA¹⁷.

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. However, it is sometimes 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 special programmes to make these medicines available to patients under defined conditions. This is commonly known as ‘compassionate use’. Even if an approval by a national competent authority (NCA) is needed for the such making an activity, such an approval is different and not equal to a full MA, so that they do not trigger the clock for any of the above mentioned exclusivity rights¹⁸.

7.2. Role of the “Global Marketing Authorisation”

The calculation of RDP and SPC periods begins at the point of the initial MA grant for that product. This is regardless of whether the authorisation is based on a ‘standard’ MA, a conditional MA or a MA under exceptional circumstances, as these are all authorisations in accordance with Article 6(1) of Directive 2001/83 and Article 14(1) of Regulation 726/2004. Thus, any process that facilitates obtaining earlier regulatory approval than currently experienced – even if it is only in a restricted patient population, or on a conditional or stepwise basis – starts the clock of RDP and the SPC protection period, which as a consequence could lead to an erosion of protection periods in subsequent indications.

¹⁶ See EMA pre-authorisation procedural advice for users of the centralised procedure of 30 August 2017 (EMA/821278/2015) under 1.9.

¹⁷ 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.

¹⁸ The EFTA Court recently confirmed this with regard to similar permissions for veterinary medicinal products in its judgment dated 9 April 2015 in the case E-16/14 (*Pharmaq AS v Intervet International BV*).

As laid out above, due to the so-called “Global Marketing Authorisation” (GMA) principle¹⁹, once a medicinal product has received an initial MA, any further product developments such as new indications, strengths, pharmaceutical forms and different presentations of existing medicinal products are considered to belong to the GMA of the initial product and will not lead to new or separate RDP periods. The consequence of the GMA is that all these product developments will have the same RDP period as that of the original initial product (i.e. maximum of 10 + 1 years from the date of the initial MA).

As the OME right is linked to a specific therapeutic indication and not to the compound the nature and scope are different from RDP as it does not protect the active substance overall but provides for an indication specific protection. As a consequence, the GMA concept does not apply to OME periods. In addition, as the OME is linked with the approval of the product in the respective orphan indication, it runs concurrently with the RDP periods as far as it concerns its initial approval.

7.3. Assessment of the identified scenarios and the impact of MAPPs

In order to fully understand the implications of adaptive licensing and MAPPs on the current existing exclusivity rights, the above mentioned 4 scenarios that are predicted to occur under MAPPs have been explored and assessed by D3.06 working group through interviews and group consensus building as follows²⁰:

a) *Scenario 1: Stand-alone MA*

In this scenario, the active substance is developed and authorised in a single indication only, and in this initial scenario the assumption is that the MA will not be withdrawn / revoked at a later point of time (“no exit”). For the purpose of this discussion, it is called a **stand-alone MA**.

In this scenario, the above-mentioned exclusivity rights apply as follows:

- In case of patent protection, the product is protected for 20 years starting with the respective patent filing as per the scope of the patent. If it is a basis patent, this protection can be prolonged by a SPC – depending on the time of MA grant – for an additional time of maximum 5 years.
- Upon authorisation, the RDP period for the 8 years of data exclusivity and additional 2 years of market protection starts.
- In case of an authorisation of the product as orphan medicinal product, it will also benefit from a 10 year OME starting with the approval date.
- Finally, depending on the timely fulfilment of the PIP obligations and the status (orphan or non-orphan), the product might benefit from a paediatric

¹⁹ The GMA concept is laid down in Article 6(1) of Directive 2001/83/EC.

²⁰ Of note: This analyses is focusing on the legal implications and does not include other considerations, e.g. whether the respective exclusivity periods are considered to be adequate for the necessary return on investment in case of earlier approval for limited patient population based on limited efficacy data and higher risk of MA suspension in case additional data cannot be provided.

reward in the form of either a 6 months SPC extension (for non-orphan products) or 2 years OME extension (for orphan products).

b) *Scenario 2: MA for product with subsequent approval of additional indications*

In this scenario, the active substance is developed in several indications with subsequent authorisations (i.e., first indication 1, subsequently indication 2). Therefore, the pharmaceutical company will obtain an initial MA for indication 1 and subsequently an authorisation for the additional indication – again, under the assumption of “no exit”.

In this scenario, with regard to the initially authorised indication 1, the explanations above under (a) apply.

With regard to the impact on the exclusivity situation due to the subsequently authorised indication 2, it must be distinguished further (1) whether for the *initial* indication 1 was approved under an orphan MA or as non-orphan, and (2) whether the subsequent indication 2 is orphan or non-orphan, too:

(1) Indication 1 and 2 are non-orphan: The authorisation of the second indication might lead to a prolongation of RDP period by 1 year of additional market protection if indication 2 provides a significant clinical benefit and is authorised within the first eight years after initial MA grant. With this regard, the Court of Justice of the European Union (CJEU) recently confirmed in its “Aclasta” decision that the GMA of a medicinal product includes all authorisations of an active substance granted to the same MAH, in particular also any subsequent authorisation of new indications, irrespective of whether the new indication is authorised under the existing MA as a variation or whether it is authorised under a self-standing MA²¹. As a consequence, the non-orphan indication 2 will not benefit from a self-standing RDP, but may only lead to a prolongation of RDP by 1 year.

(2) Indication 1 non-orphan, indication 2 orphan: In this scenario, the second indication may only be authorised under a self-standing MA as pursuant to Article 7(3) of the Orphan Regulation orphan and non-orphan indications cannot be authorised under the same MA²². If therefore the 2nd indication is authorised as an orphan product under a self-standing MA, it would benefit from its own and self-standing, indication specific OME protection. If the second indication is authorised within the first 8 years, it may also lead to a prolongation of RDP by 1 year.

(3) Indication 1 orphan, indication 2 orphan: As already laid out above, if indication 2 concerns a different condition than indication 1, the second

²¹ CJEU, *Novartis Europharm vs Commission*, joined cases C-629/15P and C-630/15P (“Aclasta”), judgment of 28.6.2016.

²² Pursuant to Article 7(3) of the Orphan Regulation, “the marketing authorisation granted for an orphan medicinal product shall cover only those therapeutic indications which fulfil the criteria set out in Article 3”. But in its second sentence, Article 7(3) allows for a sponsor of an orphan medicinal product to “apply for a separate marketing authorisation for other indications outside the scope of this Regulation”.

indication is entitled to an independent OME right and period of protection.²³ However, if the new indication 2 is within the same orphan condition, it does not give entitlement to an additional period of OME right for this second indication. As above, if the second indication is authorised within the first 8 years, it may also lead to a prolongation of RDP by 1 year.

(4) Indication 1 orphan, indication 2 non-orphan: In this scenario, the second indication does not benefit from any separate or self-standing RER: As indication 2 is not an orphan indication, it does not benefit from an OME right. Although indication 2 will need to be authorised under a self-standing MA as in accordance with Article 7(3) of the Orphan Regulation orphan and non-orphan indications cannot be authorised under the same MA, it will not benefit from a self-standing RDP, but may only lead to a 1 year extension of the original RDP for the product of up to 11 years.

c) *Scenario 3: Conditional MA subsequently gets approved for 'full' MA*

In this scenario, initially, a conditional MA was granted for the medicinal product, and subsequently, this got switched to a full MA – again, under the assumption of “no exit”.

As laid out above, a conditional MA is equal to a full MA as both are authorisations according to Article 14(1) of Regulation 726/2004. Therefore, the initial conditional approval kicks off the SPC and RDP period, irrespective of the fact that for the yearly renewal additional data will need to be provided. As a consequence, the explanations for a stand-alone MA above under (a) apply as usual.

If under such a conditional MA subsequently an additional indication is approved - which in accordance with EU Commission guideline will only be possible if also this additional indication is also approved conditionally -, the explanations above under (b) apply similarly.

d) *Scenario 4: Subsequent revocation / suspension of (conditional) MA ("exit scenario")*

In this scenario, the MA – irrespective of whether it is a full MA, a MA under exceptional circumstances or a CMA - is subsequently revoked or withdrawn (e.g., because in case of a CMA the confirmatory data under the conditions of a conditional MA or MA under exceptional circumstances were not fulfilled, or because in case of a full MA serious adverse events occurred that did lead to the conclusion that a positive benefit: risk balance is no more given). For the purpose of this discussion, this scenario is called “exit scenario”

²³ See in this respect the EMA guidance note for sponsors: “Post-orphan medicinal product designation procedure”, version of 1 December 2015 which states in paragraph 2.3: “Each orphan designation carries the potential for one ten-year market exclusivity for a particular indication. A medicine that has received several separate orphan designations for different indications can obtain more than one market exclusivities if these refer to separate designated conditions.”

Also in this scenario, existing IP and RER apply as usual. Even in the case that after initial suspension of the MA of a product and its withdrawal from the market the product later on is reintroduced - which is considered to be an extremely rare case -, the current legal framework does not foresee a way of “clock stop” in such a case. The same would be true if with regard to a CMA the conditions set out are not met and by this, the CMA is not renewed.

If, therefore, the pharmaceutical company wanted to obtain a new approval for this active substance (e.g., based on new, more compelling data, or in a new indication based on totally different data), it will not benefit from a new RDP period as the RDP clock was started with the initial approval. The same is true with regard to any SPC protection. With regard to OME, if the product is authorised in the same condition as the initial approval, it will not benefit from a new or separate OME right. Only if the new indication is in a different condition, it may benefit from a self-standing OME protection.

Thus in the 4 scenarios discussed above, with the consideration of MAPPs, existing IP and RER apply as usual.

7.4. Undermining of exclusivity rights by off-label or cross-label use

The question was raised whether and under which conditions exclusivity rights could be undermined by off-label or cross-label use, and whether this might have an impact on MAPPs.

a) Off-label use

The EU legal framework for medicinal products for human use regulates the authorisation of medicinal products by setting standards of safety, quality and efficacy. As a rule, an authorisation is required for all medicinal products before entering the EU market²⁴, and exceptions are only possible in defined cases under strict conditions²⁵. During the MA procedure, the conditions are established under which the product can be used safely and efficaciously. The Summary of Product Characteristics (SmPC) describes these terms and is the basis of information for healthcare professionals (HCPs) on how to use the medicinal product. However, sometimes products are used off-label.

Off-label use can be defined as any intentional use of an authorised product not covered by the terms of its MA and therewith not in accordance with its SmPC. Off-label use may refer to the use of the product for a different indication, in a different dosage, with a different dosing frequency or duration of use, a different method of administration, or by a different patient group (e.g. children instead of adults). EU legislation does not regulate the off-label use of medicinal products in medical practice.

²⁴ Article 6(1) of Directive 2001/83.

²⁵ These exceptions are (1) the cases defined in Article 3(1) of Directive 2001/83, (2) if a Member State makes use of the medical need exception laid out in Article 5(1), for investigational medicinal products used in clinical trials, and for compassionate use under the conditions laid out in Article 83 of Regulation 726/2004.

The prescribing of an authorised medicinal product - whether on-label or off-label - is a decision taken by the treating HCP, and the ultimate responsibility for the definition of health policy and the delivery of health services and medical care lies with the Member States (Article 168 (7) TFEU). Off-label use is meanwhile subject to national legislation²⁶, and is also recognised as a concept by EU pharmaceutical law²⁷. The General Court of the EU recently stated in the Orphacol case²⁸ that *“off-label prescribing is not prohibited, or even regulated, by EU law”* and that *“There is no provision which prevents doctors from prescribing a medicinal product for therapeutic indications other than those for which a marketing authorisation has been granted.”*

However, if an authorised medicinal product is used outside its authorised label in an indication for which another product is authorised, and if this other product benefits from an exclusivity right, these exclusivity rights may be undermined and violated. Such a finding was recently subject of the judgment of the General Court of the EU in the “Orphacol Case” with regard to the OME right:

- Subject of this case was the question whether a reference to non-authorised indications contained in the SmPC and European public assessment report (EPAR) of a product (Kolbam) constitutes a violation of the OME of another product (Orphacol) as this product is not only authorised for these indications, but also obtained an OME right covering these indications.
- The Court decided that in order to ensure the effectiveness of the OME protection of an indication of authorised product, the off-label prescribing of another medicinal product for indications covered by this OME right should not be facilitated. As the information set out in the SmPC and the EPAR of Kolbam was not limited to its authorised indications, but also contained information relating to the clinical efficacy and safety of Kolbam with regard to indications of Orphacol, the Court found that these documents were liable to facilitate the off-label prescribing of Kolbam for the Orphacol therapeutic indications, taking into account that off-label-prescription is the sole responsibility of the prescribing physician. As a result, the information was found to give rise to circumvention of the Orphacol OME, and as a result the MA of Kolbam was annulled.

b) Cross-label use

While the term "cross-label use" is not a legally defined term, it is commonly used to describe the following situation: Certain indications of the originator

²⁶ E.g., health insurance and liability legislation (liability may arise if off-label prescribing is not in line with the standard of care of HCPs, but inappropriate) to criminal law as well as to ethical and professional standards of HCPs.

²⁷ See e.g. Recital 2 of Paediatric Regulation and pharmacovigilance provisions in Directive 2010/84/EU.

²⁸ General Court of the EU, *Laboratoires CTRS v Commission*, T-452/14, judgment of 11 June 2015, paragraph 79).

product may be protected by a patent (so-called "second medical use patent") as an incentive for the development of this indication for a period of time which is longer than the protection of the compound. In recognition of the rights conferred by such a second medical use patent, the health authorities allow applicants for generic products to exclude the patent protected indications from the list of approved indications for the generic product. This "carve-out" of the patent protected indications leads to a so-called "skinny label", which in the SmPC and in the package insert leaflet (PIL) only includes or refers to the non-patent-protected indications. If irrespective of that, the generic product is prescribed and used for the protected indication, this situation is called "cross-label use".

From an exclusivity perspective, it is necessary that a longer protection of certain indications by medical use patents needs to be reflected in the way medicinal products are procured, prescribed and dispensed. Otherwise, if a generic product is dispensed for an indication for which the originator still holds a patent and for which the generic product is not authorised and labelled, this undermines the effectiveness of the second medical use patent²⁹.

c) Impact of off-label and cross-label use on MAPPs

Both off-label and cross-label use may impact products approved utilising MAPPs. If a product is authorised under MAPPs in an area of unmet medical need and is protected by an indication-specific exclusivity right, the use of other products not authorised for this indication would undermine the exclusivity rights granted to the MAH of the product being authorised under MAPPs. The same would be true if the product is developed further in additional indications, and if the MAH obtains indication specific exclusivity rights for these additional indications (e.g., via respective second medical use patents, or via OME protection).

8. Perceptual Issues and Considerations of the impact of MAPPs

In addition to assessing the concrete legal issues as defined above, concerns were raised based around identified themes pertaining to the perceptual impacts associated with MAPPs introduction. While some of these scenarios already exist today, it was felt that MAPPs accentuates these and poses potential roadblocks for adoption and uptake of MAPPs if they are neither considered nor resolved.

[Concern No 1: An earlier approval in a limited patient population has a higher chance of being a CMA and by this might be linked with a higher risk of MA suspension or revocation](#)

²⁹ See EFPIA Position Paper "New Indications & Cross-Label Dispensing" of 11.11.2015.

Under MAPPs, it is predicted that with the earlier granting of an MA it will more likely occur in the form of a CMA – that for MAPPs products a CMA could become a somewhat ‘default’ route to market (rather than an exception). While this could be seen as an advantage of *first to market*, with a relative increase in the use of CMAs comes the parallel theoretical likelihood in a greater number of MAs being revoked/suspended due to non-confirmatory data.

Since their inception in 2006, the use of and experience with CMAs has steadily increased. In the 10 years to 2016, 30 CMAs have been granted, of which 11 have been converted into “standard” MAs, 17 authorisations remain conditional, 2 have been withdrawn for commercial reasons, and importantly, none have had the MA revoked or suspended for regulatory and/or scientific reasons.³⁰ Therefore, on current evidence, the likelihood that the CMA would be suspended/revoked seems low.

Thus under the current framework an earlier initial approval dis-incentivises the further “adaptive” approval of additional indications as for all subsequent indications the time until loss of exclusivity becomes shorter and the remaining exclusivity covers lower market use (sales versus time until exclusivity expiration). Consequently, attractiveness of adaptive approach will be influenced by the adequacy of the remaining IP protection.

It is a generally held opinion that the situation under MAPPs will not be different than for any other CMA product as today. Earlier market access could even provide a benefit through extending the relative period of IP protection for the first indication. With earlier market access, the time between patent protection beginning and the first MA grant could be reduced (i.e., first MA occurring after phase II vs after phase III/IV), hence the remaining IP protection period for a compound could, in theory, be longer. To address these concerns, as part of the key early multi stakeholder dialogue, and prospective development plan, medicine developers may want to seek and obtain much greater input from regulators, HTA and patient organisations as to the likely population size for a given indication, possible indication(s) expansion and when that might occur, and early input from payers as to estimates of return. This would in turn provide important direction to medicine developers as to early estimates of total (or remaining) IP and RER periods per product and/or per indication as part of an assessment of the economic value of pursuing an adaptive pathway. Otherwise, a variety of other standard instruments for product development (e.g. standard marketing authorisation proceeding or accelerated assessment) are still available to them.

Concern No 2: Earlier market access and public availability of European Public Assessment Reports (EPAR) and clinical study reports (CSRs) leads to a circumvention of IP and RER rights

³⁰ See www.ema.europa.eu/docs/en_GB/document_library/Report/2017/01/WC500219991.pdf and www.ema.europa.eu/docs/en_GB/document_library/Report/2017/01/WC500219991.pdf.

With more products coming to market earlier and thus more publically available data on these products also becoming available earlier due to the data transparency initiatives of EMA, concerns were expressed that European public assessment reports (EPAR) and clinical study reports (CSRs) might be used by generic companies or other third parties to circumvent existing exclusivity rights, and that this would present a distinct incentive bias against a medicine developer using the routes to a MA (e.g., CMA) envisaged under MAPPs.

This concern that was raised would also be the same for products under MAPPs compared to any other medicinal products today. Access and public availability are limited to documents and information redacted of commercial confidential information (CCI)³¹. Irrespective of that, even if such information is publicly available, it may not be used by generic companies or competing originators during the RDP period. In addition, any data disclosure is not of relevance with regard to OME rights as these exist as administrative rights irrespective of whether underlying data are used or not.

Concern No 3: It will be more difficult for products under MAPPs to obtain orphan designation and OME, and even if the product benefits from OME, it will not provide effective protection.

Orphan designation and related OME are intended to provide commercial incentives that otherwise would not exist under normal market conditions when developing medicines intended for small numbers of patients. The criteria for orphan designation include in particular that the product must be intended for the treatment of a life threatening or chronically debilitating disease with a prevalence of no more than 5 in 10,000 people in the EU, and it must provide a *significant benefit* to those being affected. The engagement criteria set out under MAPPs is that the potential treatment meets a *high unmet medical need*. By definition the types of product under MAPPs may to meet the criteria for orphan designation and as a consequence benefit from OME.

With regard to the effectiveness of the OME protection, the situation for a product approved under MAPPs is not different than to a "normal" medicinal product. As laid out above, in order to provide an effective exclusivity right, indication-specific protections granted by OME have to be respected by the players in the market irrespective of whether the initial approval was granted earlier than usual.

The basis for an adaptive pathway concept is to provide access of an initial or improved treatment option within the indication(s) of the MA, as early as a positive benefit: risk balance is established, to those patients who experience a high unmet medical need. While promotion of off-label use is strictly prohibited by law, on-label prescribing is primarily guided by centrally regulated tools such as the summary of medicinal product characteristics (SmPC). Additional tools and guidelines at the

³¹ See Article 4(2) of Regulation 1049/2000. There are currently several cases pending at the European Courts about when and under which conditions documents being subject of a MAA can be considered to be "commercial confidential information". The outcome of these litigations will be equally relevant for products under MAPPs and all other medicinal products.

national level include HCP treatment guidelines, specialist certifications, or restricted reimbursement criteria. As HCPs have the freedom to prescribe a medicinal product outside the approved indication(s), it will be important that the exclusivity rights of products being authorised under MAPPs are not undermined by off-label use of other authorised medicinal products, and that in particular prescribing treatment guidelines accurately reflect the authorised MAPPs product.

Concern No 4. An early MA may adversely affect SPC resulting in loss of attractiveness of pursuing an early to market option.

Concerns were raised that an early MA (<5 years after the patent filing) will mean that there can be no compound SPC – in other words, the basic compound patent protection will last only 20 years from patent filing and could not be extended by an SPC, and this may make it less attractive to invest in necessary clinical trials for the later development of other indications.

In addition, concerns were raised as to the effectiveness of patent protection and/or RER protection in second or subsequent indications in the same product, in particular with regard to their enforcement. Specifically, obtaining an initial MA earlier than normal in some cases could mean that:

- i) a SPC was not applicable (i.e. < 4.5 years after patent filing to MA grant would not permit an SPC³²) and by this a paediatric reward would not be possible.
- ii) if an SPC is possible, it would lapse if the CMA is withdrawn (even if under current circumstances it might be considered to be extremely rare that a product later on is reintroduced into the market, in such a scenario, there would be considerable legal uncertainty as to whether a new SPC could be granted thereafter based upon later approval in a different indication), or
- iii) loss of secondary patent protection due to earlier disclosure of data in the framework of EMA's clinical trial data transparency regime.

With regard to the discussed scenarios, it may be perceived as insufficient that additional indications are only protected if these are orphan indications in a different condition, or if protected by medical use patents. In particular if a broad non-orphan indication without any second medical use patent protection is obtained - which might be the most common scenario, the only currently available incentive is a prolongation of RDP by 1 year. Thus, the business case for utilizing MAPPs should come from the *engagement criteria* and the early multi-stakeholder dialogues. Therefore, the overall business case for early access via MAPPs will be determined by several factors and, other commercial advantages that will include the exclusivity situation determined by IP and RER.

³² See both i) CJEU, *Merck Sharp & Dohme v Deutsches Patent- und Markenamt*, C125/10, judgment of 8 December 2010 and ii) EFTA Court, *Merck Sharp & Dohme v Icelandic Patent Office*, E15/17, judgment of 21 December 2017, on the so-called "negative term SPC".

9. Discussion

The current legal and regulatory framework applies to products approved under MAPPs in the same way as any other medicinal products. This is not only true with regard to the authorisation possibilities and procedures, but in particular also with regard to the IP and RERs. No direct legal roadblocks were identified. The currently available incentives are generally supportive of MAPPs, yet some uncertainties remain, in particular with regard to the risk of off-label use of cheaper products or the effective protection of additional, subsequently approved indications due to the risk of cross-label use.

With regard to RDP, the authorization of an additional indication may only lead to a prolongation of RDP by 1 year if certain conditions are met (see above), even if this additional indication is in a different therapeutic area and authorized under a separate, self-standing MA.

In addition, it was discussed on the one hand whether additional protection of further developments might be needed, while on the other hand whether existing exclusivity rights might not always provide effective protection, especially at the Member State level, and might be undermined.

The current European Commission analysis of EU incentives/exclusivity rights and the practical economics of so-called cross-label use could negatively impact MAPPs. Cross-label use across Member States could be exacerbated under MAPPs.

However, there was strong support for HTA/payer input and perspectives to be taken into consideration early in prospective planning, and that this was seen as a greater economic driver for industry and return on investment compared to IP and RER.

There was support to further map and understand the scope of necessary legal commitments of all stakeholders in MAPPs at the beginning of the process and how that might be implemented as well as the value which might be generated with these upfront commitments.

There was also a strong desire to maintain the current EU legal frameworks for IP and RER – MAPPs could operate effectively within in it. However, if in the future, the EU legislative framework is re-opened for amendment it is vital that the MAPPs concept is considered equally alongside other existing instruments to ensure that any changes to exclusivity periods can be optimized prospectively in support of MAPPs. This is particularly important in view of the current incentives analysis referred to above.³³

³³ The European Commission announced in January 2017 to conduct an analysis of the current legal framework of incentives and rewards, their nature, safeguards, possibilities to combine them for a single product and an analysis of their actual use by pharmaceutical innovators, in particular looking at the combined use of these incentives and rewards.

10. Recommendations

The current legal framework for IP and RER rights provides clear answers with regard to all 4 identified scenarios. At the same time, it does not provide any flexibility or for special solutions with regard to products approved under MAPPs. Thus recommendations for future work are as follows:

1. Building a business case for exclusivity periods under MAPPs that is both permissive and appealing to medicine developers

A practical solution to incentivise the use of MAPPs would be to develop a clear business case – this could be co-developed with medicine developers using algorithms similar to those utilized by MIT/NEWDIGS for scenario building of stratified medicines.³⁴ Further learning need to be absorbed and disseminated from case studies of ‘MAPPs-like’ products and how IP and RER considerations were accounted. Further extrapolation from products continuing through EMA’s adaptive pathways pilots are warranted to understand how early dialogues guided both pre and post MA decisions on IP and RDE.

2. Take into consideration outputs from this group

Future work in particular of the European Commission when conducting the analysis of the current legal framework of incentives and rewards, should take into consideration the outputs from this group with regard to the interplay of MAPPs and the existing IP and RERs. Reciprocal dialogues and learning could prove invaluable as MAPPs evolved further.

3. Early, prospective dialogue and considerations of all regulatory instruments available

A key driver to successfully navigating adaptive pathways for a medicine developer and to maximize market value would be to engage in the earliest possible dialogue with other stakeholders in order to get a clearer picture of the enabling tools available. This refers for example to the possibility of a CMA, the framework of orphan designation and OME, the PRIME scheme and the possibility of accelerated assessment, and the multi-stakeholder scientific advice (regulatory and HTAs). This would allow early discussions to identify well defined patient subpopulations, the practicalities and feasibility of indication expansion, a detailed evidence generation plan and steer from regulators as to the likely post marketing commitments and time frames for confirmatory data collection: *“A development programme not adherent to*

³⁴ Trusheim MR1, Burgess B, Hu SX, Long T, Averbuch SD, Flynn AA, Lieftucht A, Mazumder A, Milloy J, Shaw PM, Swank D, Wang J, Berndt ER, Goodsaid F, Palmer MC., Quantifying factors for the success of stratified medicine, *Nat Rev Drug Discov.* 2011 Oct 31;10(11):817-33. doi: 10.1038/nrd3557.

receive scientific advice was more likely to fail to receive a CMA, while an adherent development more likely to result in a CMA being granted”³⁵.

4. Mechanism to map out and manage commitment of all stakeholders

There is a need for a mechanism to map the scope of necessary legal commitments of all stakeholders in MAPPs at the beginning of the process, and to manage those commitments throughout a MAPPs product lifecycle. The exact level of sharing of information early in product development, and level of informal or formal commitments would need careful consideration in order to meet the minimum needs and expectations of medicine developers, while being sufficiently permissive for other stakeholders to engage fully in the process.

* * *

³⁵ European Medicines Agency, Conditional marketing authorization, Report on ten years of experience at the European Medicines Agency (EMA/471951/2016), 2017, slide 37.