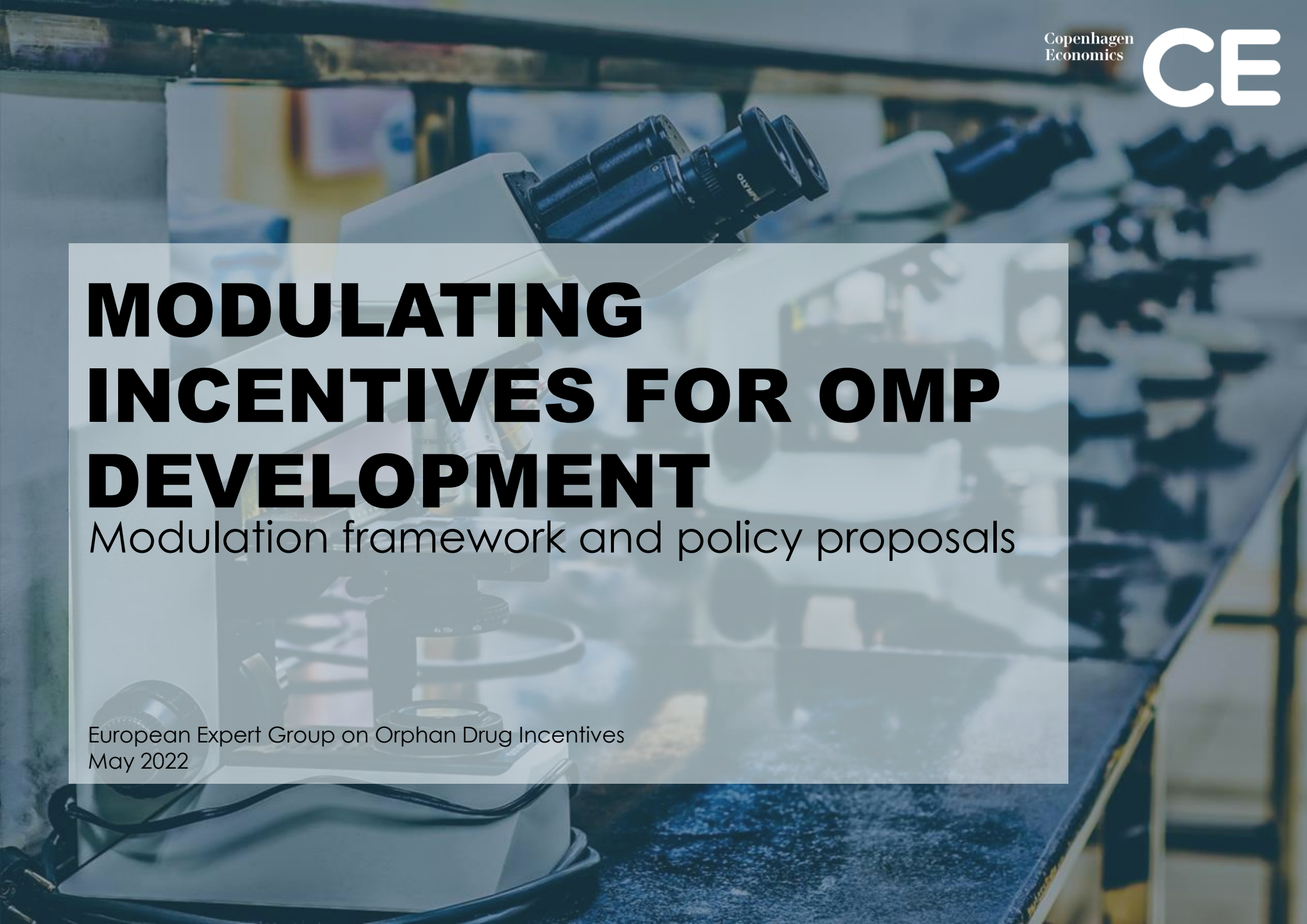

Copenhagen Economics

MODULATING INCENTIVES FOR OMP DEVELOPMENT

Modulation framework and policy proposals

European Expert Group on Orphan Drug Incentives
May 2022

European Expert Group on OD Incentives

Established in 2020, the European Expert Group on Orphan Drug Incentives (OD Expert Group) brings together representatives of the broad rare disease community, including researchers, academia, patient representatives, members of the investor community, rare disease companies and trade associations.

The group aims to become the source of ground-breaking ideas and potential solutions that will provide input to the OMP Regulation evaluation. The initiative is led by a steering group composed of EURORDIS, the Voice of Rare Disease Patients in Europe, and the European Confederation of Pharmaceutical Entrepreneurs (EUCOPE) representing several companies focused on finding new therapies for rare diseases.

The group is co-chaired by former MEP Renate Sommer and Professor Maurizio Scarpa, Coordinator of MetabERN. The following EUCOPE member companies are sponsoring and providing expertise to the initiative: Alexion, Biogen, Bristol Myers Squibb, Chiesi, PTC Therapeutics and Takeda.

Source: https://od-expertgroup.eu

This Report builds on the work of the **European Expert Group for Orphan Drug Incentives** (hereafter, OD Expert Group).

The OD Expert Group is a **cross-disciplinary group of experts** representing different **stakeholders in the rare disease community**. The group includes experts from research, academia, patient groups, rare disease companies, investors and trade associations.

The OD Expert Group worked together with Copenhagen Economics in a series of workshops and interviews to investigate how the current policy framework for OMP incentives needs to change to fit the unique challenges and needs of the OMP development landscape today, to the benefit of rare disease patients.

In this report, the OD Expert Group makes a set of policy proposals that will **improve the OMP incentive framework while reflecting the different stakeholder perspectives**.

This report presents the variety of proposals discussed in the OD Expert Group but may not reflect in detail the views of every individual member of the group.

List of acronyms

CHMP	Committee for Medicinal Products for human use
CMA	Conditional Marketing Authorisation
COMP	Committee for Orphan Medicinal products
CRA	Clinically Relevant Advantage
EC	European Commission
EEP	Early Engagement Pathway
EMA	European Medicines Agency
ERN	European Reference Network
EU	European Union
EUnetHTA	European Network for Health Technology Assessment
HTA	Health Technology Assessment
MA	Marketing Authorisation
MAA	Marketing Authorisation Application
MAUEC	Marketing Authorisation under Exceptional Circumstances
MCPC	Major Contribution to Patient Care
ODD	Orphan Drug Designation
OMM	Operational Model for Modulation
OMP	Orphan medicinal product
SME	Small and medium-sized enterprise
R&D	Research and development
TDPD	Target Development Profile Document

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1. INTRODUCTION AND KEY PRINCIPLES

The OMP Regulation may entail a modulation of incentives for different categories of OMPs

The archetype approach to modulation

In its Inception Impact Assessment (IIA) of the Orphan Medicinal Products (OMP) Regulation, the European Commission proposes the use of a *modulated* approach to OMP incentives. This means that the level of incentives provided will differ across products depending on their unique attributes and subsequent needs. The OD Expert Group has demonstrated that modulating market exclusivity (ME) alone will not suffice in directing attention towards rare diseases for which no authorised treatments exist, or *the 95%* - especially if modulation only consists of a reduction in the current ME period. However, the OD Expert Group still recognises that a careful approach to modulation should focus incentives where they are most needed, leading to an overall efficient policy framework.

Therefore, the OD Expert Group has designed a model for incentives modulation that aims to inform the Commission's thinking on the topic. The **Operational Model for Modulation (OMM)** consists of **3 main archetypes** of rare disease development projects. These archetypes differ in terms of their investment case, the barriers to and needs for development, and therefore also the type of solutions needed to attract investment. In particular, the archetypes are informed by the main needs along the OMP development path (see page 7), as identified by the OD Expert Group[1], and by real-world examples obtained through semi-structured interviews with OMP developers.

The OMM derives from a wider, conceptual archetype framework, that differentiates between 5 different archetypes of rare disease development projects, see page 22 for overview. While the conceptual framework more accurately describes the heterogeneous nature of rare disease development projects and continues to serve as an important backbone to the OMM as well as future policy discussions, we have geared our proposal for modulation towards the solutions that can be implemented within the scope of the OMP Regulation, resulting in 3 Archetypes of OMP development projects. This also serves the purpose of having a more simple, workable, and predictable modulation framework. Nonetheless, truly moving the needle on the 95% in Europe requires broad multi-stakeholder collaboration and policy action outside of the scope of the OMP Regulation.

It is worth noting that, in modulating the incentives available to OMPs, **two different routes** are being discussed currently within the rare disease community and policymakers. The first route, as explored by the European Commission, works by categorising OMPs according to the *extent* that they meet unmet medical needs, including their availability across EU member states, as well as according to the *characteristics* that they embody, such as whether they are repurposed medicines or targeted for multiple indications. Incentives are then granted accordingly, depending on where the medicines are placed in the hierarchy of unmet needs and other characteristics. This route **will not** serve to speed up the development of innovative OMPs that can meet the continuously evolving needs of patients.

The second route looks at the provision of incentives through an investment case perspective. By categorising OMP development projects into one of the three archetypes based on the cumulative risks along the development path, resulting in variedly favourable investment cases for individual projects, just enough incentives and support are provided to make the investment case for each project positive. This route will promote the development of medicines in a cost-effective way while having the flexibility to meet evolving patient needs, as it does not require defining and updating the concept of unmet needs as innovation in rare diseases continues to grow. This is the approach explored by the OD expert Group and presented in this document.

The modulation framework presented in this paper follows and emphasizes **5 principles** (see pages 4-6 for more information):

1. Maintain broad ODD and modulate within
2. Modulate according to differences in the investment case
3. Do not use unmet need definition to modulate
4. Legal certainty and predictability are key
5. Incentives need to include and go beyond modulation of ME

1) See OD Expert Group (2021). "Orphan medicine incentives: How to address the unmet needs of rare disease patients by transforming the European OMP landscape", available here.

An effective and efficient modulation framework needs to follow 5 key principles

We outline **5 principles** that are key to ensuring that any effort of modulating incentives for OMP development ultimately benefits rare disease patients.

1. **Maintain broad ODD and modulate within**
2. **Modulate according to differences in the investment case**
3. **Do not use unmet need definition to modulate**
4. **Legal certainty and predictability are key**
5. **Incentives need to include and go beyond modulation of ME**

1. Maintain broad ODD and modulate within

The OMP Regulation is, and should continue to be, based on a system of incentives to encourage the broad development of OMPs across different rare diseases. The broad Orphan Drug Designation (ODD), applicable for treatments addressing a condition affecting no more than 5 in 10,000 individuals in the EU, should be maintained. This is because the basic set-up of the OMP Regulation, with an ODD and related incentives, has visibly worked to attract investment in rare diseases. The ODD is also an important label for companies to attract investments. With the ODD, the medicine is officially recognised as "orphan" also at the market access stage where it can achieve, on average across Europe, a higher payment per patient than other medicines, because of the small patient population affected by the condition.

A more restrictive[1] or cumulative[2] prevalence threshold for ODD, which are both on the Commission's table, likely have far-reaching consequences on the investment in OMP development that go beyond the sheer loss of opportunity for scientific advice and market exclusivity. Moreover, a more restrictive ODD prevalence threshold may severely hamper attractiveness to invest in more prevalent rare diseases where high unmet needs are still present. Therefore, we suggest to maintain the current threshold of orphan designation but allow for modulation of incentives within.

2. Modulate according to differences in the investment case

Modulation should be based on the investment case for launching research and development in a specific rare disease or disease area. The investment case approach takes the crucial role of investors into account and enables identification of diseases areas where the investment case is either particularly weak or particularly strong given current incentive levels. We find that the presence of a market, with identified patient populations and established price points, as well as an existing regulatory and market access pathway, borne out of regulator and payer familiarity with a given condition/class of products, are main drivers of the investment case for OMPs.

First, the investment case differs markedly between:

- development projects for which no basic and development-ready research exists
- development projects for which there is disease knowledge and some research activity but no proven market
- Development projects for which there is already a market with one or more approved treatments.

Pioneering research and development in rare diseases where no prior translational basic research exists is a very uncertain undertaking. Often, these projects do not yet have a commercial focus, but are rather more investigative in nature – the main objective is to establish and upscale understanding of the disease, on which possible development of a therapy can be based. Therefore, the investment case is often weak and sometimes non-existent. This group is likely to include the most difficult rare disease development projects from an investment case perspective, such as rare diseases with a particularly slow disease progression and the very rarest of diseases, affecting as few as a handful of patients in all of Europe.

Developing and launching a first-to-market rare disease treatment, either a first-in-condition product or a new technology, often requires a much higher level of investment and risk-taking from the OMP developer than launching a

1) I.e. a prevalence threshold below the current threshold of 5 in 10,000 persons, therefore excluding OMPs addressing more prevalent rare diseases. // 2) I.e. Cumulative prevalence across the targeted indications.

An effective and efficient modulation framework needs to follow 5 key principles

second- or third-to-market product. With no established clinical endpoints from previous clinical trials, the first-to-market OMP developer must spend considerable resources in engaging with regulators and payers to establish disease understanding and agreement on appropriate endpoints.

These discussions are difficult, given the heterogeneous challenges and clinical trial designs of rare diseases. The first-to-market OMP developer often also plays a large role in finding relevant patient populations and establishing diagnosis and care infrastructures, which are complex and costly tasks. Lastly, the first-to-market OMP developer must demonstrate treatment value and determine an appropriate price level, often followed by lengthy and difficult pricing negotiations.

Importantly, developing and launching treatments for rare diseases where a (small) variety of authorised treatments exist is not risk-free, as these projects face other unique challenges, in particular regarding uncertainties with demonstrating Significant Benefit (SB), which may undermine the investment case.

Finally, medicine repurposing as well multi-indication development may or may not represent a less risky investment case, as opposed to the development of completely novel medicines, as the rare conditions they address may still be completely unexplored. In fact, they are both considered key to addressing the 95%, enabling exhaustive and efficient innovation. Therefore, a modulation framework, that is built on investment case logic provides sufficient incentives to ensure continued innovation of known medicines and active substances while avoiding overcompensation.

3. Modulation should not be based on a restrictive definition of unmet need

Modulation should not be based solely on a restrictive and static definition of unmet need.

The interpretation of what constitutes "unmet needs" varies in content and has distinct meanings to different stakeholders. While crucial, the absence of any treatment is not the only unmet need to consider. Unmet need differs between patients and evolves over time. Rare diseases have complex and inconsistent clinical manifestations, which can change over time and between patients. Similarly, the needs of patients also evolve over time.

Although a key element in the (lack of) investment case for many OMPs, the prevalence of an given condition does not always determine the amount of innovation that takes place. For instance, although uncommon, some very rare diseases today have more R&D activity and authorised treatments than less rare diseases. In applying a modulation approach, we therefore find it more worthwhile to consider the amount of R&D that takes place and the number of, and variety in, authorised treatments on the market.

Additionally, most rare diseases lack disease-modifying and curative treatments today. Therefore, it is difficult for policy makers to determine which development projects will (not) address unmet needs. Moreover, the SB criterion implemented in the current regulation ensures that only those medicines are designated as "orphans" that continue adding value to patients, i.e. meet needs that so far have not been met.

4. Legal certainty and predictability are key

Any modulation must provide legal certainty and predictability. This means that investors must be able to know *before* taking the investment decision which types of incentives a project will be eligible to and under which conditions. This means that any modulation approach needs to specify *when* OMP projects will and can be categorised into a specific archetype and what measures are needed to ensure predictability over time. This implementation point requires a careful impact assessment.

5. Incentives need to include *and* go beyond modulation of ME

Any modulated framework needs to include additional incentives in addition to the modulation of market exclusivity. In other words, a modulation approach that seeks to address the 95% of rare diseases that currently

An effective and efficient modulation framework needs to follow 5 key principles

lack authorised treatment must offer additional incentives to what is available today. Here, relying solely on market protection instruments (e.g. additional years of market exclusivity) is unlikely to substantially increase the investment case.

In contrast, any downward modulation that includes reducing incentives for R&D in specific disease areas automatically runs the risk of type II errors, i.e. of under-incentivising development projects that would be beneficial for rare disease patients. Therefore, it is important that any downward modulation is done in a careful manner and only for those rare disease projects that truly do not require additional incentives for development. Here, it is crucial to understand the positive externalities that derive from continued innovation in areas where development already takes place, where incremental innovation can lead to advances in disease knowledge, diagnosis and clinical development for diseases with significantly less R&D activity and in the development of advanced therapy medicinal products. In addition, the innovation model of pharma companies is based on lifecycle management, in which multi-indication product innovation is a central element to decrease risk and a key facilitator of wider investment in OMP development.

Moreover, as a vital incentive for OMPs, any downward modulation of ME needs to remain relevant on top of the data and market protection period (8+2 years). Any ME below the duration of the data protection period will reduce protection from other products with similar mechanism of action but will delay generics from filing before the end of the data protection period (currently 8 years after approval) and from entering before the end of the market protection period (currently 10 years after approval). Lastly, while market and data protection adds one year of protection for subsequent indications, ME is indication-specific and supports the risk and lifecycle management approach of OMP developers. OMP Regulation should continue to see subsequent indications as unique development projects, facing additional costs and risks.

In our modulation approach, we focus on proposals 5, 7 and 8 of the OD Expert Group

1 Need to improve the R&D ecosystem for basic research and company take-up of development

- **1.** Form an EU rare disease hub for large-scale collaboration, data sharing and generation, and diagnosis.
- **2.** Provide guidance and incentives for translational basic research
- **3.** Form a Rare Disease PPP fund for basic research and early development
- **4.** Establish a coherent policy framework for the use of RWE → 1 3 4

2 Need to improve the system of financial incentives and rewards

- **5.** Modulate market exclusivity based on agreed criteria
- **6.** Introduce additional financial incentives, such as a transferable voucher or tax credits for drug development

3 Need to improve the flexibility, predictability and speed of the regulatory pathway

- **7.** Strengthen EMA's role in advising OMP developers through the OMP pathway → 4
- **8.** Increase legal certainty around the concept of Significant Benefit → 4
- **9.** Adopt guidelines on the use of alternative treatments (e.g. off-label use and pharmacy preparations) in the presence of approved OMPs
- **10.** Adapt the regulatory pathway to the specificities of OMP groups with additional challenges

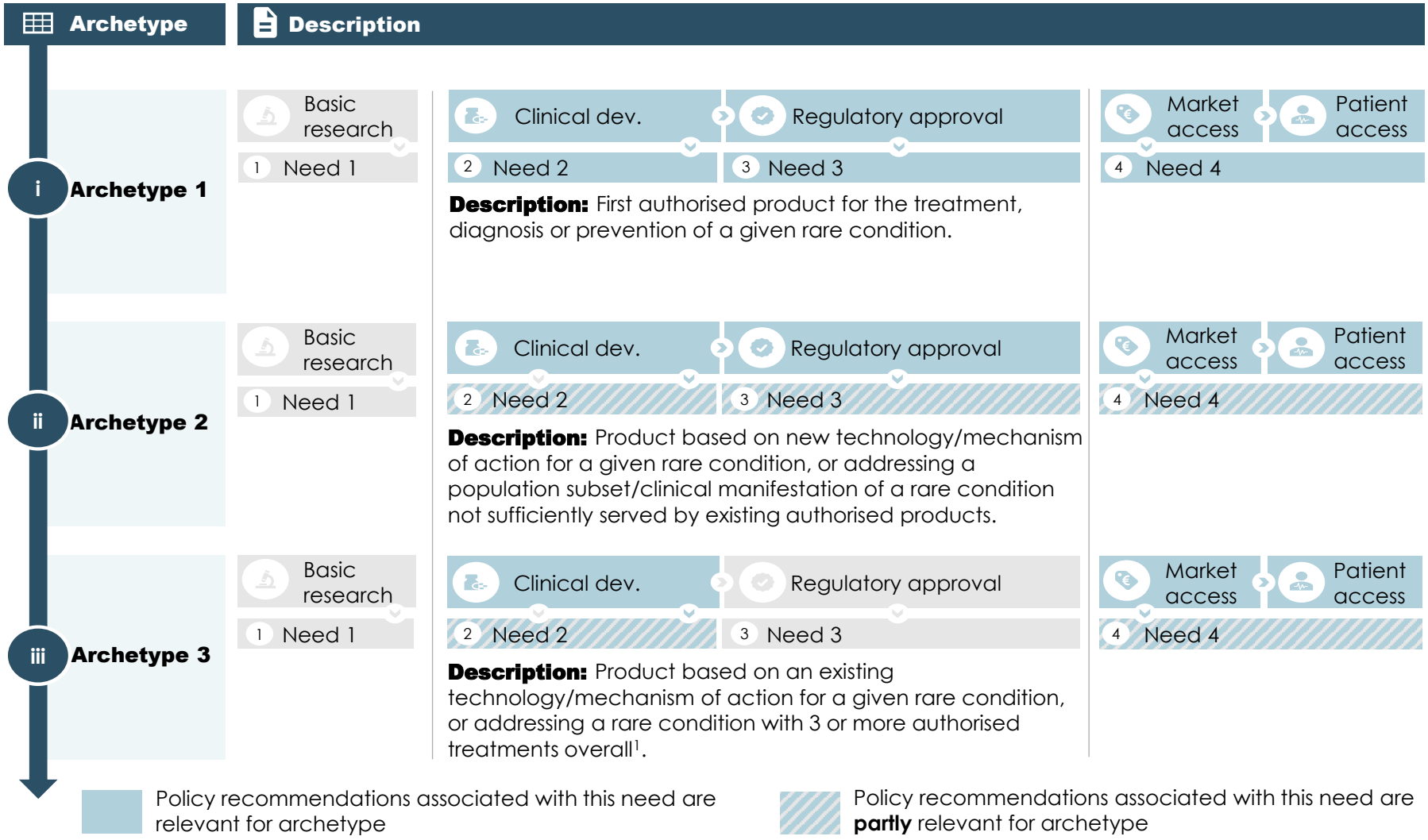
4 Need to improve the coherence and predictability of demand and pricing for OMPs

- **11.** Establish an iterative early dialogue for EMA-HTA bodies and OMP developers
- **12.** Create a common EU value assessment for OMPs
- **13.** Pilot a common EU access pathway for "priority" (extremely rare) OMPs
- **14.** Facilitate homogeneous access to OMPs across EU Member States

Proposals within scope of the work

2. THE OPERATIONAL MODULATION FRAMEWORK

The operational model for modulation consists of 3 archetypes of OMP development projects



1) Existing generic formulations do not count in the total number of existing treatments

Archetype 1

Description
This archetype of rare disease projects is characterised by **a total lack of approved treatments**, despite a level of existing scientific knowledge and R&D activity. Rare disease projects belonging to this archetype are pioneering in very new areas of research. However, they fail to proceed in or beyond clinical trials – pointing to challenges associated with demonstrating efficacy and value at the regulatory (and later likely market access) stage.

Identifier
An OMP project belonging to this archetype is a first-in-condition products, i.e. it is the first authorised product for the treatment, diagnosis or prevention of given rare condition.

Barriers
The main challenge for OMP developers in developing an OMP belonging to this archetype is that they embark on an untested authorisation and access pathway where risks of successfully demonstrating efficacy and value against infeasible criteria are high. They are likely to face difficulty advancing in traditional clinical trial settings and regulatory inflexibility for new, innovative treatments, leading to long development times and high rates of attrition.

With no authorised products, there exists no proven market for OMPs belonging to this archetype, meaning that the OMP developer needs to conduct all the "ground-work", such as establishing a price and disease-specific healthcare and diagnosis infrastructure.

Examples
- **Lysosomal storage disorders, such as MPS III**
- **Limb-Girdle muscular dystrophy**
- **Aromatic l-amino acid decarboxylase (AADC) deficiency**
- **Charcot-Marie-Tooth disease**

OD Expert Group policy measures addressing relevant needs of the archetype

2 Need to improve the system of financial incentives and rewards	**5.** Modulate market exclusivity based on agreed criteria
	6. Introduce additional financial incentives, such as a transferable voucher or tax credits for drug development
3 Need to improve the flexibility, predictability and speed of the regulatory pathway	**7.** Strengthen EMA's role in advising OMP developers throughout the regulatory pathway
	8. Increase legal certainty around the concept of Significant Benefit
	9. Adopt guidelines on the use of alternative treatments in the presence of appr. OMPs
	10. Adapt the regulatory pathways to the specificities of groups of OMP
4 Need to improve the coherence and predictability of demand and pricing for OMPs	**11.** Establish an iterative early dialogue for EMA-HTA bodies and OMP developers
	12. Create a common EU value assessment for OMPs
	13. Pilot a common EU access pathway for "priority" OMPs
	14. Facilitate homogenous access to OMPs across EU member states

Solutions within focus of our work relevant for the Archetype

Archetype 2

Description
This archetype of rare disease projects is characterised by a considerable amount of R&D activity, i.e. the **basic foundations** of disease understanding and care, as well as one or a few (less than 3) treatments, exist. An OMP belonging to this archetype is based on a new technology or mechanism of action, or addressing a subset of a population or a feature of a rare condition not sufficiently served by existing authorised products. Although the needs of some patients are addressed with already approved treatments, the treatment offering is unvaried, sub-optimal, and fails to serve all patient sub-populations or all manifestations of the disease.

Identifier
An OMP project belonging to this archetype is a product that is based on a new technology/mechanism of action for a given rare condition, or addressing a population subset/clinical manifestation of a rare condition not sufficiently served by existing authorised products.

Barriers
The main barriers include regulatory inflexibility for new technologies, e.g. around the concept of significant benefit, and rigidness for accepting new clinical endpoints or making use of biomarkers (e.g. when old endpoints have become irrelevant). This similar uncertainty is met later down the line with interactions with HTA bodies/ payers. Moreover, there is less interest and pressure from the payer perspective to bring further treatments to patients that are already have a treatment option (even if non-transformative).

Examples
- A disease-modifying treatment for **Amyotrophic Lateral Sclerosis (ALS)**[1]
- A disease-modifying treatment for **Wilson's disease**[2]

OD Expert Group policy measures addressing relevant needs of the archetype

2 Need to improve the system of financial incentives and rewards	**5.** Modulate market exclusivity based on agreed criteria
	6. Introduce additional financial incentives, such as a transferable voucher or tax credits for drug development
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Solutions within focus of our work relevant for the Archetype

1) Current authorised treatments for Amyotrophic Lateral Sclerosis are palliative // 2) Current standard of care, since 1958, consists of zinc cation (currently sold under brand name "Winzin"), which blocks absorption of copper from diet and improves symptoms of disease over time.

Archetype 3

Description
This archetype consists of a broad range of OMP development projects, that are characterised by a considerable amount R&D activity, growing scientific knowledge and various treatment options. OMP development projects belonging to this archetypes are based on a strong foundation of research and development, but the offering of existing treatments and healthcare processes and infrastructures may or may not be quite sufficient to provide patients with the best possible care. Thanks to the innovation and increased disease understanding that has taken place, care systems are on their way to becoming more attuned to the conditions and the unique needs of patients affected by the conditions.

Identifier
An OMP development project belonging to this archetype is a product that is based on an existing technology or mechanism of action for a given rare condition, or address a condition for which 3 or more authorised treatments exist overall.

Barriers
The main barriers concern issues on the demand side, and in particular with market and patient access, where there is still opportunity for health systems to mature further by working together with OMP developers to provide better care for patients. We have uncovered that there is still a vastly different understanding and acceptance from regulators and HTA bodies/payers depending on the amount of competing products on the market. More treatments options on the market mean more attuned regulatory and market access processes, more receptive health systems, clear price points, and lower risk.

Examples
- **Spinal muscular atrophy (SMA):** three authorised treatments
- **Hereditary Angioedema (HAE):** more than three authorised treatments
- **Multiple Myeloma:** more than three authorised treatments

OD Expert Group policy measures addressing relevant needs of the archetype

2 Need to improve the system of financial incentives and rewards	**5.** Modulate market exclusivity based on agreed criteria
	6. Introduce additional financial incentives, such as a transferable voucher or tax credits for drug development
4 Need to improve the coherence and predictability of demand and pricing for OMPs	**11.** Establish an iterative early dialogue for EMA-HTA bodies and OMP developers
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Solutions within focus of our work relevant for the Archetype

1) This is an indicative number for operative purposes. Separate assessment should be done to determine the appropriate cut-off.

3. POLICY PROPOSALS

Modulation of market exclusivity

Market exclusivity (ME) is the main incentive of the OMP Regulation, protecting OMPs from competition from similar medicines[1] for the same therapeutic indication for a period of 10 years. Currently, the period of 10 years applies to all orphan-designated medicines that have been granted centralised marketing authorisation. The ME period can be extended by two additional years upon the completion of a fully compliant paediatric investigation plan (PIP).

Modulating ME refers to the graduation of the ME incentive to different groups of OMPs. We propose the following modulation of ME for the three archetypes, differing in terms of their investment case:

Archetype 1: For OMP projects belonging to Archetype 1, we propose an increase of the ME period to **twelve (12) years.** Two additional years of ME compensates for the high level of regulatory and market access uncertainty, and in particular, the long duration of time that it takes to find patients, due to the lack of or immature diagnosis infrastructure and undefined patient population, and to achieve fist-in-condition pricing agreements.

Therefore, additional two years of ME would increase the attractiveness to develop Archetype 1 OMPs, also in the case of possible conditional marketing authorisation (CMA) or marketing authorisation under exceptional circumstances (MAUEC). CMAs and MAUECs often prompt challenges at the market access stage, when payers require diverging levels of evidence to establish pricing agreements. Therefore, an additional two years of ME is also likely to incentivise developers to pursue resource-consuming and uncertain CMAs and MAUECs and to undertake post-authorisation research.

It is important to note that an increase in the period of ME needs to be coupled with other incentives, as ME alone is not enough to overcome the challenges that Archetype 1 OMPs face along their lifecycle. An increase in ME from 10 to 12 years has been estimated to increase the net present value of a representative ultra-orphan OMP by 7%[1], which may be higher or lower, given the expected competition on the market following expiry of ME and the duration of other periods of protection.

Archetype 2: For OMP projects belonging to Archetype 2, we propose maintenance of the current ME period of **ten (10) years.** Maintaining the current period of ME will ensure continued innovation of OMPs that rely on ME as a key incentive, therefore avoiding Type 2 errors[2].

Ten years of ME compensate for the challenges associated with demonstrating benefit over existing technologies/treatment options and acceptance of new clinical endpoints at the approval and market access stages. The regulatory and market access assessments are deemed inflexible to innovative products, especially when the benchmark is an indirect comparison or based on outdated clinical end points.

Moreover, although price points will already have been established in the rare diseases that these OMPs address, it may be very difficult for OMP developers to negotiate prices that provide fair return to the even higher cost and risk profiles of very innovative, and potentially curative, OMPs.

Archetype 3: For OMP projects belonging to Archetype 3, we propose a reduction of the ME period to **eight (8) years.** A reduction of no more than two years will likely continue to drive the level of innovation that we see today, without the risk of Type 2 errors.

While the existence of treatment means that market dynamics are better understood, and patient groups and specialists are already engaged, OMPs belonging to Archetype 3 are likely to face significant hurdles with generation of evidence due to difficulties in patient recruitment and demonstration of significant benefit under higher and uncertain standards for evidence, especially in the case of indirect comparisons.

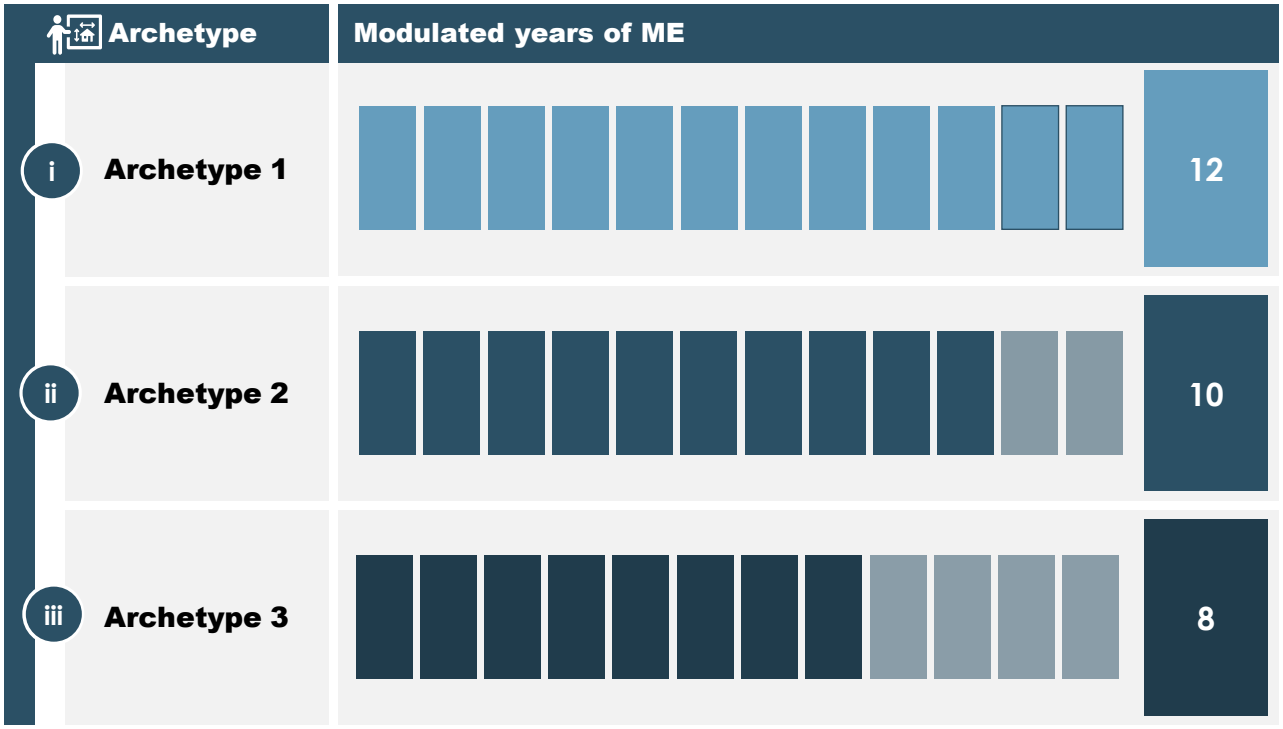
A reduction in ME has shown to starkly and negatively affect the profitability of an average OMP by as much as 23.4% following a two-year reduction and as much as 80% following a five-year reduction, turning the net present value

1) Copenhagen Economics (2021). Innovating for people living with a rare disease: Why partnerships are key for the European OMP ecosystem // 2) I.e. under-incentivising development projects that would be beneficial for rare disease patients.

Modulation of market exclusivity

negative in the case of the latter and deterring any rational developer from investing in such projects[1]. A reduction below eight years will also put EU at a strategically disadvantageous position against the US ecosystem of OMP development, where the level of incentives are overall higher – especially when accounting for time and ease of market access.

OD Expert group proposal for modulation of ME



1) Berdud et al., OHE Consulting Report (2020)

Strengthening EMA's role in advising OMP developers through the pathway

The EMA offers developers various opportunities to receive guidance along the regulatory pathway, from procedural guidance and assistance navigating the pathway, to generating robust evidence for market authorisation applications (and to a limited degree market access). These opportunities include, but are not limited to, scientific advice (and protocol assistance for OMPs), the PRIME scheme, and the EUnetHTA-EMA parallel consultation.

The impact of scientific advice (SA) has been studied since its adoption in 1996 and its correlation with market authorisation success is clear, also in the case of OMPs[1]. The number of SA requests has also steadily increased since the establishment of the procedure, demonstrating that developers are increasingly acknowledging its value. SA is, however, provided through a non-iterative process and is largely bound by regulatory capacity, meaning that review and time to advice can take considerable time.

The PRIME scheme, while only adopted in 2016, has accepted applications from 53 OMPs, of which 16 have obtained an MA. Though the PRIME scheme has been considered a success on many parameters, its selective uptake process means that not all OMP developers that could benefit from PRIME support receive it. OMP developers also need to present proof of concept (or proof of principle if SME or academic sponsor) with sufficient clinical evidence before being eligible for PRIME, meaning that the opportunity for important early advice is lost.

EUnetHTA-EMA parallel consultations are valuable interactions for the OMP developers, allowing them to receive earlier and more aligned evidentiary advice from both the regulators and HTA bodies. This process is, however, currently offered on a very selective basis and not open to interested sponsors on a fee-basis. For example, the EUnetHTA 21 Consortium provide a maximum of 8 joint scientific consultations beyond May 2021[2].

Despite these support programs provided in connection with regulatory processes, OMP developers face a number of frictions along the regulatory pathway. The regulatory pathway is deemed uncertain and inflexible towards the unique challenges of OMPs, both in the way developers are required to meet evidentiary standards and in the interactions between developers and the regulatory actors[2]. With the wealth of regulatory and scientific expertise that already exists within and outside the EMA, better deployment of appropriate competencies and greater collaboration between actors can create the regulatory environment needed to guide a great number of OMPs through regulatory pathway in a more optimal way. EMA can provide a modulated level of support for different archetypes of OMP projects, ensuring that more OMPs are successful on the regulatory pathway, while managing resources in an efficient way.

Archetype 1 and 2: We propose to develop an early engagement pathway (EEP) targeting Archetype 1 and 2 OMPs, offering 5 unique features that will significantly decrease development and regulatory risk.

1. **Early disease/disease group outcome measure meetings** to discuss and align on outcome measures with other members of the industry, COMP, relevant EMA working parties, and patient representatives. These should precede other elements of the EEP, focusing on challenges and outcomes relevant to the particular disease or group of diseases. The meetings should be open to all members of the industry with early OMP projects indicated for the same/similar disease in the pipeline. Most importantly, the outcome measure meetings include patients on the selection and development of clinical endpoints. Such an approach has been organised in the case of Duchenne Muscular Dystrophy, where early multi-stakeholder outcome measure meetings were considered a success for all actors involved[3].
2. **Dedicated case manager from the time of ODD to MA** that oversees the project and feasibility of the development plan from the regulatory perspective, while deploying the appropriate expertise from an assigned case group when needed. Formed by the case manager, the case group should include members of the COMP, CHMP, patient representatives, EUnetHTA, and

1) // 2) OD Expert Group (2021) // 2) https://www.eunethta.eu/jsc/ // 3) See Straub & Mercuri (2018), https://www.nmd-journal.com/article/S0960-8966(18)30189-5/fulltext //

Strengthening EMA's role in advising OMP developers through the pathway

potentially EMA's list of European experts/EMA working parties. In addition to interactions around planned milestones and processes, case managers act as single and flexible gateways for advice for OMP developers throughout. A requirement and success factor of the relationship between the case manager and OMP developer is **joint problem solving** against mutual success criteria.

3. **Early project kick-off meeting** with the case manager and assigned case group, including members from the CHMP, COMP, EUnetHTA, and patient representatives, to align on efficacy end points and development plans, type and level of evidence required at MAA and at the market access stage. These features will be documented in the target development profile document (TDPD), see point 4 below.
4. **Target development profile document (TDPD)** as a tool for regulatory communication, drafted prior to and at the early project kick-off meeting and updated throughout development. The case manager maintains the TDPD together with the OMP developer. The purpose of the TDPD is to ensure that OMP development plan is efficient and generates the required evidence for MA and HTA assessments, including assessment of SB. It outlines the overall purpose of the OMP and its key regulatory and development details. The TDPD should resemble the target development profile of the UK's Innovative Licensing and Access Pathway and FDA's Target Product Profile[2].
5. **Regular milestone meetings** with the case manager to track status of development, evidence generation, status on significant benefit (if applicable), and to update the TDPD. The frequency of the meetings should be decided in the kick-off meeting and adjusted to the specific development plan of the project. Members of the case group should be included in the meetings that coincide with bigger milestones (e.g. conclusion of a trial). Patient representatives can be invited directly in the meetings or indirectly via pre-submitted question and contact forms.

Throughout the EEP, patients play a central role in providing direction and input to the development plans of Archetype 1 and 2 OMPs with the systematic inclusion of patient representatives in the assigned case group. This level of patient engagement builds on existing initiatives, such as EMA's pilot for CHMP early contact with patient organisations[1] , yet with even earlier and more ingrained involvement from the time of initial ODD.

The involvement of the CHMP, COMP and EUnetHTA will enable better alignment on evidence required by different actors at different phases of the OMP lifecycle. Moreover, a systematic involvement of the EUnetHTA will enable early cost-benefit assessments and preliminary value dialogues.

In order to balance limited resources with the need for innovative OMPs, Archetype 1 projects are automatically eligible to the EEP from the time of initial ODD, while EMA assesses the eligibility of Archetype 2 projects on a case-by-case basis, given the disease area/group, characteristics of the project and availability of resources.

All developers of OMPs, including academic sponsors, SMEs and larger biopharmaceutical companies, are eligible for the EEP.

The EEP should be jointly financed by companies and the EMA. Substantial fee reductions should apply to SMEs and academic sponsors.

Archetype 3: Maintain current regulatory pathway with **significant benefit dialogues with the COMP and EUnetHTA**, preceding and during the MA stage. Involving the EUnetHTA in the SB decision will provide HTA recognition to be carried over from the approval stage to the market access stage, therefore removing the need to carry out a separate SB assessment with each EU member state.

1) https://www.ema.europa.eu/en/documents/other/pilot-phase-chmp-early-contact-patient/consumer-organisations_en.pdf // 2) See

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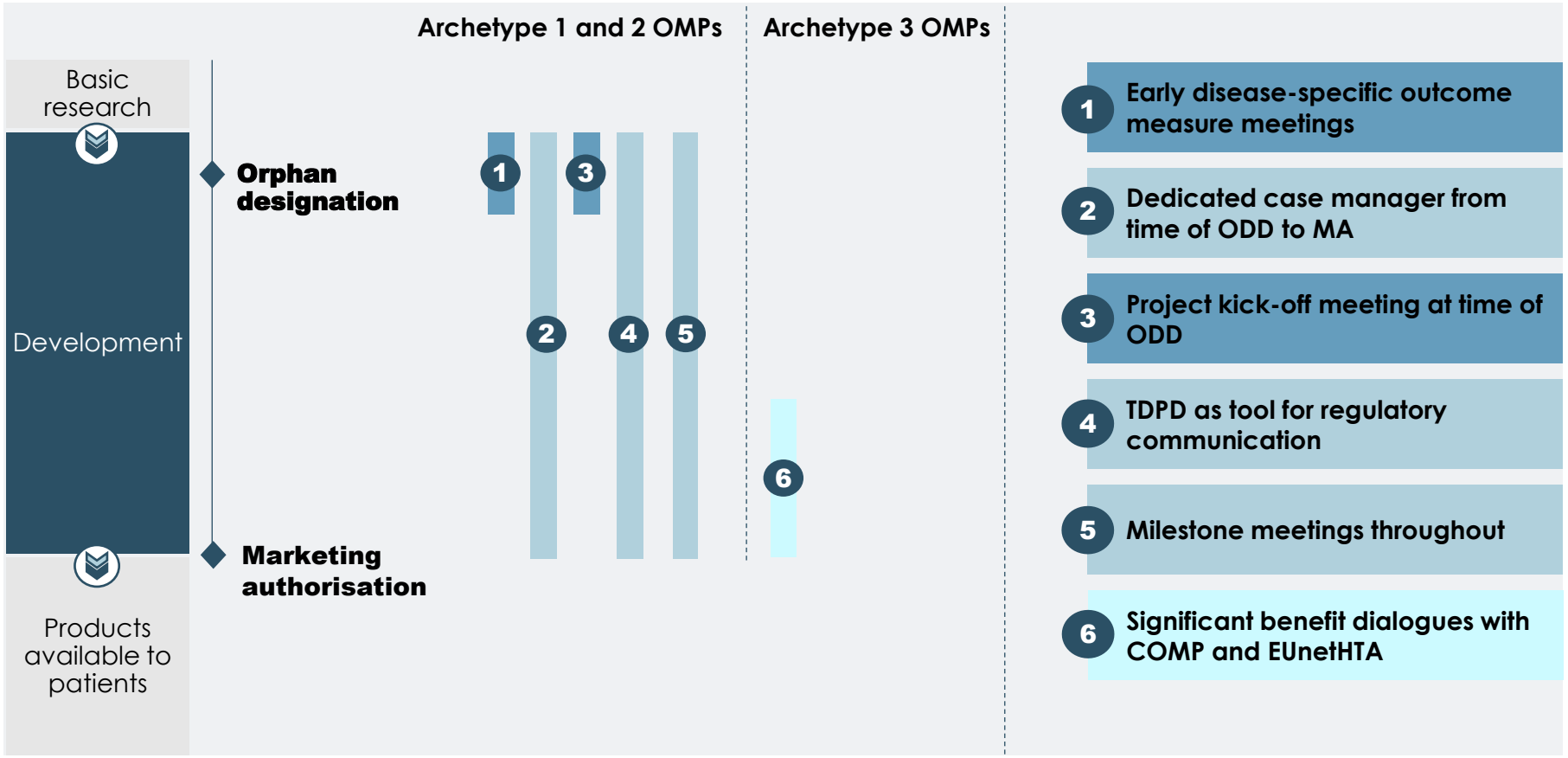
Early Engagement Pathway (EEP)



Refining the criteria for and assessment of significant benefit

Significant benefit (SB) is an important premise of the EU orphan designation. It incentivises innovation in rare diseases where authorised treatments exist, ensuring continued and incremental development in patient care and in addressing unmet medical needs. SB should therefore be maintained as an integral part of the OMP Regulation.

SB is demonstrated at the time of ODD, most often based on assumptions and very early clinical data, and at the time Marketing Authorisation application (MAA), based on a thorough clinical comparison of all approved OMPs. The criteria and assessment on which SB is currently based does however pose unnecessary risks in the OMP development path, potentially disincentivising investment in OMPs.

Rare disease clinical trials typically enrol fewer patients and are more likely to be non-randomized, single arm studies. This poses challenges in demonstrating SB, when only indirect comparisons can be made. Although methodology guidelines exist for inferring relative effectiveness with indirect comparisons, the lack of standard methodological approaches implies that demonstrating SB is uncertain and prone to considerable inconsistencies, depending on the methodology used. For example, underlying data from comparable studies are often heterogenous and inconsistent, therefore affecting the reliability and comparability of results for indirect assessment. This challenge is only amplified when the methods and type of evidence required for demonstrating SB at the market access stage diverge from those at the approval stage. The SB label carries no definite meaning beyond the approval stage, meaning that SB is most often separately reassessed by national HTA bodies at the time of market access, causing great uncertainty and an unnecessary duplication of efforts from both the OMP developers and authorities.

Moreover, there is often a discrepancy between the level of data required for a Conditional Marketing Authorisation (CMA) and for demonstration of SB, meaning that an OMP may risk losing the ODD if the level of evidence available at the time is not sufficient to support significant benefit.

Lastly, SB benefit on the grounds of major contribution to patient care (MCPC), either in terms of improved availability or ease of use, is rarely demonstrated and/or accepted. This is because it is much broader and variable as a concept in comparison to assessment of efficacy or safety (clinically relevant advantage, CRA), and there exists no standard criteria and methodology for assessing it. To base SB on MCPC, the product must also be equally efficacious and safe as comparators. Most importantly, the patients are not systematically included in the discussions to set the threshold for SB or MCPC.

In order to reduce uncertainty and improve predictability around SB, it is therefore important that concepts and the scientific contents of the criteria for and assessment of SB are refined. Such refinement includes the following:

1. The EMA and EUnetHTA to devise a standard method and criteria for indirect assessment for the demonstration of SB. These need to be clearly outlined in a publicly available methodological note.
2. Recognition and acceptance of SB in the market access relative effectiveness assessments. Uniform contents of and requirements for SB can be achieved through EMA-EUnetHTA dialogues prior to MA.
3. In the case CMA, exemption from SB re-assessment at the time of CMA. SB to be assessed only at the time of converting CMA into MA.
4. Clear criteria for and assessment of MCPC, including early development of relevant outcomes together with patients in project- and/or disease-specific meetings.

Refining the criteria for and assessment of significant benefit

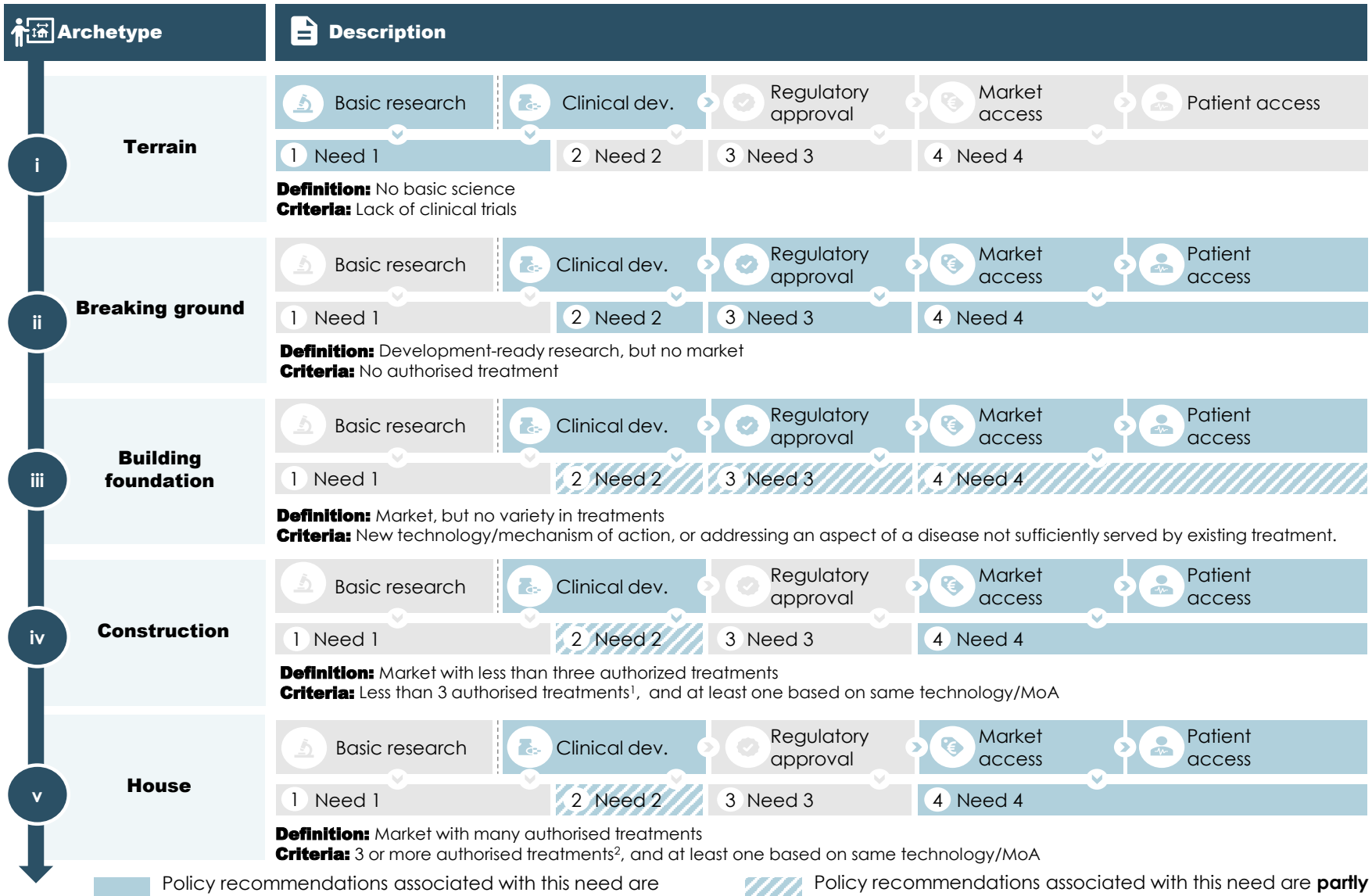
4 policy asks for refining the criteria for and assessment of SB

1. **A standard methodology for indirect assessment**, outlined in publicly available methodological document
2. **Recognition and acceptance of SB in REAs at the market access stage**, with uniform contents of and requirements for SB established in EMA-EUnetHTA dialogues prior to MA.
3. In the case of CMA, **exemption from SB re-assessment at the time of CMA**, with SB re-assessment taking place only at the time of converting CMA to full MA.
4. **Clear criteria for and assessment of "major contribution to patient care"**, including early development of relevant outcomes with patients.

4. BACKGROUND MATERIAL

CONCEPTUAL FRAMEWORK FOR MODULATION

The conceptual modulation framework



1) This is an indicative number for operative purposes. Separate assessment should be done to determine the appropriate cut-off. Applies to each population subset // 3) This is an indicative number for operative purposes. Separate assessment should be done to determine the appropriate cut-off. Applies to each population subset