Copenhagen Economics

INNOVATING FOR PEOPLE LIVING WITH A RARE DISEASE

Why partnerships are key for the European OMP ecosystem

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Intended for EU Policy Stakeholders

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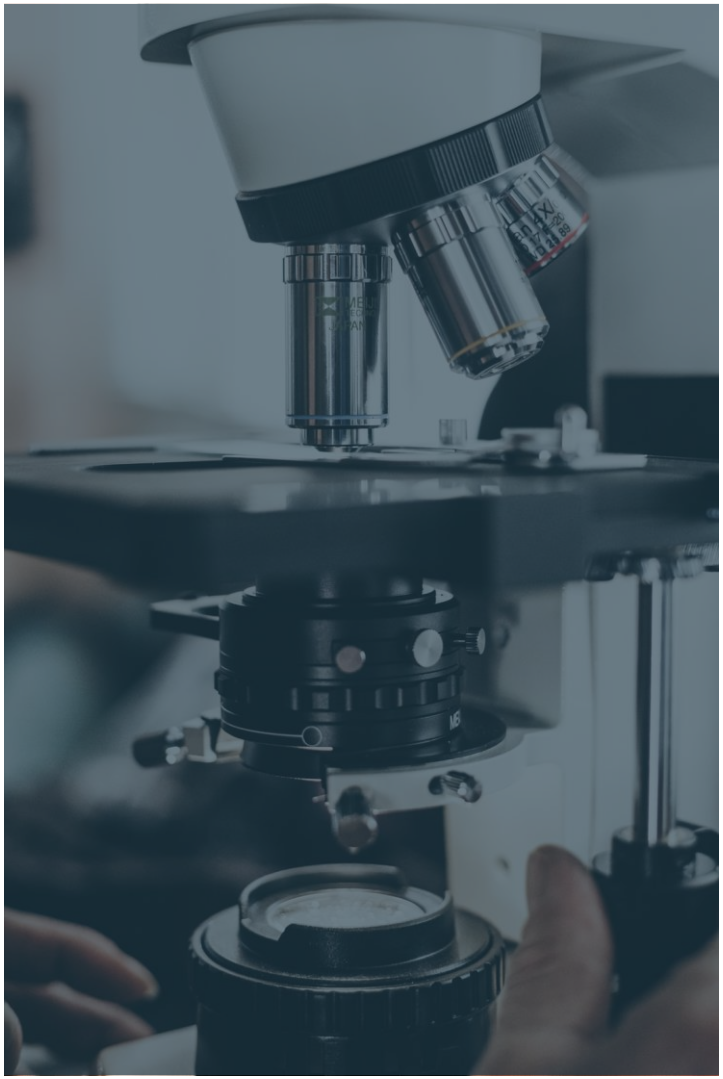

Executive summary

With the revision of the European Orphan Medicinal Product (OMP) Regulation, Europe has a chance to review its policy framework for medicines addressing rare diseases.

A disease is considered as "rare" when it affects no more than 5 in 10,000 people.[1] Rare diseases are often life-threatening or chronically debilitating and can lead to a stark reduction in the life expectancy of and quality of life for the patient. Even though rare diseases are individually rare, they constitute a common health issue collectively: today, we know of more than 6,000 rare diseases that together affect over 30 million people in Europe.[2] That is approximately the total population size of the Benelux countries.

Tackling rare diseases is important, because living with a rare disease has severe effects on the quality of life of patients and the people who take care of them.[3] Today, many rare disease patients are still likely to remain undiagnosed or are diagnosed very late after a true odyssey through healthcare systems. Next to their impact on the individual patient, rare diseases also place a heavy burden on society due to the cost of care and the socio-economic burden from lack of participation in societal and work activities. It therefore makes sense for Europe to have a strong focus on delivering innovative treatments, healthcare system infrastructures and to improve diagnosis for these patients.

THE EU OMP REGULATION HAS BROUGHT ADVANCES FOR RARE DISEASE PATIENTS

Today, the situation of rare disease patients has significantly improved compared to two decades ago. Rare diseases have received increased attention by a growing number of medicine developers and the number of authorised products has increased from below 10 in 2000 to close to 200 in 2021.[4]

This increase is in large part attributable to the OMP Regulation[5] that was put into place in the year 2000 to set incentives that could attract more development in rare diseases. These incentives include a 10-year market exclusivity period, protocol assistance from the European Medicines Agency (EMA), fee reductions for regulatory procedures, and EU-funded research for OMP development. The Regulation works in tandem with national level health policies, which determine the market access pathway, pricing, and healthcare system infrastructure for delivery of the medicine to patients.

Importantly, for a medicine to benefit from the incentives under the Regulation, it is not sufficient for the addressed condition to be rare (i.e. to have a prevalence of 5 in 10,000 or less) but the treatment must also bring significant benefit over existing treatments. This ensures that only development that brings true benefits to patients compared to existing treatments is incentivised. A continuous focus on addressing unmet needs has therefore been built into the Regulation from the start.

BIG GAPS STILL EXIST ON ADDRESSING RARE DISEASE PATIENTS' NEEDS

Despite significant improvements, unmet needs still persist among rare disease patients. An obvious unmet need are the 95% of rare diseases that today have no authorised treatment. Prevalence estimates suggest that these 95% affect a small fraction of the rare disease patient population. In fact, almost 85% of rare diseases have a prevalence of less than 1 in 1,000,000.[6] This means that these 95% of diseases are likely to be the extremely rare diseases that only affect few patients scattered across Europe.

Importantly, unmet needs of rare disease patients go far beyond the 95% and cover at least four further dimensions:

First, within a disease area for which authorised treatments exist, these treatments may not be effective for specific patient groups and may not be transformative or curative. Second, even where effective treatments are available, they might not make it to the patient because the patient does not get diagnosed in the first place. Third, patients' opportunities to access OMPs across European countries are still unequal, with patients in some countries facing no or significantly delayed access to a specific authorised treatment. Fourth, beyond issues with diagnosis and access, patients still need to navigate a fragmented healthcare system during their patient journey. This creates a burden also on their caregivers who often need to invest significant time and resources to coordinate care. Addressing unmet needs therefore means devising policy solutions that allow for progress to happen across all of these dimensions.

If Europe manages to address these unmet needs, a child born with a rare disease 20 years from now will be in better place than current rare disease patients: this child and his/her parents will be able to get a swift diagnosis, will have at least one treatment available that works for him/her and will be in a position to access the treatment and specialist doctors and care no matter where he/she lives in Europe. Moreover, his or her voice will be listened to throughout the entire patient journey and medicine lifecycle.

1) European Commission (1999), article 3, recital 1(a) // 2) Wakap et al. (2020), pages 165 and 168 // 3) EURORDIS (2017a), page 8-9 // 4) European Medicines Agency (2021a), page 14 and Aartsma-Rus et al. (2021), Figure 2 // 5) European Commission (1999) // 6) Wakap et al. (2020), page 165

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The last OMP Regulation was in place for more than two decades and we must assume that the revision of the OMP Regulation will set the policy framework for at least the next 20 years. Hence, the time is now to develop a framework that will deliver on unmet needs by tackling the barriers that still hamper innovation and patient access and that leaves Europe below its potential for addressing rare disease patients' needs. This report outlines seven recommendations, one for the revised OMP Regulation and six going beyond the Regulation.

WHAT THE REVISED OMP REGULATION MUST DO

Latest research shows that barriers to addressing unmet needs exist along the OMP lifecycle starting from insufficient basic research, over issues with identifying the best evidence base for bringing medicines through regulatory and market access processes, to lack of equal patient access to medicines across Europe. To address these barriers, the existing legislative tools within scope of the OMP Regulation have been insufficient.

Yet, much of the policy debate today focuses on recalibrating these existing policy incentives to direct innovation towards greatest unmet needs. The European Commission's proposals of more restrictive criteria for orphan designation and a modulation of incentives according to the type of OMP developed pursue this direction. We have analysed the nature of the barriers to OMP development and access today and the relative potential of currently proposed solutions to incentivise more development of and access to OMPs in areas of unmet need. Based on our analysis, we make the following seven recommendations.

Recommendation 1
Evolve the current incentive framework by maintaining current orphan designation thresholds, but allowing for recalibration of incentives.

Our analysis of orphan developers' incentives shows that the basic set-up of the Regulation, with an orphan designation threshold of 5 in 10,000 and coupled with a significant benefit requirement, has worked to attract investments into rare diseases and should be maintained. This is first and foremost because the orphan designation is an important label for developers in this space to continue to attract investments and will allow to drive innovation into areas of unmet need.

At the same time, there is room for a recalibration of the incentives attached to the orphan designation to reflect the heterogeneity of the rare disease landscape today and to focus resources where they are most needed. This means increasing incentives in areas that have so far attracted insufficient investment, and recalibrating incentives in well-defined areas where this will not have an impact on the progress in standard of care.

However, increasing incentives cannot only focus on existing tools, such as adding number of years of Market Exclusivity for OMPs in areas where little R&D happens. This is unlikely to have a significant impact on the 95%. Instead, Europe needs a step-change in the way we approach all stages of the development lifecycle from basic research to patient access.

Our analysis shows that the remaining barriers today are of a different nature than they were two decades ago: they emerge in the interplay between two or more actors with markedly different success criteria. These types of challenges change the game for the type of solutions that will prove effective going forward. Effective solutions must bring several actors around one table with a shared goal. Effective solutions therefore require partnerships.

EFFECTIVE SOLUTIONS BEYOND THE OMP REGULATION REQUIRE PARTNERSHIPS AS AN INTEGRAL PART OF THE OMP LIFECYCLE

Partnerships are driven by the prospect of greater value creation for the individual party than an individual actor would be able to create alone. Partnerships have the potential to bring up the level of basic research ready for development. They also have the potential to improve the chances of success for an OMP that was successful in the clinical development phase to make it through regulatory approval and market access to patient delivery. Partnerships can also help with Europe's goal of broader, swifter and more equal access to medicines across member states. We therefore recommend for Europe to make partnerships an integral part of the OMP lifecycle, with a strong anchor at the policy level. We find that six partnership-based solutions will help tackle barriers along and across the development lifecycle, see page 8.

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Many of these solutions build on current initiatives and structures. We propose to lift those initiatives and structures to partnerships at European and national level. Compared to current solutions, these partnerships will require leadership from EU and national policy makers that engages all actors across the OMP lifecycle (researchers, developers, payers, regulators, patients). Finally, they ask Europe to go beyond a perspective on mutual learning to partnerships designed to deliver tangible benefits at scale for all involved.

Recommendation 2
Set up a public-private partnership for basic research funding in rare diseases

The lack of basic research is a key barrier to development within the 95%.[1] Boosting basic research requires more and smarter funding that leverages data and the integration of research communities across Europe. This ensures more effective and targeted research for every euro spent. We therefore recommend a Private Public Partnership (PPP) fund focused on rare diseases to boost funding of basic research in underserved areas integrating learnings from platforms such as IMI, IHI and the European Joint Programme on Rare Diseases. Here, European Reference Networks (ERNs) have the potential of becoming an important platform and infrastructure.

Recommendation 3
Create an early evidence partnership between developers, regulators and payers

A major barrier to innovation in rare diseases is the lack of clarity on requirements for the evidence needed to get the treatment approved by regulators and to demonstrate value at the market access stage. Early, iterative dialogues between developers, EMA, HTA bodies and payers that follow a partnership logic will allow making feasible plans for the evidence required at different stages of the lifecycle and therefore increase predictability for all. We therefore propose an early evidence partnership between developers, EMA, HTA bodies and payers that could build on and integrate learnings of ongoing programmes like the EMA-EUNetHTA parallel consultation, Impact HTA or the UK ILAP.

Recommendation 4
Develop European best practice for value-based contracting to unlock wider adoption across Europe

The pricing of innovative treatments in the face of uncertain evidence on effectiveness often becomes a source of tension between pharma developers and payers and leads to a situation where too few OMPs are reimbursed for a too small set of patients, thereby hindering patient access. Innovative, outcome-based payment models (often called 'value-based' contracting) are an effective a way of better sharing the risk between actors and making sure that budget concerns do not get in the way of the patients receiving the medicine. However, today, these models are not sufficiently exploited in the European market access landscape and insufficient experience with these models hampers their take-up.

We therefore propose for EU and national level policy makers to develop, together with payers and industry, best-practice guidebooks for value-based contracting. These will serve to lower barriers for engaging in these partnerships and encourage their widespread use across EU member states. They should also build on real-world evidence, see recommendation 6.

Recommendation 5
Create a European forum to develop equity of access solutions

Rare disease patients across Europe have unequal opportunities to access available therapies depending on where they live.[2] While innovative payment models and early evidence dialogues have the potential to support broader and faster access to medicines across Europe, they may not be sufficient to solve access issues in the least wealthy EU countries. Here, lack of access is also caused by issues around the affordability of treatments and poor healthcare system infrastructure where the lack of diagnosis and experts prevent patients from getting the needed treatment.

Rules directed at only one party, e.g. an obligation for pharma developers to launch, are unlikely to solve the issue with unequal access because the reasons underlying it are many and complex and

1) Aartsma-Rus et al. (2021), page 7 // 2) IQVIA (2021), page 19

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require several actors to work together. We therefore recommend a European forum for equity of access solutions that could focus on two key measures: first, provided there is solidarity among EU member states and a change in the current approach to issues like International Reference Pricing and parallel trade, tiered-based pricing can contribute to better accessibility and affordability for OMPs reflecting the economic differences across the 27 EU member states. Second, partnerships that strengthen the healthcare and diagnosis infrastructure in the concerned countries could ensure that differences in ability to get diagnosed are decreased. Here, The Global Commission to end the diagnostics odyssey for rare disease children can lend inspiration.

Recommendation 6
Create trust in RWE through a European learning network

Data plays a crucial role for OMP development, from basic research, over clinical development to regulatory approval and market access. The unique issue for rare disease development is thereby often that clinical trials often cannot be conducted as per the common Double Blinded Randomised Controlled Trial standards or that standard thresholds for clinical significance cannot be met[1]. An obvious solution for this problem is to complement any evidence from clinical settings with data from the real world in order to generate so-called real-world evidence (RWE). While developers and other bodies collect a lot of this data already, it is not systematically exploited in the European regulatory and market access processes, as it is not a source of evidence that has traditionally been utilized in marketing authorization applications (MAAs). To harness this potential, we propose a European learning network based on partnership principles that implements the use of RWE into the policy framework. Such a network could build on the many initiatives, such RWE4Decisions, that already provides for mutual learning in this space, but will go further by developing one European common practice of integrating RWE.

Recommendation 7
Integrate patient voices across the OMP lifecycle

The voice of patients is vital at all stages of the OMP lifecycle because patients are the ultimate recipients of treatments and an important source of knowledge and data both for the initial development phase of a treatment and for its further development. Currently, procedures and data systems do not capture the patient perspective sufficiently and leave the potential of patient data under-utilised. Involving patients and patient organisations more will allow developers, regulators and payers to make better decisions all along the lifecycle. We therefore propose to build on existing initiatives such as PARADIGM, EUPATI and EURORDIS Community Advisory Board Programme, to develop concrete, data-driven measures for engaging patients and integrating patient data at different decision-points.

WHAT NEXT: RARE DISEASES AS A PUBLIC HEALTH PRIORITY FOR EUROPE

If Europe could make this partnership model work, it could put the region in a leading position for OMP development. Designing partnerships as an integral part of the OMP development lifecycle is taking Europe on a path for more effective but also more complex solutions. Setting them up and making them work will therefore require a high level of leadership, dedication and resources by all, but most importantly building a high level of trust between all stakeholders. To support such a joint effort, rare diseases need to be considered a public health priority by EU and national policy makers. The joint efforts in fighting the Covid pandemic have taught us that this works.

1) Equator Network (2023)

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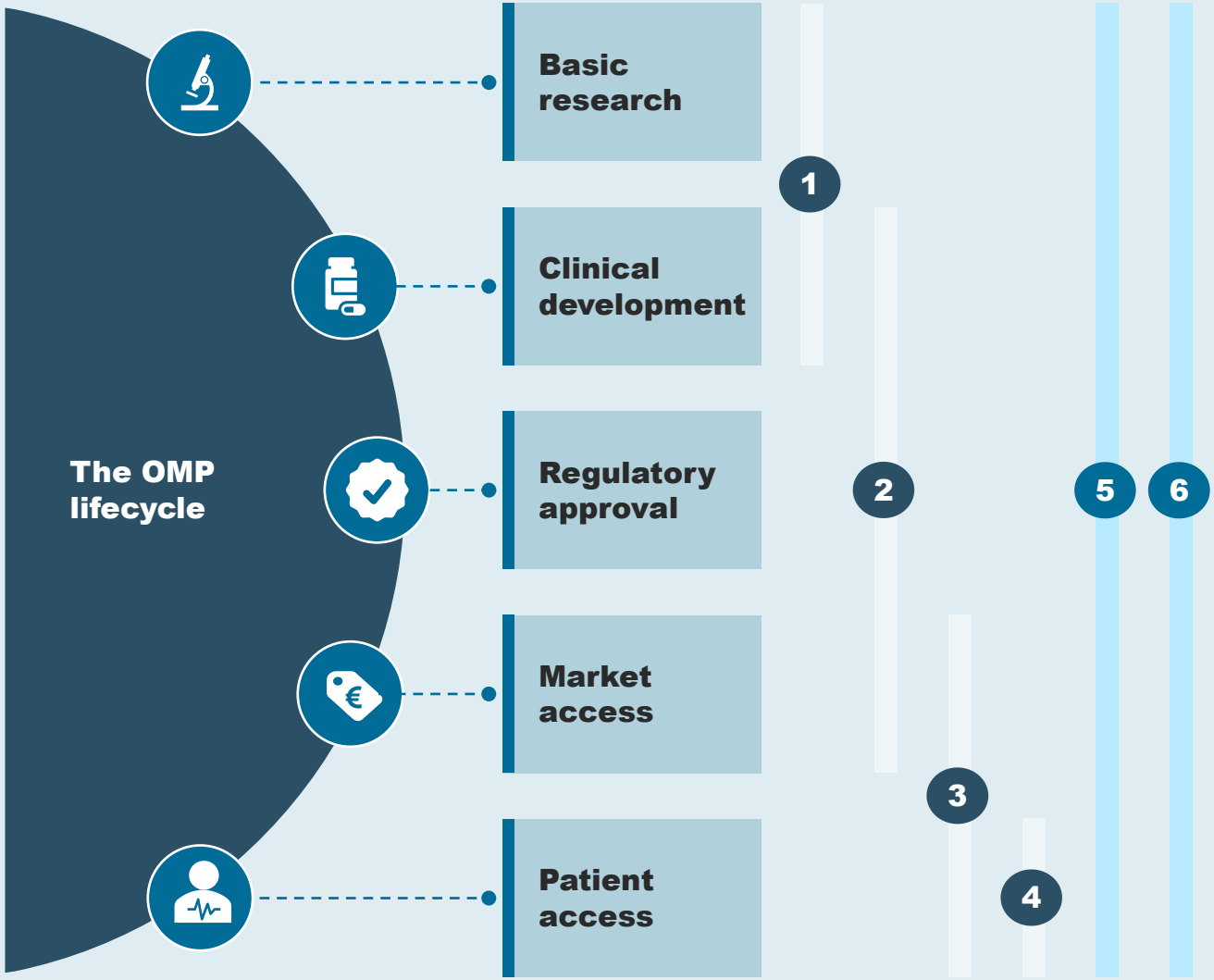
Six partnership-based solutions will help tackle barriers along and across the OMP lifecycle



1. Set up a public-private partnership for basic research funding in rare diseases
2. Create an early evidence partnership between developers, regulators and payers
3. Develop European best practice for value-based contracting to unlock wider adoption across Europe
4. Create a European forum to develop equity of access solutions
5. Create trust in RWE through a European learning network
6. Integrate patient voices across the OMP lifecycle

List of acronyms

BBB	Blood-brain barrier
CF	Cystic Fibrosis
CNS	Central Nervous System
DMD	Duchenne Muscular Dystrophy
EFPIA	European Federation of Pharmaceutical Industries and Associations
EJP RD	European Joint Programme on Rare Diseases
EMA	European Medicines Agency
ERN	European reference network
ERT	Enzyme replacement therapy
EU	European Union
EUCOPE	The European Confederation of Pharmaceutical Entrepreneurs
EUnetHTA	European Network for Health Technology Assessment
HAE	Hereditary Angioedema
HTA	Health Technology Assessment
RCT	Randomised Control Trials
RoW	Rest of the world
RWD	Real-world Data
RWE	Real-world Evidence
SOC	Standard of care
SPC	Supplementary Protection Certificate
IF	Intestinal failure
IRDiRC	International Rare Diseases Research Consortium
MA	Marketing Authorisation
MPS	Mucopolysaccharidosis
NBS	Newborn screening
OD	Orphan Designation
OMP	Orphan Medicinal Product
PPP	Public-private partnership
R&D	Research and development
rNPV	Risk-adjusted net present value
WGS	Whole Genome Sequencing

Glossary of key terminology in this report

Incentive	Any measure meant to promote the development of medicines to treat rare diseases
Indication	The labelled use of a specific drug (an OMP) for treating a particular disease
Investment Case	Assessment of the viability of an investment from an investor's perspective
Marketing Authorisation	The approval to market a medicine in European Union Member States
Market Exclusivity	10-year period after the marketing authorisation of an orphan medicine when similar medicines for the same indication cannot be placed on the market
Orphan Designation	A status assigned to a medicine intended for use against a rare condition. The medicine must fulfil certain criteria for designation as an orphan medicine so that it can benefit from specific incentives
Return on investment	A measure for the amount of return on a particular investment, relative to the investment's cost. Ex-ante ROI: estimated return that investors can expect to earn from an investment at the end of a specific period. Expected ROI: the anticipated profit or loss on an investment that takes into consideration systematic and unsystematic risk
Tiered pricing	A pricing method used by companies to differentiate the prices of their products and services based on specified target markets
Real-world data	Observational data not gathered from randomised controlled trials
Real-world evidence	Evidence on the usage and potential benefits or risks of a medical product derived from analysis of (real-world) data
Significant benefit	A criterion that must be met to qualify for Orphan Designation (by the EMA) if a satisfactory (authorised) method of diagnosis, prevention or treatment of a condition concerned already exists. In order to be of significant benefit, the medicine must demonstrate comparative efficacy and effectiveness and be of major contribution to patient care.

1 THE CHALLENGE

Rare diseases are a public health priority for Europe

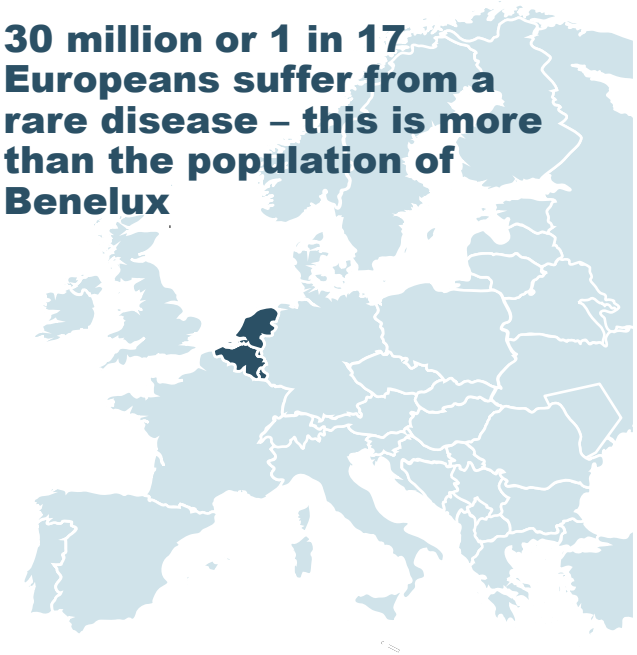
Rare diseases are an important health issue for Europe

Rare diseases are diseases that only affects a few people in a population. In Europe, a diseases is classified as rare when it affects no more than 5 in 10,000 individuals.

Rare diseases are a common health issue

While each individual rare disease concerns only few patients, collectively rare diseases affect a considerable share of the EU population. Current estimates indicate that up to 30 million EU citizens may be living with a rare disease[1]. This is more than the total population size of the Benelux union and represents approximately 1 in 17 Europeans. Hence, rare diseases are a common health issue and therefore need to be considered a **public health priority.**

30 million or 1 in 17 Europeans suffer from a rare disease – this is more than the population of Benelux



Importantly, estimates of the total number of people affected by rare disease are uncertain. This is in large part due to the difficulty of diagnosing rare diseases. Consider for example a family doctor that diagnoses and treats patients in her community. When she encounters a child with symptoms that could be caused by many diseases, she would likely not pinpoint a very rare disease as the first possibility. Moreover, registries where she could seek input might not be informative as they are often not up to date. For these reasons, approximately 50% of rare disease patients remain undiagnosed today[2], and 25% have waited anywhere between 5-30 years for diagnosis[3]. On top of that, misdiagnosis is very common - resulting in insufficient course of care[3].

We know of more than 6,000 rare diseases

Currently, the scientific literature points to over 6,000 identified rare diseases of which more than 70% are of genetic origin, and many are chronic and life-threatening.[4] The true number of rare diseases is still unknown, with some sources saying that there could be more than 10,000.[5] In addition, rare diseases are being identified at unprecedented rates with 250–280 new diseases described annually.[6]

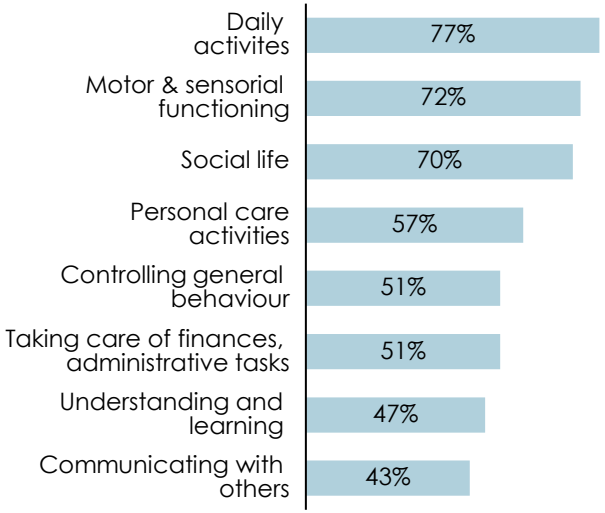
Rare diseases severely affect patients' and carers' quality of life

The chronic and life-threatening nature of many rare diseases means that they significantly impact patients' quality of life. The impact of living with a rare disease goes far beyond physical health issues, affecting all aspects of patients' lives – from education, employment, social life and planning for the future.

A 2017 EURORDIS survey revealed the pervasiveness of the impact of living with a rare disease, with 77% of patients stating that they have difficulties performing daily activities and 70% mentioning that their social life is impacted by their disease, see Figure 1.

Figure 1. Share of surveyed patients experiencing difficulty

Percent of total respondents



Source: EURORDIS (2017a), graph 1

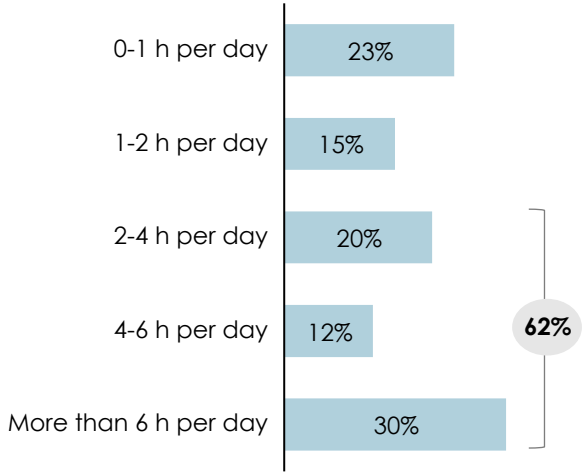
The impact is even worse for *undiagnosed* rare disease patients for whom effective medical and social care is not available. For these patients, the health outcomes can be the most severe and they commonly report feelings of exclusion, isolation and stress[7].

1)Wakap, et al. (2020), 168 // 2)) Graessner et al. (2021) // 3) Lancet (2009) and EURORDIS (2016). 41% // 4) Wakap et al. (2021), page 165 // 5) Haendel et al. (2020) // 6) Dawkins et al (2018), page 11 // 7) SWAN UK, the Wilhelm Foundation, EURORDIS, RVA, CORD, ASrid, NORD (2016), page 3

Rare diseases are an important health issue for Europe

Rare diseases also place a heavy burden on the **lives of patients' caregivers** who are often their close family and overwhelmingly (at 64%) the patients' mothers[1]. The time spent by carers on care-related activities is substantial, with 62% of surveyed carers spending above 2 hours and 30% spending more than 6 hours per day helping the patient, see Figure 2.

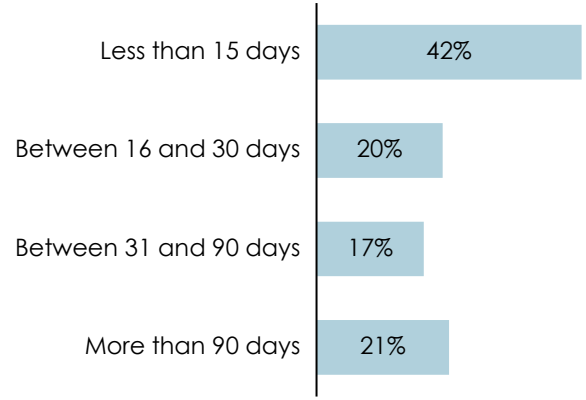
Figure 2. Time spent by caregivers on caring for the patient
Percent of total respondents



Source: EURORDIS (2017a), graph 4

Finally, the **work lives** of both carers and patients are significantly impacted: 35% of patients and carers surveyed by EURORDIS declared being engaged in part-time employment rather than full-time employment, which is significantly lower than the 17% average across the general population[2]. Moreover, from those that do work, 21% of respondents stated to have been absent from work more than 3 months in one year, for example due to physician appointments, see Figure 3.

Figure 3. Time spent by caregivers on caring for the patient in a year
Percent of total respondents



Source: EURORDIS (2017a), graph 11

These figures alone demonstrate that suffering from a rare disease puts the individual and their caregivers on a poorer path in life – financially and socially.

The socio-economic costs of rare diseases are high

Rare diseases place a significant cost not just on patients and their caregivers but also on society[3]. This includes significant healthcare expenditures through hospitalisations, physician visits, and the cost of medicines as well as socio-economic losses through lost educational and labour market participation for both the patients and their caregivers[4].

No comprehensive research on the total cost of rare diseases for European societies exists[5]. Most cost-of-illness studies are disease-specific and are limited in the field of rare diseases[6]. A study from 2019 indicates that the cost of 379 rare diseases on US society amounts to a staggering $997 billion a year, with total labour market productivity losses amounting to approximately 44%[7]. In Europe, the annual cost, including both direct and indirect costs, associated with 10 rare diseases ranged between 3,937-209,420 EUR (2010 values) per patient across 8 different countries.[8] Departing from these examples, the total socio-economic cost for Europe from rare diseases is likely to be substantial.

1) EURORDIS (2017a) // 2) Ibid. // 3) Yang et al. (2022), see also Every Life Foundation for Rare Diseases (2021) // 4) Ibid. //5) Delaye et al. (2022) // 6) Pérez et al (2021) // 7) Yang et al. (2022), see also Every Life Foundation for Rare Diseases (2021) // 8) López-Bastida et al. (2016)

Today, rare disease patients are better off than 20 years ago

Today, the outlook of rare disease patients in Europe is more promising than two decades ago. Next to a higher level of awareness for and recognition of rare diseases, Europe has developed a vibrant research and development community dedicated to improving the lives of rare disease patients. Five main achievements are worth highlighting.

1. The number of authorised orphan medicines has increased

Since the year 2000, the R&D activity in rare diseases and the number of available authorised treatments in Europe have markedly increased. Since then, over 2,200 medicines have obtained an orphan designation in the EU and more than 190 orphan medicines have been authorised[1]. Between 2015 and 2020 alone, the number of authorised OMPs grew by 81%, see Figure 4.

This growth has been supported by a rise in R&D activity: between 2006 and 2016, EU clinical research activity in rare diseases grew by 88% annually – more than any other comparable region in the world[2].

2. The number of companies with rare disease focus has soared

Next to the involvement of other stakeholders (researchers, patients), the increase in the number of OMP-focused companies has supported the rise in development. In the year 2001, only three pharmaceutical companies had orphan-designated authorised products on the market. Since then, more than 120 unique sponsors have received marketing authorization for OMPs in Europe[3].

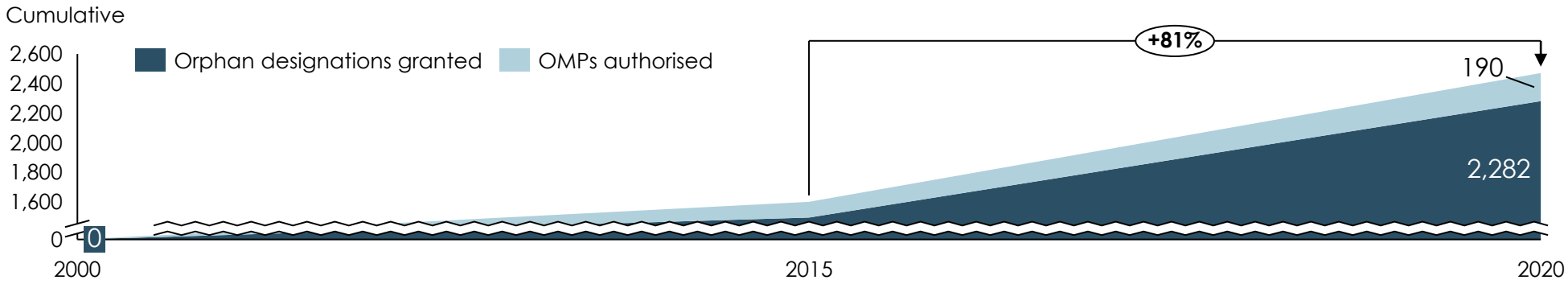
3. The work of patient groups has increased awareness

Digitalisation and social media have played a role in connecting rare disease patients and in fuelling the growth of patient groups and communities. Rare disease patient groups, which are becoming increasingly more formalised in their engagement with researchers and pharmaceutical industry[4], have played a significant role in raising awareness and directing attention to rare diseases.

4. Europe's rare disease ecosystem delivers continuous innovation

Innovation activity in the rare disease space drives constant improvements beyond existing standards of care. Many of the current OMP development projects in the global pipeline use new technologies such as cell and gene therapies[5]. In fact, a survey of approximately 180 expert physicians identified that over a third of the most transformative medicines over the past few decades were developed for rare diseases[6]. This means that, even in disease areas with high R&D activity, unmet medical needs continue to be addressed with better, more effective treatments.

Figure 4. OMP applications submitted, designations granted and authorised



Source: European Medicines Agency (2021a)

1) European Medicines Agency (2021a) // 2) Pugatch Consilium (2019), page 8 // 3) EURORDIS (2021) // 4) Health Europa (2019) // 5) America's Biopharmaceutical companies (2020) // 6) EFPIA (2021)

The main driver of the success since 2000 has been the EU policy framework for orphan medicine development

The successes in the development of authorised OMPs have not occurred by chance. A good twenty years ago, policy makers at EU and national level put in place a policy framework aimed at increasing the number of authorised treatments available to and accessible by rare disease patients across the EU. Similar initiatives for the development of OMPs were introduced in the US and Japan in 1983 and 1993 respectively.

Introduced in the year 2000, the **OMP Regulation** aimed at ensuring higher availability of OMPs by attracting more development via several EU-level policy incentives[1]:

- A ten-year market exclusivity (ME) period, providing protection for designated OMPs from other similar medicines.
- Protocol assistance from the European Medicines Agency (EMA)
- Fee reductions during the market authorization (MA) process
- EU-funded research for OMP development aimed at increasing research in rare diseases.

The incentives are only available for designated OMPs. To qualify for an orphan designation, a medicine must be intended for the treatment, prevention or diagnosis of a disease that is life-threatening or chronically debilitating and the disease must not affect more than 5 in 10,000[2]. Moreover, the medicine must be of significant benefit to patients if satisfactory (authorised) methods of diagnosis, prevention or treatment of the condition concerned exist.

Although not all OMPs authorised today can be directly attributed to the OMP Regulation, recent estimates indicate that more than half of OMPs authorised between 2000-2017 were developed as a result of the OMP Regulation[3].

In addition to the OMP Regulation, other important rare disease development-focused EU and national initiatives exist today. Some notable examples include the European Reference Networks (ERNs), the Solve-RD initiative and the European Joint Programme for Rare Diseases (EJP RD).

In facilitating collaboration, exchange of knowledge and funding in rare diseases, these initiatives have increased the overall focus on rare diseases and shaped the current policy framework. Moreover, these initiatives have laid the ground for a R&D ecosystem for rare diseases in Europe, by brining together stakeholders from across the community, including academia, the pharmaceutical industry, policy makers, patient groups and clinicians.

The **revision of the OMP Regulation** is a moment to take stock of what this framework and ecosystem have achieved and where more work must be done.

> The EU Orphan Regulation has contributed to important strides in the field of rare diseases and development of orphan medicines. Since the Regulation was introduced, more products have come on the market. There is also a promising pipeline of products under development, that may bring real value to patients for whom currently no treatment options exist."
>
> *Source: European Commission (2019)*

1) European Commission (1999, 2020) // 2) European Medicines Agency (2021). Orphan Designation: Overview // 3) Dolon (2020)

The challenge for the rare disease community today is to tackle remaining unmet need

Despite the clear positive impact of the OMP Regulation and other rare disease-focused efforts in Europe, the needs of European rare disease patients are still far from met. Across rare disease patients, unmet needs exist along five different dimensions:

1. **Lack of authorised treatment**
2. **Lack of effective, transformative or curative treatment**
3. **Lack of developed care support system**
4. **Lack of support for caregivers**
5. **Lack of or delayed access to treatment**

1. Lack of authorised treatment

Although the number of authorised OMPs have increased significantly, the OMP Regulation has not achieved consistent investment in and development of OMPs across diseases. Today, 95% of rare diseases remain without authorised treatment[1], see Figure 5. While this seems like a large number, the lack of authorised treatment is, however, especially a problem among the very rarest diseases. In fact, roughly 80% of rare disease patients suffer from 149 of the most prevalent rare diseases[2], many of which have authorised treatment options[3].

80% of rare disease patients suffer from 149 of the most prevalent rare diseases

However, addressing the 95% of rare diseases then also means tackling areas where research and development is particularly difficult due to the extremely low number of affected patients. Moreover, although research and development in rare diseases is constantly expanding in scope, much of the activity clusters around a few therapeutic areas and diseases – leaving other areas unaddressed. Between 2000-2019, 67% of OMP designation applications targeted the same three disease areas, see Figure 6. Between 1999 and 2017, among rare diseases with registered clinical trials, six (0.4%) diseases accounted for over a thousand registered clinical trials while 28% had only one registered trial globally[4]. For some rare diseases there is no ongoing clinical activity at all: more than 80% of the known rare diseases (listed on Orphanet) have no record of clinical trials[5].

The first challenge for Europe is therefore to spur both research and development activity to the extremely rare and complicated diseases where no authorised treatment exist.

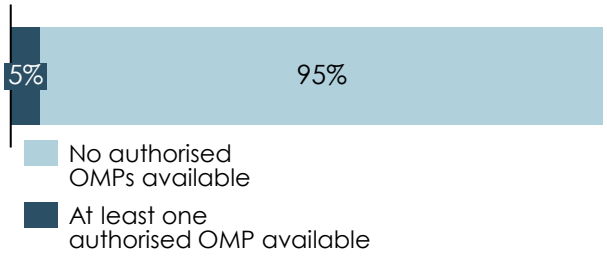
Example: Sanfilippo Syndrome

Sanfilippo syndrome, or MPS III, is a rare genetic disorder, that affects the brain and begins in early childhood. MPS III eventually causes a vegetative state and a premature death. Due to the early onset and severity of the disease, most patients never reach adulthood. Today, no authorised treatments are available that could reverse or slow down the progression of the diseases. One main reason for this is the difficulty that early onset and fast disease progression present for recruiting patients into clinical trials. The neuronal nature of the symptoms of Sanfilippo Syndrome also makes it difficult to treat patients with other forms of care.

Sources: Pearse and Lacovino (2020) and US National Library of Medicine (2019)

Figure 5. Share of rare diseases with and without authorised treatment

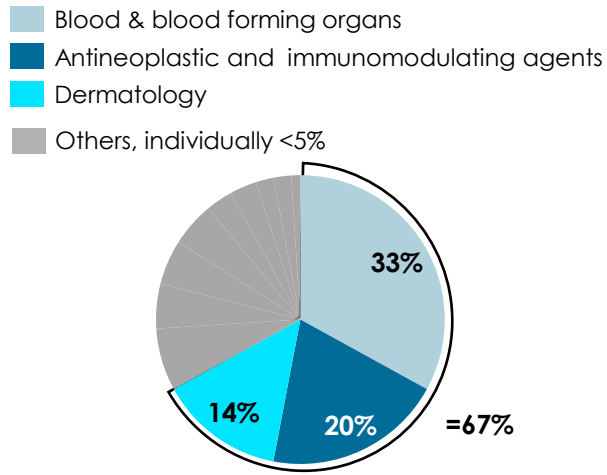
Percent of all known rare diseases



Source: European Commission (2020)

Figure 6. Share of ODD applications per disease area

Percent of all ODD applications, 2000-2019



Note: Based on OMP applications between 2000 and 2019.
Sources: EMA (2019)

Notes: 1) Note that there may be treatments available for some of the 95% of rare diseases without an authorised OMP such as off-label prescriptions. // 2) 79% of rare disease patients suffer from 149 of the most prevalent diseases, with prevalence between 1 and 5 in 10,000, see Wakap et al. (2020), Figure 4 // 3) Out of the 142 EMA approved OMPs by 2017, 43% (61) are indicated for a rare disease with prevalence between 1 and 5 in 10,000, see European Commission (2020), Figure 5. The number of rare diseases covered might be lower since more than one OMP could be approved for the same indication // 4) Sakate et al. (2018 // 5) Ibid.

The challenge for the rare disease community today is to tackle remaining unmet need

2. Lack of effective, transformative or curative treatment

Having one or more authorised treatment options does not imply that the needs of patients suffering from a given rare disease are met. In other words, unmet needs persist even within the 5% of rare diseases where an authorised treatment exists. This is because, in most cases, the treatment available is neither transformative nor curative, i.e. it does not yield full or partial disease stabilisation or bring about a health state where no further treatment is required for a period of years[1].

Moreover, the clinical manifestations of rare diseases are so complex and varied that a treatment that is effective for one sub-population may fail to meet the needs of another sub-population suffering from the same disease. Similarly, an effective treatment for a given treatable patient population today may become an ineffective treatment in the future as the disease develops.

The second challenge for Europe is therefore to ensure that innovation and development continue for those rare disease patients that have not yet received effective, transformative or curative treatment.

3. Lack of developed care support system

Even with effective treatment, the supporting system of care for a patient may be under-developed and represent an unmet need for patients.

Rare disease patients need more than just authorised effective treatments - from precise and timely diagnosis, over accessible expert physicians to efficient access to care in the healthcare system. For rare diseases, a key challenge is that existing knowledge often sits at geographically dispersed institutions and with a few disease specialists – and when the knowledge is not shared optimally, the result is that patients across Europe do not have equal standard of care or the same chance of receiving correct diagnosis2.

In addition, caregivers report a systemic lack of communication between different service providers when it comes to the care of rare disease patients. Often, caregivers therefore need to also undertake the role of coordinators and researchers of potential therapies2. Moreover, because rare disease patients need to engage with several healthcare contact points, often more than three on a monthly basis, receiving care becomes a very time-consuming and often financially burdening task, when counting lost work hours and cost of travel.

The third challenge for Europe is therefore to develop support systems that allow proper, well-coordinated patient care beyond the availability of medicines. While increasing the availability of OMPs has been the primary goal of the OMP Regulation, it should not be seen as the only objective of the continued development in this area.

Example: Cystic Fibrosis

Cystic fibrosis (CF) is one of the better addressed rare diseases, and advancements in antibiotics, nutritional and pulmonary therapies have significantly improved the health outcomes for patients with CF.

However, the needs of patients with CF are not considered "met", for instance, there is a lack of treatment that prevents or halts the progression of complications in the organs affected by CF. For instance, there are no effective treatments to address infection, inflammation, irreversible lung disorders and extra-pulmonary complications.

Therefore, the existing treatments are not necessarily the **best nor a broad enough option** for all CF patients suffering from the many manifestations of the disease.

Source: West and Flume (2018)

1) Faulkner et al. (2018)

The challenge for the rare disease community today is to tackle remaining unmet need

Example: Chronic hypoparathyroidism

Chronic hypoparathyroidism is a rare, debilitating endocrine disease. Due to its rarity, disease awareness is lacking and its symptoms are often unknown among primary care and specialised clinicians. This means that patients might remain undiagnosed for a long time after the onset of symptoms, seeing 6 physicians on average in connection with their disease.

Moreover, once diagnosis has been made, treatment plans and supporting care vary considerably across countries. For example, according to a recent patient survey, only 11% of diagnosed hypoparathyroidism patients in the UK regularly see a specialised endocrinologist.

Source: Hadker et al. (2014) and Shire (2017)

Example: Intestinal failure

Intestinal failure (IF) is the rarest form of organ failure and it prevents the body from being able to absorb nutrients, fluids and electrolytes needed for survival. This means that IF is a debilitating condition, forcing patients to receive intermittent parenteral nutrition, to endure long periods of hospitalisation and to undergo many medical procedures.

The ESPEN guidelines are the most recognised guidelines on the safe and effective management of IF, and include description of the necessary multidisciplinary care team and plan for IF as well as a blueprint for healthcare systems to design and deliver appropriate options for IF patients.

However, ESPEN guidelines are not consistently implemented across Europe, and only approximately 50% of European countries have national IF guidelines. As a result, IF patients may be forced to move away from their home country to receive care in another country with a more mature IF care infrastructure.

Sources: Staun et al. (2007), Pironi et al. (2016) and Takeda

4. Lack of support for caregivers

Many rare disease patients require daily support from their caregivers, which can be both mentally and physically taxing. While the needs of the patients are the key consideration in assessing unmet needs, it is essential to also understand and address the nature and extent of the unmet needs that exist among caregivers. Feelings of depression, anxiety, stress, isolation, worries about the future and lack of information are commonly reported among caregivers[1]. Those unmet needs affect caregivers' ability and capacity to provide care for rare disease patients - thereby affecting also the patient.

The fourth challenge for Europe is therefore to provide better, more comprehensive support and knowledge to caregivers to help them navigate the often lonely, difficult and emotionally taxing journey of caring for patients with a rare disease.

Example: Duchenne Muscular Dystrophy

Caregivers of patients with Duchenne Muscular Dystrophy (DMD), a severe, progressive and rare muscle-wasting disease with loss of strength, function, and flexibility in the muscles. DMD greatly impacts health-related quality of life and may result in reduced family function, anxiety, depression, pain, stress, sexual dysfunction, and lower self-esteem.

Moreover, caregivers of DMD patients report significant work life and productivity impacts as a result of hours devoted to informal care on a daily basis. These impairments are associated with national differences in DMD care, availability of financial and social support schemes and general cultural aspects.

Sources: Landfeldt et al. (2018) and Sinha et al. (2017)

5. Lack of or delayed access to treatment prevents patients from receiving best possible care

Since OMPs are launched individually in each member state, a union-wide market authorization (i.e. *availability*) does not ensure union-wide *accessibility* for patients.

Policy makers have identified the lack of equal access to authorised OMPs as an unmet need in Europe. In some member states, patients have either no access or significantly delayed access to a specific authorities treatment. EFPIA'S W.A.I.T. Survey by IQVIA (2021) finds that, as of April 2021, access[1] to the 47 OMPs that obtained an EMA MA between 2016 and 2019, ranged from 96% in Germany to just 2% in Latvia, see Figure 7 on the next page. For OMPs that did become accessible in this time span, the delay – defined as the gap between EMA authorisation and first accessibility – varies greatly.

1) IQVIA (2021)

The challenge for the rare disease community today is to tackle remaining unmet need

Median delay has been found to be just over 100 days in Germany to close to four years in Poland, see Figure 8.
The fifth challenge for Europe is therefore to improve the time to and level of access to OMPs for patients across the EU.

Figure 7. Orphan rate of availability in selected EU countries

Share of orphan drugs approved between 2016 and 2019 accessible

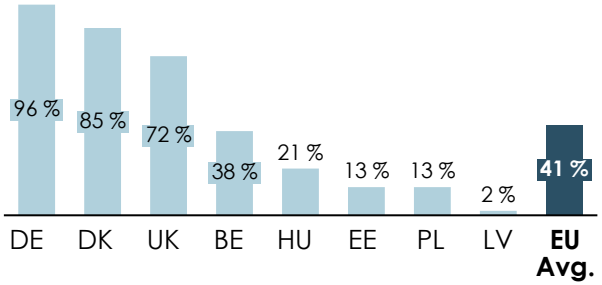
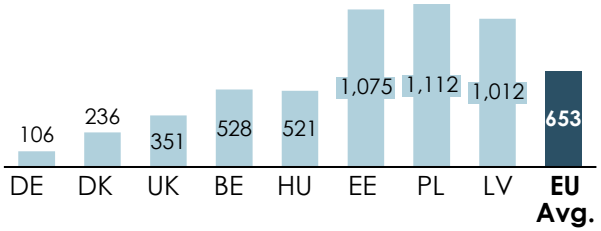


Figure 8. Average orphan drug delay in selected EU countries

Days until accessibility of orphan drugs approved between 2016 and 2019



Source: EFPIA (2020); EURORDIS (2017b)

Drivers of unequal access to OMPs across EU member states

Unequal access to OMPs across EU member states can be linked to various drivers, including: factors affecting market attractiveness for OMP developers, issues concerning pricing and payment of OMPs as well as regulatory processes.

MARKET ATTRACTIVNESS

1. The number of patients and the maturity of a given market are the main drivers of unequal access, as pharma companies first pursue markets with most demand.

2. Existing competition, both directly from currently accessible medicines and indirectly through the preferences of health professionals, may lead to delayed or missing launches.

3. Risk of **parallel exports** is a key consideration behind launch decisions, as companies may suffer from a degree of cannibalisation.

PRICING & PAYMENT

1. Country income increases both speed and probability of launch in a given country as it increases the ability and willingness to pay for novel treatments.

2. Healthcare budgets and priorities differ among EU member states, and as a direct consequence, the access to medicine will vary.

3. Reference pricing, both implicitly and explicitly, is an additional barrier to equal access to OMPs, as it leads to staggered launches, therefore causing delay.

REGULATORY PROCESSES

1. Time and costs of national reimbursement processes are two main barriers to equal access, and both vary greatly between member states.

2. Misalignment on evidence and value further delays or obstructs market launch, as HTA processes very often differ from one country to the next.

3. Slow patient delivery and insufficient diagnosis infrastructure within countries further delays the access to medicines beyond P&R processes.

Sources: OHE (2017); European Commission (2020)

The challenge for the rare disease community today is to tackle remaining unmet need

The time is now to shape a new policy framework for rare diseases

It is clear that, since its inception in the year 2000, the OMP Regulation has spurred the development of more life saving medicines to an underserved patient group. The core elements of the OMP Regulation are therefore important to build on when moving into the future. At the same time, it is evident that something more is needed to deliver quality of life improvements to the people living with rare diseases that have not experienced improvement in treatments up until now.

The last OMP Regulation has been in place for more than two decades. Hence, we must assume that the revision of the OMP Regulation will set the policy framework for at least the next 20 years.

Our common goal should be that a child born with a rare disease 20 years from now can get a swift diagnosis, can have at least one treatment available that works for them, can access the treatment and specialist doctors and care no matter where they live in Europe and can become an important partner in further development – to their own benefit and to the benefit of others. The big question now is therefore: **what does Europe need to do to achieve this goal?**

2 THE DIAGNOSIS

TODAY'S UNMET NEEDS REQUIRE NEW TYPES OF SOLUTIONS

The European OMP lifecycle is the backbone for innovation in rare diseases

For successful innovation and medicine development to happen and to reach patients, many actors need to engage with each other along the **OMP lifecycle**, see Figure 9.

It all starts with **basic research**. This is the groundwork that uncovers the basic disease mechanism. Without this knowledge, most often produced by academic researchers, companies are not well positioned to engage in own pre-clinical and **clinical development**. It is also at that point companies evaluate whether or not to take up development, based on a careful weighing of the balance between the expected return and the expected costs and risks involved in developing the medicine and bringing it to the market.

Once a positive decision has been taken, the developer will bring the OMP through a clinical development phase and, if that is successful, apply for market authorisation for the OMP from the European Medicines Agency (**regulatory approval**) for which they must demonstrate a positive risk-benefit balance of the OMP. The OMP will also undergo the assessment for maintenance of the orphan designation which is only granted if the condition meets the 5 in 10,000 prevalence threshold and no other similar authorised satisfactory treatment exists for the indication. If a similar authorised treatment for the same condition already exists, the developer is required to prove significant benefit of the OMP compared to the existing treatments.

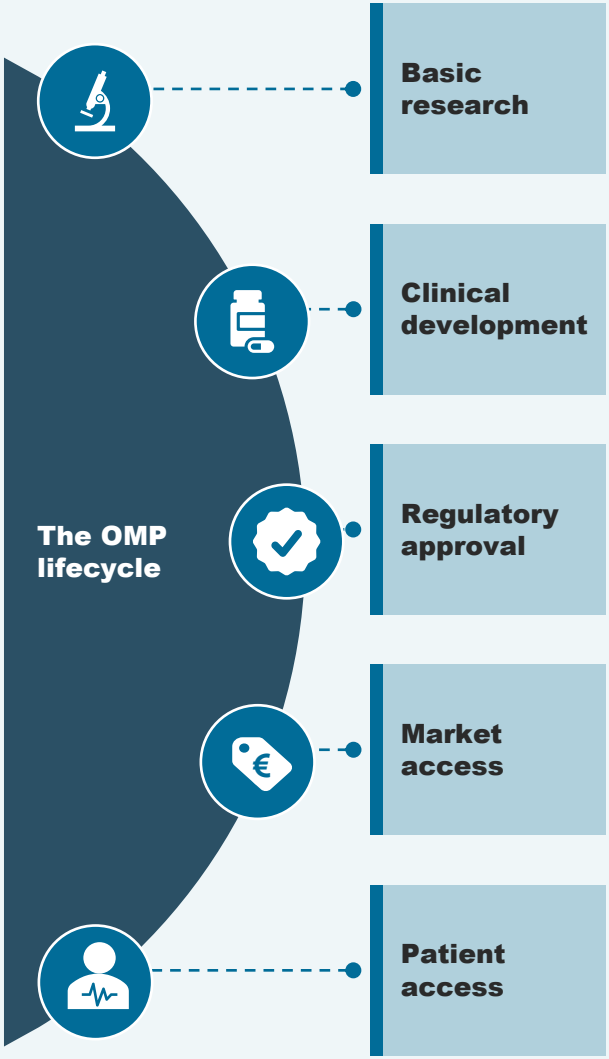
After marketing authorisation, the developer will launch the OMP through reaching pricing and reimbursement agreements in the different EU member states (**market access**), where both HTA bodies and payers are closely involved in securing price and reimbursement.

The final piece of the OMP lifecycle is **patient access**, which goes beyond the mere pricing and reimbursement agreement to ensure that the OMPs eventually reach patients. This requires physicians to prescribe the medicine including a suitable healthcare infrastructure fit for uptake, i.e. that supports diagnosis, treatment and follow-up of patients.

What happens along the OMP lifecycle strongly impacts the ecosystems' ability to deliver innovative medicines from basic research until patient access. In addition to other factors such as the potential therapeutic impact of a new medicine, the *expected* outcomes at each stage drive the developers' initial decision to move ahead with a development project.

Hence, when assessing how Europe can shape its policies to tackle unmet need, we therefore need to take a holistic look at the entire OMP lifecycle, understand which barriers exist and how they impact developers' decisions to go ahead (or not) with specific development projects.

Figure 9. OMP lifecycle



The OMP Regulation revision is an opportunity to address remaining barriers in the OMP lifecycle

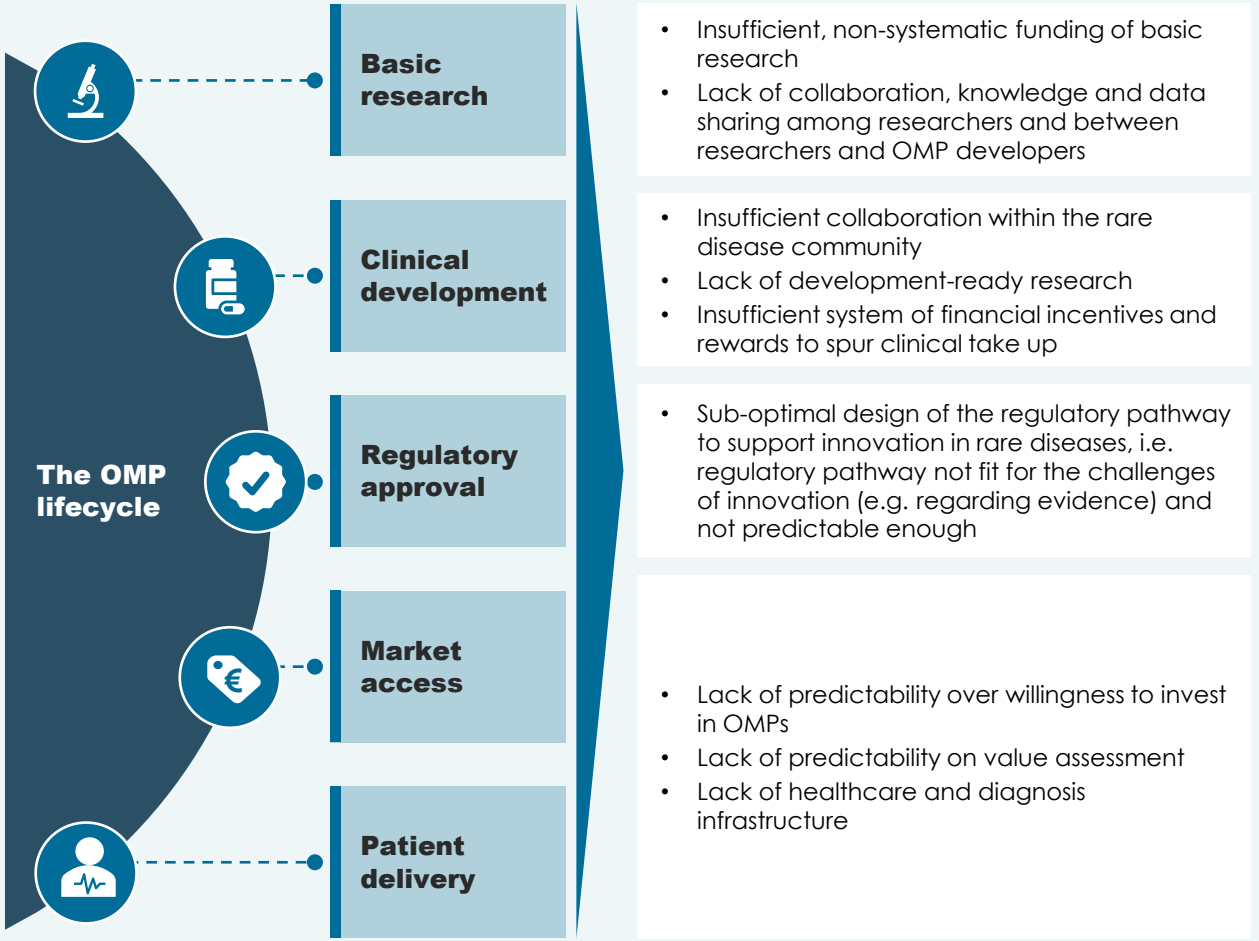
Several publications have investigated the barriers to broader medicine development and more equal patient access to medicines across Europe. The consensus of these publications is that barriers can be found all along the OMP lifecycle: from basic research over regulatory approval to market and patient access, barriers exist for delivering on unmet needs.

In particular, four main barriers need addressing to bring innovation and (timely) access where it is currently lacking[1], see Figure 10.

First, insufficient development in rare diseases can be traced back in large part to the basic research and clinical development stage, where basic research and understanding of disease mechanisms is still lacking or not mature enough to be taken up into development.[2] In particular in the extremely rare diseases, basic research may be non-existent with few or no researchers dedicating their attention to the disease and the animal/cellular models crucial to medicine development not being available. Without development-ready research as a point of departure, OMP developers cannot enter into clinical development of treatments.

Tackling unmet need in rare diseases therefore means increasing the amount of development-ready research available. The barriers to that are on the one hand insufficient funding and on the other hand a lack of collaboration, knowledge and data sharing among researchers and between researchers and OMP developers.[3] Increasing basic research therefore requires larger and more systematic funding efforts coupled with an R&D ecosystem with better collaborative infrastructures.

Figure 10. Barriers to tackling unmet need along the OMP lifecycle



1) Aartsma-rus et al. (2021) // 2) For further reading on the lack of basic research, see Aartsma-rus et al. (2021) pp. 4-11 // 3) Rare2030 (2021) p. 10

The OMP Regulation revision is an opportunity to address remaining barriers in the OMP lifecycle

Second, the current financial incentives offered to the OMP Regulation are by themselves insufficient to steer development within areas without authorised treatment.[1] In fact, protection from competition has so far proven to be an insufficient incentive for development of orphan medicines in the very rare disease space where the competition over the medicine's lifetime is a far weaker threat for the investment case than failure at the approval or market access stage. Hence, targeted financial incentives may be required on top of other measures to attract development into previously underserved areas.[2]

Third, the European regulatory pathway for approving orphan medicines and conferring orphan designation is not optimally designed to support innovation. The reason is that it does not always fit the challenges of innovating in orphan medicines, such as showing clinical significance with very small trial populations or well known end-points in a fairly unknown rare disease. Lack of collaboration with the access pathway further down the line creates risks that may discourage investments by companies.[3]

Fourth, the current heterogeneous market access landscape across Europe creates uncertainties about member states' willingness to invest in OMPs. Uncertainties on how to assess an OMP's added value currently and in the future, the supporting evidence and the needs of patients, lead to market access failures for innovative medicines or only partial or late launch in certain member states. Often reimbursement is entirely denied or restricted to only specific sub-populations.[4]

An underdeveloped healthcare and diagnosis infrastructure and tight healthcare budgets exacerbate this problem and lead to a situation where patients in particular in the least wealthy EU member states lack access to medicines, a lose-lose situation for all involved.

Novel solutions need to go beyond the current OMP Regulation

The revision of the OMP Regulation is an opportunity to address these barriers. The nature of the barriers and challenges demonstrates that solutions beyond the narrow remit of the OMP Regulation are necessary to tackle unmet needs. However, the current proposals by policy makers are concerned with recalibrating the current incentive framework. This can be seen when looking at the options for revision that are currently discussed.

1) Aartsma-rus et al. (2021) // 2) For a detailed analysis of the effect and need for financial incentives, see Dolon (2020) // 3) Aartsma-rus et al. // 4) OHE(2020)

The current policy focus on recalibrating the existing tools is insufficient to address unmet needs

Current policy proposals focus on a recalibration of the existing framework

The Commission suggests a revision of the orphan designation criteria and adjusting the main incentive, market exclusivity, to "direct the development in areas of greatest 'unmet medical need'".[1] This amounts to 'modulating' the incentive framework in such a way that it will not only add incentives in underserved areas but also take away incentives in areas where they are no longer needed.

Policy makers have advanced three types of proposals. First, policy makers seek for ways to restrict the orphan drug designation or the related incentives to a *smaller* set of OMPs. For the orphan designation, the suggestion is for instance to lower the applied prevalence threshold (currently set at 5 in 10,000) or to introduce a cumulative prevalence threshold for subsequent indications. This would mean that fewer OMPs would be eligible to be designated as an orphan drug compared to today. In the same vein, a further proposal is to modulate the level of incentives (e.g., the number of years of market exclusivity) for different categories of designated orphan medicines. Policy makers consider employing categories such as whether the OMP is innovative or not, repurposed or not, a subsequent indication, or whether it addresses a (pre-defined) unmet need. OMPs that are considered repurposed, not innovative, addressing a subsequent indication or not addressing an unmet need would thereby receive lower incentives (a shorter market exclusivity period).

Second, policy makers seek for ways of improving incentives for developing OMPs in areas that have so far been underserved, such as in areas where no (authorised) treatment exists. Currently, the Commission considers existing incentives within its toolbox (added years of market exclusivity, added scientific advice) as options to improve incentives.

Third, to achieve broader access to OMPs across Europe, policy makers would like to link the granting of existing incentives to an obligation for the developer to place the OMP on the market within all member states in need as soon as they receive a marketing authorization.[1]

Recalibration must support incentives to develop for unmet need

The recalibration of (or a modulated approach to) incentives is a way to reflect the heterogeneity of the rare disease landscape today where some disease areas attract more development than others. It allows for our society to focus resources where they are most needed. Successful recalibration of incentives means providing a framework where the incentives provided through policies are *just enough* to incentivise a developer to go into a specific disease area. This goes both for the developer addressing unmet needs within an area where authorised treatments already exist and a developer that brings the first authorised treatment to the market. Therefore, the current proposals of the Commission will need to be assessed as to how they will impact developers' incentives to continue investment or to go into new areas where no one has invested to date.

We have analysed the Commission's proposals in light of the existing barriers to OMP development. We also illustrate how the current policy proposals may affect the economic viability of developers' investments in the development of OMPs. We do so by means of a quantitative model of the effect of a proposed revision on two hypothetical orphan investment cases, see Box 1.

Box 1. Economic viability of OMP development

Next factors such as the unmet need of patients and the potential therapeutic impact of a new treatment, expected profitability plays a key role in OMP developer's initial investment decision. A company will engage in OMP development if the investment case is economically viable, i.e. if the expected return compensates them for the costs, time and risks of the development project. Therefore, it is useful to assess changes in the policy framework in terms of their impact on the expected profitability and investment incentives through their effect on costs, time and risks of OMP development projects across different disease areas and technologies.

In practice, this is a valuation exercise that can be conducted through standard valuation tool such as risk-adjusted NPV models (rNPV model). We have used an rNPV model to estimate the impact of possible revisions of the OMP Regulation on the profitability of two hypothetical OMP development projects: a more average rare disease and a very rare disease project, which differ in terms of prevalence and achievable payment level. The inputs to the model are based on literature studies and Takeda's experience.[2]

1) European Commission (2021) // 2) See Appendix for a detailed overview of the model inputs and assumptions.

The current policy focus on recalibrating the existing tools is insufficient to address unmet needs

Our analysis leads to two key findings:
First, to ensure a continuous investments in orphan medicine development, the basic set-up with an orphan designation based on a 5 in 10,000 should be maintained.

Second, while incentives provided through the OMP Regulation can be recalibrated according to well-defined categories, additional incentives must go beyond the old tool of market exclusivity to direct investment towards the 95% of rare diseases without authorised treatment. Here, a real step-change in the type of solutions is needed.

Our recommendation is therefore to evolve the incentive system put into place by the OMP Regulation and to seek measures that go beyond the current Regulation to address the 95%.

Maintain the basic OMP Regulation set-up with current orphan designation threshold

The basic set-up of the OMP Regulation, with an orphan designation (OD) and related incentives for designated orphan medicines, has visibly worked to attract investment in rare diseases, see Chapter 1. Importantly, a treatment does not receive an orphan designation purely based on the rare nature of the disease (5 in 10,000) but based on proof that it provides significant benefit over similar approved treatments for the same condition. This ensures that only those medicines that bring clear benefit to patients are rewarded and that newly approved orphan medicines continuously improve on the standard of care.

At first sight, the main benefit from the orphan designation are the incentives granted under the Regulation, such as the market exclusivity, scientific advice and fee waivers. However, the orphan designation also has an additional, even more important function: the 'orphan label' conveyed through the designation is a key factor for companies to attract investments. This is because it allows for the medicine to be 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. This higher payment per patient is required to recoup the upfront investment and risk taken given the small patient population. Some countries, such as Germany and France, orphan medicines even have special market access pathways.[1]

Given this link between the orphan label and market access conditions, the Commission's suggestion of lower or cumulative prevalence thresholds for orphan designation is likely to have far-reaching consequences on the investment in OMP development that go beyond the sheer loss of opportunity for scientific advice and market exclusivity.

First, any orphan medicine losing this orphan label will likely face substantially lower willingness to pay by key member states which through international reference pricing will spill over into other European and non-European countries. This may considerably dampen investment incentives. In our modelling analysis, we illustrate around an average OMP how the loss of the orphan label can lead to a substantial reduction in expected profitability, in our example of between 41 and 72% compared to a situation with orphan designation. Such a stark reduction in expected profits is likely to reduce investments, see Box 2.

Second, the proposed measure is likely to affect areas where unmet needs still exists. Even within the least rare of rare diseases, patients only have a single authorised treatment available or further development is required to meet the needs of a subpopulation. Such thresholds may therefore be counterproductive to policy makers' goals of tackling unmet needs.

Third, a cumulative threshold for subsequent indications may lead developers to focus their attention on the higher prevalence indications first and to refrain from developing the OMP for further lower prevalence indications. This would defeat the purpose of the revision to bring more development into the rarest of rare diseases. Moreover, the cumulative prevalence threshold currently considered by the Commission would affect the basic innovation cycle of OMP developers where known molecules are approved for further indications based on clinical research, which constitute economically good use of scarce development resources.

These aspect together mean that the downside of more restrictive criteria for orphan designation in the form of dampening investment where it would still be needed is likely to be larger than the upside. Maintaining a broad designation based on the current prevalence threshold will be important to continue attracting investments into OMP development for unmet need.

1) See OHE (2017)

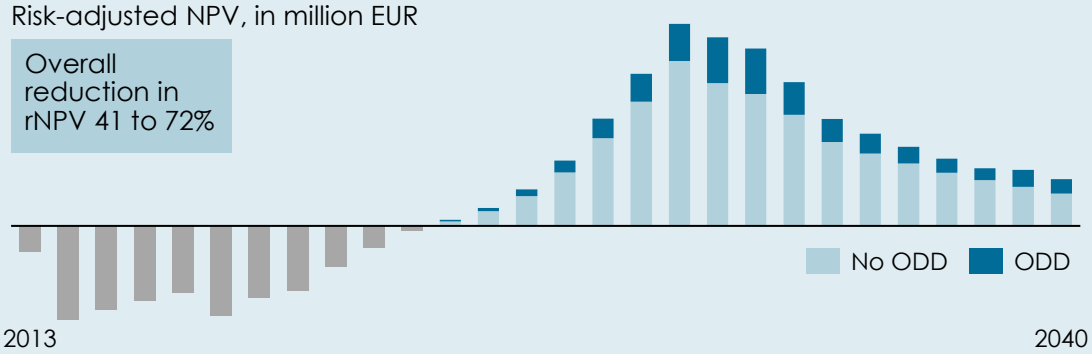
Box 2: loss of OD eligibility can considerably dampen investment incentives in orphan development

The loss of eligibility for orphan drug designation would reduce profitability of the orphan development project via two effects.[1] *First*, the orphan label is linked to a higher achievable payment per patient compared to non-orphan medicines, which is required to recoup investment across a small patient population. As a result, in the absence of this orphan label, payers may only grant a lower payment per patient. It is difficult to estimate how much lower this may be as it depends on many factors, such as the national level pricing and reimbursement rules, rare disease and OMP type. Here, we illustrate the effect of the loss of OD eligibility linked to a reduction in achievable payment between 30 and 60%[2] in Europe and in most (90%) of non-EU and non-US (RoW) sales.

Second, the orphan drug designation provides the main incentive foreseen by the OMP Regulation, the 10-year market exclusivity. As a result, in the absence of the orphan drug designation, the developer expects faster revenue erosion due to earlier competition from generic versions of the OMP and similar OMPs for the same indication that do not provide significant benefit. The magnitude of this effect depends on the extent to which the market exclusivity provides additional years of protection compared to other protection tools, such as patents, and on the extent to which competing products are expected to reach the market. Compared to patents, market exclusivity provides additional protection against *similar* medicines for the same indication (unless they prove significant benefit). Due to data limitations, we make the simplifying assumption that market exclusivity provides the same protection as the other protection tool, i.e. we do not model the additional protection against similar medicines.

Under these assumptions,[2] the loss of orphan designation results in a 41-72% reduction in profitability, see Figure 11. This confirms the crucial role of maintaining the criteria for orphan designation set in the current OMP Regulation. Irrespective of the achievable price, value-based contracting should be used as a tool to ensure that pure pricing considerations do not become a barrier to patient access, see pages 45-48.

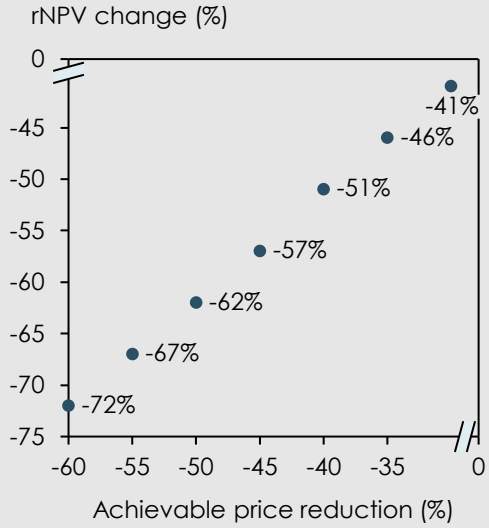
Figure 11. Effect of the loss of orphan designation on the profitability of a hypothetical orphan development project



Modelling assumptions

Achievable payment	Loss of orphan designation results in a reduction in achievable payment in the EU, assumed between 30 and 60%. Due to international reference pricing, it also results in a lower achievable payment in most (90%) of volumes sold in the Rest of the World (RoW, i.e. non-EU and non-US countries).[2] It is assumed to have no effects in the US.[2]
Market exclusivity	The loss of orphan designation causes the loss of protection from market exclusivity (e.g. years of protection from market exclusivity go from 10 to 0). See page 29 for the assumptions concerning generic entry.

% rNPV change with different assumptions on payment reduction



1) We do not model the increase in costs due to the loss of fee waivers nor the possible effects of protocol assistance on the probability of success at the regulatory stage or Phase III clinical trials. 2) Values are chosen to illustrate the variation of effects caused by different drops in achievable price levels 3) See Appendix for a detailed overview of the model inputs and assumptions

Evolving the current policy framework is useful but not sufficient

Modulation of incentives must go beyond market exclusivity

A modulation of incentives makes sense in an environment where OMP development projects differ strongly in terms of their investment case. Today, a developer is likely to see higher barriers, costs and risks when pioneering in a disease area where no one else has gone before than in an area where the R&D community, patient communities, and regulatory and market access pathway have already been established. While modulating incentives to reflect these differences is conceivable, modulation categories need to follow a systematic study of the economic viability of investments across disease areas and technologies. It also needs to follow clear and predictable rules.

The most important question is, however, *which* incentives should be modulated.

The current policy discussion focuses mostly on the modulation of the main incentive within the OMP Regulation, a 10-year period of market exclusivity. Market exclusivity provides protection from competition from similar medicines for the same indication and it runs in parallel with other protection tools: patent protection and SPC, market protection and data protection. Market exclusivity provides the developer with some certainty that she will make, during the first years of the OMP being on the market, the revenues needed to recoup up-front investments in the development of the treatment. Importantly, market exclusivity only protects a given OMP from competition of similar OMPs that do not provide significant benefit to the treatment in question.

The current incentive system, relying on market exclusivity as the key incentive, has not spurred development within 95% of rare diseases. Therefore, a natural starting point for policy makers to improve incentives could be to increase the number of years of market exclusivity. A closer analysis of such a proposal shows that this unlikely to be an effective tool on its own.

First, additional market exclusivity years would only be a useful tool in cases where the developer faces a decision of "take up or no take up" into clinical development. In most cases however, clinical development does not exist because basic research is insufficient. Hence, an increase in years of market exclusivity is not the appropriate tool to address the barrier behind a large part of the 95%. Market exclusivity can only be considered as a tool in those cases where the developer faces the decision of clinical development but does not find it economically viable to do so.

Second, in the cases where basic science exists but unmet needs prevail, additional years of market exclusivity may not improve the investment case substantially enough. In many cases, the lack of protection from competition is not the main dampening factor of economic viability. Often diseases within the 95% are extremely rare such that any one condition is unlikely to attract many developers at the same time and a developed product may never or only very late experience generic entry. In these circumstances, the value of market exclusivity in addition to other protection periods is likely to be limited.

Even in cases where protection from competition has a value, additional years of market exclusivity alone are unlikely to turn a majority of non-viable development projects into viable ones. Our model of a hypothetical very rare OMP illustrates that even if we assume probabilities of generic entry and revenue erosion similar to an average medicine, the increase in expected profitability from two years of additional market exclusivity is 7%, see Box 3.

Therefore, policy solutions need to go beyond the known tool of market exclusivity to direct investments towards the 95% of rare diseases without authorised treatment.

Box 3: Adding market exclusivity years alone is unlikely to direct investments towards the 95%

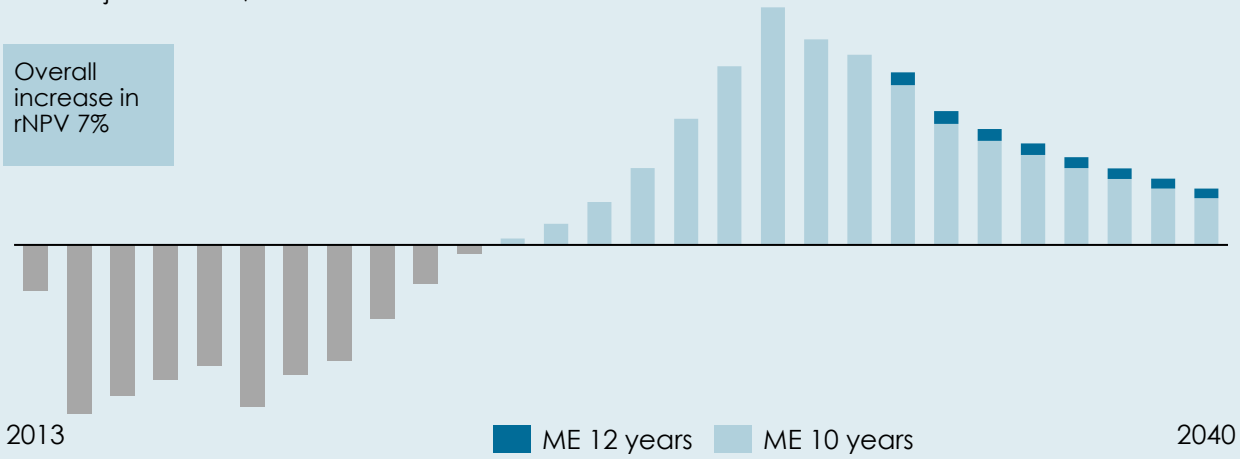
An increase in length of market exclusivity results in delayed generic entry and delayed revenue erosion, in cases where and to the extent that market exclusivity provides additional years of protection compared to other protection tools. This is because the effective protection provided by market exclusivity depends on the length and timing of the other protection tools. Market exclusivity often provides additional protection in the case of longer development periods, where patents are expected to expire earlier along the OMP lifecycle. As in the previous example and due to data limitations, we make a simplifying assumption that market exclusivity provides the same protection as the other protection tool, i.e. we do not model the additional protection against similar medicines.

For this example, we assume that generic entry will occur after expiry of the latest protection period with a probability of 44% and result in a progressive revenue erosion starting from 45%. Based on these assumptions, two additional years of market exclusivity result in a limited increase in profitability, 7%, see Figure 12.

This shows that, while it is crucial to maintain these basic incentives provided by the OMP Regulation, simply adding years of market exclusivity is unlikely to improve the economic viability of developing within the 95% to a point where it attracts substantial additional investments. This remains the case even if we assume a higher probability of generic entry in absence of ME. Hence, innovative solutions, based on partnerships that go beyond the narrow scope of the OMP Regulation are required.

Figure 12. Effect of an increase in length of market exclusivity on the profitability of a hypothetical very rare OMP development project

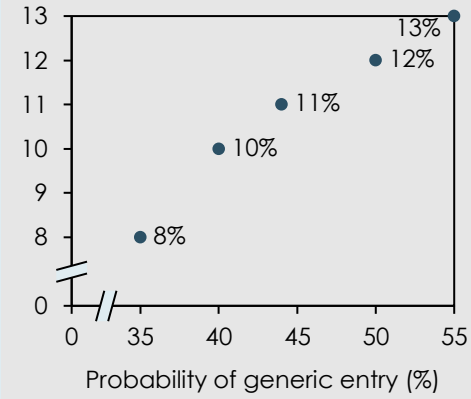
Risk-adjusted NPV, in million EUR



Modelling assumptions

Market exclusivity	The length of market exclusivity is assumed to be 2 years longer, i.e. from 10 to 12 years
Generic entry	A longer market exclusivity delays generic entry and the associated revenue erosion to the extent that market exclusivity provides additional years of protection compared to the other tools. Generic entry is assumed to occurs after expiry of the latest protection tool among patents, data exclusivity and market protection, market exclusivity. Generic entry occurs with a probability of 44% and a progressive erosion of revenues starting from -45% in the first year.[1]

% rNPV change with different generic entry assumptions



1) Assumption based on van der Schans et al. (2021)

Effective solutions require a partnership approach

If using habitual tools neither directs investments towards the 95% or allows Europe to address unmet needs, we need to rethink what effective solutions look like.

Today, most of the barriers along the OMP lifecycle seem to emerge in the interplay between two or more actors often with markedly different success criteria. This completely changes the type of solution that will prove effective going forward.

Effective solutions 'of tomorrow' must deliver along the following three dimensions:

First, effective solutions require two or more actors – multistakeholder – instead of one. The OMP Regulation succeeded based on a unidirectional logic: improving incentives and thereby development of new medicines for pharmaceutical companies through legislation. As soon as the legislation providing orphan designation and 10 years of Market Exclusivity (ME) was in effect, it changed companies' and investors' investment case for developing OMPs and they responded by allocating more resources to the development of OMPs. This stands in contrast to today's challenges where policies need to incentivise many actors at the same time.

Second, because effective solutions create value through the interplay between two or more actors, legislation alone will not achieve the goal. Instead, the actors need to change approaches to problem solving in a way that creates better outcomes for all of them. This cannot be achieved through passing legislation alone, as it requires organisations – companies, authorizing bodies, payers, health care professionals – to change their behaviours. Changing behaviours requires organisations to focus on change management, realign governance structures and train for new skills.

Third, effective solutions require the needed changes in behaviours to fit a collaboration between markedly different organisations with different measures of success. One thing is to make a multistakeholder collaboration between similar types of organisations work. Companies and public bodies will often have experience with engaging in collaborations or networks with organisations similar to themselves with the purpose of developing products or sharing insights and experiences. The familiarity with the other actors allow them to more easily combine their expertise to develop for example a new medicinal product, or more easily integrate insights and best practices from another public body into their own public organization.

A different challenge is to make multistakeholder collaboration across organisations, with different success criteria and different business models succeed. Here, successful collaboration requires a level of 'empathy' between the collaborative actors. This presupposes an understanding what drives success and risk with the other actors in order to develop solutions that create value for all actors. To build that level of insight and empathy is no trivial task and requires companies and organisations to have a strategic focus.

The term that best describes the framework that binds the above three dimensions together is *partnerships*.

One example of such a partnership in the innovation space is **the Shonan Health Innovation Park** which seeks to overcome challenges of translating basic science and technologies into applications for patients by forging partnerships in health innovation and commercialisation, see Box 4.

Box 4: The Shonan Health Innovation Park as a powerful partnership for innovation step-changes

In 2018, Takeda transformed its Shonan Research Centre in Fujisawa City, Japan, to the **Shonan Health Innovation Park** (Shonan iPark) in an effort to establish a life science ecosystem open to the world. Bringing researchers, industry, venture start-ups, government and academia together, this initiative aims to form a true co-location ecosystem for collaboration and co-creation, resulting in the incubation and acceleration of research and transformation of cutting-edge science into impactful health solutions for patients around the world.

Today, bringing innovative medicines to the market is becoming increasingly difficult and there is a growing disconnect between the translation of basic science and technologies into applications for patients. The Shonan iPark aspires to overcome these challenges by forging partnerships in health innovation and commercialisation, where partners can optimise each others' technologies, expertise and resources through inter-business, interdisciplinary and international collaboration. Shonan iPark has already achieved a number of scientific and business milestones, including for instance an international partnership with National Horizons Centre in England and the launch of a new market access pathway in Japan for pioneering life sciences companies.

Since 2018, Shonan iPark has grown to more than 2,000 employees from over 110 partners. Takeda has signed its ownership rights to the Shonan iPark trust and currently engages in the partnership as a flagship tenant, committing to leading the development of the ecosystem.

Shonan iPark: ecosystem of inter-business, interdisciplinary and international collaboration

Sources: Takeda (2020) and Shonan iPark (2022)

Effective solutions require a partnership approach

Partnerships are complex but effectful

Partnerships are driven by the prospect of greater value creation for the individual party than the individual party would be able to create alone. The right situations for bringing in partnerships are consequently when individual actions of one party have an impact – an externality – on another party. Without a partnership the one part will not factor in the impact of its actions on the other part thereby potentially reducing the total value.

These circumstances are reflective of how the barriers along the OMP lifecycle must be addressed. Compared to the instruments of the OMP Regulation (i.e. bilateral incentives such as market exclusivity), partnerships are a more complex solution, but carries the promise of being more impactful in addressing the barriers that exist today, see Figure 13.

An example is in the regulatory approval process. Once phase III of the clinical trials have been successfully concluded, the next challenge is to get the medicine authorised. To succeed in bringing efficacious and safe medicines to the market, the regulatory body, EMA in the EU, and the company have a relationship that would fit well with a partnership. They have a common goal of getting life changing and safe medicines authorised, but engagement procedures and data requirements for authorisation may not fit a new technology embedded in a first-in-class medicine. One can imagine how a transactional approach to such a challenge might lead to a negative decision around authorisation alone due to a lack of a common ambition to overcome the uncertainties that come with a new technology that poorly fits the standard procedures. A partnership approach based on common ambitions and a trustful problem solving environment, *might* come to a positive decision purely thanks to a different approach to problem solving, not to the intrinsic effect and safety of the medicine.

Our illustrative modelling of the investment case for an average OMP shows how a partnership between OMP developer, regulator and HTA/payers can be an effective tool for improving the expected profitability of the development project, making a real difference in increasing investment incentives, see Box 5.

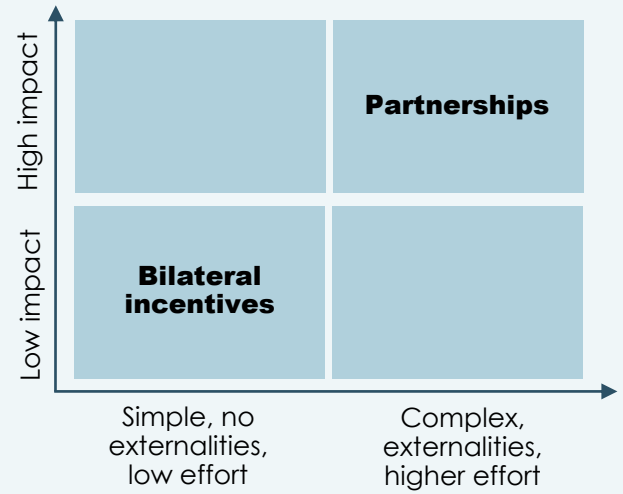
Next level partnerships

This example of a partnership approach to problem-solving between a public authorising body and a private company represents a next level of partnerships with the additional challenge that comes with two actors with markedly different success criteria and business models. Where many companies and public bodies have experience with like-for-like partnerships or experience sharing networks with organisations similar to themselves, fewer have experience with multistakeholder partnerships involving many different business models that challenges the fabric of partnerships namely the ability of each party to cater for the other actors' success through the externalities of own actions. Succeeding with partnerships is needed to unlock innovation and bring therapies to the people living with rare diseases that are still experiencing great needs that are not met.

If Europe could make this partnership model work, it could put the region in a leading position for OMP development.

Thinking further ahead, this approach to partnerships between companies, EU and national public bodies, patient organisations etc. across Europe could have ramifications beyond rare diseases. It could serve as a model for the broader healthcare and life sciences industry and ultimately as a blueprint for how Europe reinvents itself across the entire economy.

Figure 13. Solution types available to policy makers



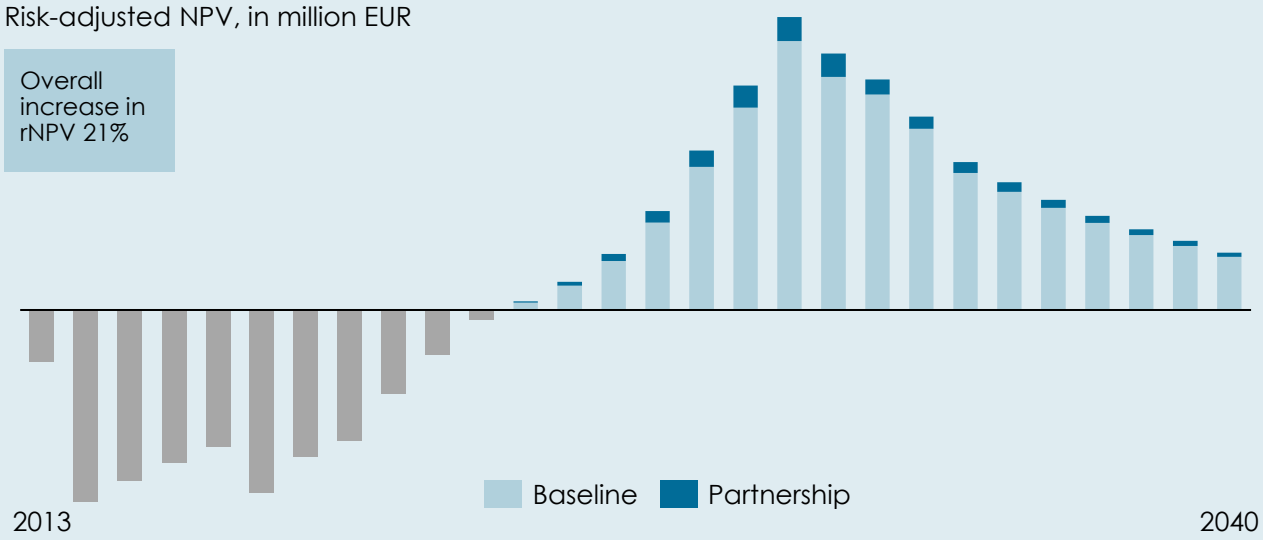
Box 5: Partnerships can make a real difference in increasing investment incentives to address unmet needs

A successful partnership[1], despite not being a direct financial incentive, can substantially improve economic viability of investing in an orphan medicine from the developer's perspective. Here, we take the example of a partnership between OMP developer, regulators and HTA/payers centred around bringing clarity and certainty early on around evidentiary requirements for innovative OMPs.

At regulatory and market access stages, the lack of a common understanding on evidentiary requirements may lead to a lower probability of success at the regulatory stage (probability to maintain OD and to get marketing authorization). It may also lead to an overall longer time for achieving market access and a lower probability of getting a pricing & reimbursement agreement for a large part of the patient population.

For this example, we assume that such partnership has the potential of improving probabilities of succeeding in regulatory approval and market access, leading to a higher likelihood by 5 percentage points of getting OD and MA, a three months shorter time for market access, and an increase in expected risk-adjusted revenues by 10% (due to a higher probability of succeeding pricing and reimbursement). Under these assumptions, a partnership could increase ex-ante expected profitability of the hypothetical very rare OMP by 21% thereby substantially improving investment incentives. The larger the increase in probabilities of success the larger the positive effect on expected profitability.

Figure 14. Effect of partnership solution between OMP developers, regulators and HTA/payers on the profitability of a hypothetical very rare OMP project



Modelling assumptions

Effects of partnerships solutions with regulators and HTA/payers

A partnership between OMP developer, regulator and HTA/payers based on evidence is assumed to:

- Increase the probability of succeeding in maintaining the orphan designation through more certainty around proving significant benefit by +5%[2]
- Increasing the probability of obtaining the marketing authorization through clearer evidence requirements by +5%[2]
- Shorten the time required for market access by 3 months[2]
- Increase the achievable payment per patient and the probability of obtaining a pricing and reimbursement agreements, resulting in a 10% increase in revenues[2]

1) A successful partnership adds value to all parties involved: to regulators that approve the right medicines, to payers and healthcare systems that get access at better conditions for more patients, and finally for the patients that get access to more treatments. // 2) Assumption based on our experience and Takeda's knowledge.

3 THE SOLUTION
HOW PARTNERSHIPS CAN TRANSFORM THE OMP LIFECYCLE

Partnership-based solutions can transform the European OMP lifecycle

Six partnership-based solutions will move the needle for Europe

Alongside an evolved incentive framework, partnership-type solutions are an effective tool to solve the challenges that Europe faces in addressing so far unmet needs. But what kind of partnerships does Europe need?

In the following we show how partnerships can address specific challenges and barriers at different stages of the OMP lifecycle. Based on existing examples of partnerships, we make six concrete proposals for partnership-based solutions along the OMP lifecycle, see Figure 15. Many of these solutions build on current initiatives and structures. Together these solutions will allow Europe to make significant advances on the different dimensions of unmet need that exist today.

Partnerships require careful design

Partnerships will take Europe on a path for more effective but also more complex solutions. Setting them up and making them work requires careful design. What does it take to drive successful partnerships? We distil the key enabling factors across partnerships, and for each individual proposal. Across all partnerships, we find that success is driven by strong prioritisation and partner selection topped with three behaviours, see Box 6: expressions of each actors' own interests, creating trust through empathy and development of the capacity required to engage in the partnership.

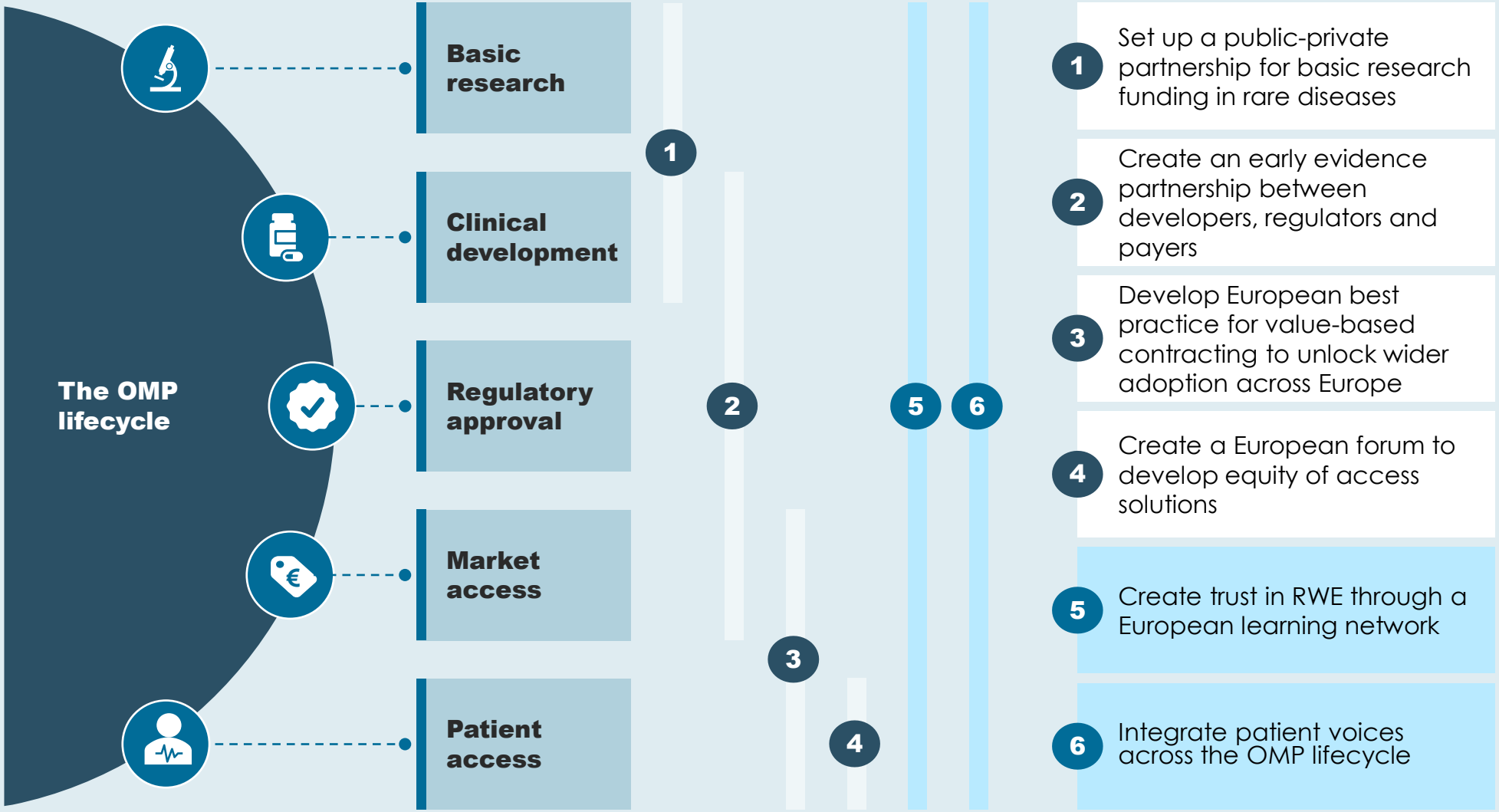
Rare diseases as public health priority

Compared to current solutions, the partnerships suggested in this report will require a different level of leadership from EU and national policy makers that brings all relevant actors in the OMP lifecycle around one table (researchers, developers, payers, regulators, patients). Finally, they ask Europe to go beyond networks for learning and exchange to partnerships that need to deliver tangible benefits for all involved.

Such a joint effort requires a high level of leadership, dedication and resources by all, but most importantly building a high level of trust between all stakeholders. To support such a joint effort, rare diseases need to be considered a public health priority by EU and national policy makers. Only elevating rare diseases to a healthcare priority can instil focus needed for Europe to make such a step-change. The efforts in fighting the Covid-19 pandemic have taught us that this works.

Partnership-based solutions can transform the European OMP lifecycle

Figure 15. Six partnership-based solutions will help tackle barriers along and across the OMP lifecycle



Partnership-based solutions can transform the European OMP lifecycle

Box 6. Key enabling factors for partnerships

Strategic prioritisation of product or technology area

Partner selection

Express own interests

It is the responsibility of any party in a collaboration or in a formal partnership to consider own interests first. If any part of a potential partnership is consistently unhappy, a successful partnership is not possible.

Own interests should be clearly articulated but this does not mean that any party should have their interests fulfilled at any point in time. The world is dynamic and partnerships should reflect this. It may very well be that one partner benefits today, while the other tomorrow. As long as interests are aligned such that everybody wins more over time than a transaction could deliver, partnerships are able to create true value.

Considering interests in a successful partnership also entails well-defined outs. If the partnership becomes superfluous, actors must have relatively cheap and easy ways to terminate the partnership to avoid destroying the value that the partnership initially brought.

Trust through empathy

Since the value of a successful partnership is rooted in working together and achieve more than would be possible alone, building a high level of trust is integral to initiating successful partnerships.

Because the partnership is driven by acknowledging that each individual party's actions have ramifications for the other actors, much of the trust is build around a constant curiosity – empathy – to understand the other actors' success criteria, risk dimensions – their fundamental business model.

On top of empathy comes the need for the logic – that decisions taken in the partnership to appear sound - and even building interpersonal relationships between the individual persons involved in the partnership through sharing of personal experiences.

Develop through capacity

One final hurdle to pass in the development of the successful partnership, is making it agile and flexible enough to encompass unforeseen events and prosper from developments such as new technological opportunities that might not have been foreseen in the start of the partnership.

The real world changes, interests change and partners change. If the partnership framework is too rigid to accommodate these changes, the value it once created may erode, and the partnership dwindles.

To stay on top of these opportunities and behave flexibly requires building an organisation around the partnerships with the necessary capacity, skills and focus in the day-to-day operations that drives forward the partnership. Moreover, frequent partnership health check-ins exploiting the validity of articulating own interests and leveraging the existing trust is a tool that allows for a dynamic and developing partnership.

Sources: Copenhagen Economics based on Frydlinger et al. (2019), Jacobides (2019), and McKinsey (2021).

Public-private partnership for basic research funding

Funding and collaboration for basic research are key pillars in addressing the 95%

Basic research is the starting point of all OMP development and its funding is an important fuel to the European OMP ecosystem. Without basic research, there can be no clinical development, as OMP developers depart from it to investigate and develop targeted and novel treatments. The lack of (translational) basic research is an important explanation for lack of authorised treatments in 95% of the known rare diseases. Basic research may not exist at all in a given disease area, or, if it exists, it is insufficiently evolved to be ready for companies to take it up into clinical development.[1]

The scarcity and fragmentation of expertise in rare diseases makes basic research a prime example of an area that profits from increased scale by lifting both funding and collaboration to a European level.

Only a small number of European countries have funded research on rare diseases through very dedicated programmes[2]. The EU has supported these efforts in the rare disease field with more than EUR 2.4 billion attributed to over 800 research and innovation projects, the majority of which are collaborative.[3] Currently, the European Joint Programme for Rare Diseases (EJP RD),[4] running until 2023, leads the most systematic and coordinated funding efforts for rare diseases basic research in Europe. Moreover, programmes like the E-Rare Consortium[5] have enabled the collaboration of national funding organisations.

In addition to funding, research collaboration also benefits from scale. Today, the European Reference Networks (ERNs), adopted in 2017, have established a base infrastructure for pan-European collaboration in rare disease research and diagnosis. However, there are still some recognised issues with the ERN infrastructure, mostly concerning lack of legal basis and member state involvement, that challenge its sustainability and full use. Outside of the ERNs, rare disease knowledge and data still predominantly sits within geographically dispersed and disconnected research programs, disease specialists, and small biotech companies - and within different, non-standardised databases.[6] This makes it difficult to share and leverage existing resources in a systematic way, which leads to delays in for instance diagnosis and patient recruitment for clinical trials. Moreover, it is currently not possible for actors to have an overview of where research and development is already taking place and what areas remain unaddressed. Several Europe-wide initiatives aim at overcoming these challenges - one noteworthy example being the FAIR Virtual Platform,[7] driven by the EJP RD.

Fostering basic research requires larger scale and smarter funding

If Europe's ambition is to develop better treatments for people living with rare diseases, it needs to foster basic science in the areas where currently none or only insufficient basic research exists.

This requires two changes: First, Europe has to increase funding in this area. Without an increase in the level of funding, more basic research is not achievable. Second, Europe has to fund basic research in a "smart" and efficient way by leveraging data and the integration of research communities. This needs to be paired with more coordination of funding efforts, strategically directing funding into underserved areas and introducing more guidance and conditionality to achieve development-ready research.

Smart funding of rare disease basic research requires a high level of coordination, collaboration and sharing of resources. This requires all key stakeholders involved in basic research and development to play their part.

What next?

We propose that Europe strives to organise rare disease funding for basic research in a single PPP funding entity, including joint financial and in-kind contributions of both public and private funders. This fund should rely on a European collaborative data infrastructure that connects today's scattered research communities in rare diseases on one network. Here, the ERNs have the potential of becoming an important platform and infrastructure.

1) Aartsma-rus et al. (2021) // 2) CORDIS (2022) // 3) European Commission (2021) // 4) EJP RD (2023). See link // 5) ERA-LEARN (2022) // 6) Kodra et al (2018) // 7) EJP RD (2023). See link

Public-private partnership for basic research funding

The fund should target previously underserved disease areas following clear and transparent rules and continuously evaluate progress in order to re-allocate funds from the those making less progress to those making more progress. Using the data infrastructure, funding can address disease areas with positive externalities, where results in one disease can be used to advance insights into another. This allows for exploiting both scale and scope of a data network.

Such a partnership has the potential to:

- Overcome fragmentation by creating a central overview and coordination of all European rare disease funding efforts,
- Flexibly direct funding in areas of most unmet need
- Make funding conditional on commonly set outcomes
- Overall, allow more effective research for every EURO spent

We have already seen various successful examples of multi-stakeholder healthcare funding partnerships that can serve as inspiration, such as the Global Fund, the IMI and E-Rare consortium, see Box 7 on the next page. Moreover, we have seen Europe-wide initiatives to centralise rare disease knowledge resources and improve the findability, accessibility, interoperability and reusability of existing and new data that any basic research-focused funding PPP should integrate with, see Box 8 page 41.

Key enabling factors for funding partnerships

- **Establishing concrete objectives:** the strategic objectives of a PPP, and the targeting funding programs within it, should be clearly concretised as to ensure relevance and focus.
- **Securing wide-representation and scale of funding** as to leverage existing financial resources, build a sense of shared responsibility, and to truly contribute to scientific advancements.
- **Clearly assigned contributions and rules for all actors:** in order to leverage diverse expertise and to ensure order, transparency, and fair and unbiased decision-making.
- **Measuring impact and outcomes** to track success, reallocate funds to maximise impact, and maintain trust from funders and the wider community. This enabled by clearly specified objectives of the funding programs.
- **Data-driven collaboration** to reap economies of scale and scope thereby maximising uptake-ready results per funding EUR.
- **Cross-utilising commonalities and acquired knowledge** across rare diseases by funding targeted disease areas where the positive externalities are strongest, i.e. where insights can advance development in other rare diseases.

Public-private partnership for basic research funding

Box 7. Experience of funds

Innovative medicines initiative

The Innovative Medicines Initiative (IMI) is an EU-wide PPP, with the primary objective of speeding up the development of, and the access to, innovative medicines – particularly in areas of high unmet need. This is achieved through the collaboration between key players in health research, including research institutions, pharmaceutical industries, SMEs, patient organisations and regulators.

The financing is equally shared by the European Commission and European pharmaceutical companies, who contribute though in-kind contributions. So far, the IMI has secured a budget of EUR 5.3 billion for the IMI1 and IMI2 programs in the period 2008 to 2024, already allocated to over 170 innovative projects, addressing a wide range of drug discovery and development, including priority disease areas such as antimicrobial resistance and rare diseases.

Under the proposal for a Single Basic Act, the Commission is proposing to launch the Innovative Health Initiative (IHI), the next PPP under Horizon Europe, which will build on the experience of the IMI programs to advance more patient-centric innovation to address unmet needs.

Sources: IMI (2022a; 2022b; 2022c)

E-rare consortium

The E-rare consortium enables transnational collaborative research in rare diseases, by linking responsible funding bodies that combine scare resources and fund rare disease research through Joint Transnational Calls. The latest E-rare-3 programme, running from 2014 to 2020, built on the experience and efforts of its predecessors, the E-rare-1 and E-rare-2, with a specific focus on implementing the International Rare Diseases Research Consortium's (IRDiRC) guidelines for rare disease research in Europe and beyond.

The E-rare-3 secured a budget of EUR 23.3 million, thanks to the contributions of 25 participants and the EU Horizon 2020 programme, accounting for approximately 25% of the total funding.

The E-rare programs have collectively funded 119 independent projects over ten joint calls. Among many others, some of the greatest achievements of the programmes include the identification of new genes associated with rare diseases (e.g. Machado-Joseph Disease) and the development of accurate and usable models to predict survival of patients (e.g. those suffering from ALS).

Source: CORDIS (2022)

The global fund

The **Global Fund** is an innovative multi-stakeholder partnership between governments, civil society, technical agencies, the private sector and patients, dedicated to accelerate the end of AIDS, tuberculosis and malaria. The Global Fund mobilises and invests funds into country programs run by local experts, who liaise with Global Fund's independent panel to revise, monitor and evaluate the plans and progress throughout the program period.

The Global Fund raises funds in three-year cycles, known as replenishments, with 93% of the funds originating from donor governments. The remaining share comes from the private sector, foundations, and other innovating financing initiatives. Every year, the Global Fund invests more than USD 4 billion into country programs. For example, in the period 2020-2022, the Global Fund has allocated funds to over 100 countries.

Since its establishment, the Global Fund has saved over 44 million lives from the AIDS, tuberculosis and malaria. Moreover, the Global Fund supported 21.9 million people on antiretroviral therapy for HIV and provided 188 million mosquito nets in 2020.

Source: The Global Fund (2022a; 2022b)

Public-private partnership for basic research funding

Box 8. Experience of data and research collaboration

ARDAT

ARDAT is a 5-year program, running from 2020 to 2025, under the Innovative Medicines Initiative (IMI) that aims to deliver knowledge, tools and standards needed to speed up the development of advanced medicinal products (ATMPs), with a specific focus on rare diseases caused by a gene mutation. ARDAT, consisting of 34 members from EFPIA companies and SMEs to public organisations, has secured a budget of EUR 25.5 million, of which over 50% comes from in-kind contributions from EFPIA companies. With this backing, this initiative will drive two processes:

1. Developing better, standardised models for predicting product immunogenicity in humans and building understanding of the metabolism of gene/cell therapy in patients.
2. Engaging with regulatory authorities, patient advocacy groups, charities and sponsors establish a centralised biobanking infrastructure for patients receiving approved therapies or included in gene or cell therapy trials and to streamline regulatory processes for these kinds of therapies.

These processes will improve precision and effectiveness of therapies and decrease development costs of bringing such therapies to patients.

Source: IMI (2022d)

Fair virtual platform

The FAIR Virtual Platform belongs in EJP RD's Pillar 2 "coordinated access to data and services for transformative rare diseases research" work package. It aims at rationalising, optimising and increasing the potential of existing resources and services, in order to decrease fragmentation and maximise the potential of Europe's rare disease research. The platform will enable users to find relevant resources, such as catalogues of registries, biobanks, data platforms, animal models, cell lines and service infrastructures and research data from a single, centralised location – therefore uniting resources and accelerating rare disease research.

Though led by the EJP RD, this is a joint undertaking of the wider European rare disease community, built around the experience and resources of the ERNs.

Source: EJP RD (2022)

Screen4care

Launched in September 2021, Screen4Care (under the IMI) will run over the course of 5 years to identify existing resources and initiatives in the field of newborn screening (NBS) and artificial intelligence-based tools, to be integrated into a large cross-sector ecosystem for rare diseases. This initiative consists of 35 members, bringing together a wide range of industry, universities and other research organisations, and most importantly, patient organisations such as EURORDIS. Screen4care has been assigned a budget of EUR 25 million and will be coordinated by University of Ferrara.

In NBS, the program plans to screen 125 genes of 80 rare diseases using Whole Genome Sequencing (WGS) to enable quicker diagnosis and disease management. In digital technologies, the program plans to pool available databases into a meta-data repository amenable to machine learning and to further develop and repurpose existing AI algorithms to identify patients early through electronic health records.

Source: IMI (2022e)

Early evidence partnership between developers, regulators and payers

Lack of clarity early on concerning evidentiary requirements from regulators and HTA bodies/payers contributes to uncertainty and market access failures

One of the single most important challenges for bringing innovative medicines to the market and innovating in areas where little R&D takes place is to collect the right type of evidence that can support success both at the regulatory stage (supporting positive risk/ benefit balance and significant benefit) and the market access stage (demonstrate value added to payers). This is particularly the case for very rare OMPs where the small patient population challenges the feasibility of the standard randomised control trial (RCT) set up. The following challenges can be observed across Europe:

First, evidentiary requirements differ between regulators and HTA/payers across Europe. In particular, across Europe, we observe a disconnect between the decision taken at the regulatory stage (e.g. where an OMP is considered to bring significant benefit or received conditional marketing authorisation) and the market access stage where that same benefit is not recognised or the evidence is deemed too uncertain.[1] These differences might not constitute a barrier per se, but they make navigating the European regulatory and access pathways more cumbersome and resource-intensive for developers.

Second, the lack of clarity on the evidentiary requirements for stages early on in the development process drives high uncertainty and longer development and market access times.[2] Failing to agree on required evidence early can also cause (partial) failure of market access when HTA/payers requirements do not accept the evidence collected to obtain regulatory approval. This issue particularly concerns new treatments (new class of products, mechanisms of action, or gene therapy) whereby regulators and payers have to determine afresh which evidence should be considered.

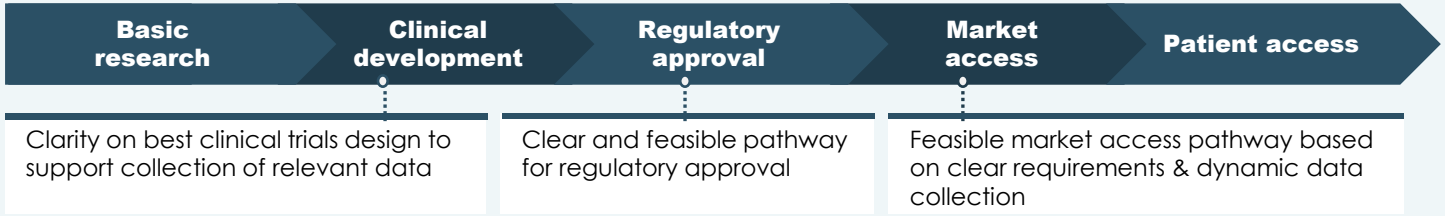
Third, the issue for many OMPs is one of timing, whereby the data to further improve the evidence-base for efficacy, safety and relative clinical and economic value can only be collected once the medicine is delivered to patients[3], through patient registries. This means that decision-making processes both on approval and pricing and reimbursement need to become more dynamic, taking into account new evidence instead of one-off decisions based on a complete ex-ante evidence base.

Early and iterative dialogues on evidence requirements are needed

If Europe wants to drive more development within the 95%, the hurdle of evidentiary requirements is a key one to tackle. The challenge is to re-think and co-design the OMP development pathway such that the right kind of dialogues happen with the right stakeholders at a sufficiently early stage to agree on a feasible pathway for evidence generation.

The improvement of clarity on the evidence base for different decision points requires all stakeholders (developer, EMA, HTA bodies payers) to engage in a dialogue that starts early (in time for clinical trial design) and continues as the OMP makes it through the lifecycle. Importantly, the patient perspective needs to be integrated throughout[4]. Such an early dialogue should support evidence development for the different decision-points along the OMP lifecycle, see Figure 16.

Figure 16. Benefits across the development path of early partnership with regulators and payers based on evidence



1) EURORDIS (2017b) // 2) Aartsma-rus et al. (2021)// 3) Moseley et al. (2020) // 4) Ibid.

Early evidence partnership between developers, regulators and payers

Early dialogues therefore have the potential to shorten timelines between approval and reimbursement decisions, increase predictability of the approval and subsequent reimbursement processes, and overall lower the failure rate.[1]

What next?

Building upon existing initiatives, EU policy makers should develop a forum for an early evidence partnership between regulators, HTA/payers and OMP developers. Such a forum should build on current formats such as PRIME, Impact HTA and EMA-EUnetHTA parallel consultation, see Box 9. Recent experience on the EMA-EUnetHTA pilot demonstrate the usefulness of this type of parallel advice. They also point, among other things, to the need for

- A sustainable financial framework increasing capacity to meet demand from developers
- Clear documentation of advice in a single document that is reused at different decision-points
- The need to involve all relevant stakeholders in a structured manner, especially payers.

Importantly, such a forum should go beyond a dialogue-format to include a partnership logic that aims at delivering tangible results for all involved. In practice, the outcome of these partnerships should be a development plan based on agreements on (i) relevant endpoints, (ii) the type of data (including RWE) that should be collected and how, (iii) the points at which different types of evidence can be expected and what that may mean for dynamic decision-making and the subsequent regulatory and market access pathway (e.g. conditional marketing authorisation, conditional reimbursement, the use of innovative payment models). The starting point for these discussions should be patients' needs and perspectives such that what is measured and assessed reflects what matters to patients and their experience.[2]

In the case of very rare diseases where standard RCTs are not feasible, these early dialogues should also be a forum to co-design a feasible pathway to bring these OMPs to patients. For instance, this could entail a clear plan between OMP developers, EMA and HTA/payers that foresees regulatory approval based on sufficiently convincing evidence of clear benefit and "acceptable" risk, which is then further supported by evidence through post-authorization studies. This resembles the conditional marketing authorization pathway but has the benefit of involving HTA/payers in the dialogue such that market access perspective is included early on, which is instrumental for further data collection including RWE.

Key enabling factors for early evidence partnerships

- **Sufficient capacity to meet demand**
- **Involvement of all stakeholders** in approval and reimbursement decision
- **Early engagement** during the development phase. This allows OMP developers to design clinical trials fit for collection of the necessary evidence
- **Clear and documented advice** on requirements and timeline on feasible pathway especially for very rare OMPs
- **One stop shop document** that can be re-used and amended at different decision-making points
- **Guidance, acceptance and trust to leverage the use of RWE** to support regulatory approval and market access.

1) EURORDIS (2017b) // 2) See discussion on patient partnerships on pages 53-56

Early evidence partnership between developers, regulators and payers

Box 9. Experience of partnership between developers, regulators and payers

EMA-EUnetHTA parallel consultation

Following a pilot in 2010, the European Medicines Agency (EMA) and the European Network for Health Technology Assessment (EUnetHTA) offer a program based on parallel consultations. The aim of the program is to allow developers to obtain feedback early on from regulators and HTA bodies to facilitate the generation of optimal and robust evidence that satisfies the needs of both regulators and HTA bodies. To participate in the program, developers are requires to submit an application in response to an open call. The selection criteria for participation in the program are: the medicine should bring benefits to patients through a new model of action for the indication, target a life-threatening or chronically debilitating disease and address an unmet need (no available treatment or unsatisfactory treatment).

This program provides useful experience and a starting point for a next generation partnership. In particular, a step forward will be ensuring a wider coverage of such a program to a larger set of OMPs. This will require the allocation of additional resources from the EMA and HTA bodies.

Sources: EMA (2016; 2022b; 2022c)

Innovative Licensing and Access Pathway (ILAP)

The Innovative Licensing and Access Pathways (ILAP) is a special access program that recently launched in the UK with the aim to accelerate the time to market and facilitating patient access to medicines. Permanent partners are the Medicines and Healthcare products Regulatory Agency (MHRA), the National Institute for Health and Care Excellence (NICE), the Scottish Medicines Consortium (SMC), All Wales Therapeutics and Toxicology Centre. In addition, NHS England and NHS Improvement are supporting partners. The program comprises an Innovation Passport designation, a Target Development Profile (TDP) and provides applicants with access to a toolkit to support all stages of the design, development and approval process.

This is an example of how early dialogues and partnerships that include regulators, HTA bodies and payers from an early stage of development can facilitate access to medicines. An EU-level partnership could be inspired from this initiative and take the learning that will come from the experience in the UK.

Source: UK Government (2022)

Temporary authorization for use (ATU)

In France, the Temporary Authorization for Use (ATU) program provides early access to medicines for patients with a severe or rare disease with high unmet need and for which no authorised therapeutic alternatives. The French National Agency for Medicines and Health Products Safety (ANSM) grants the ATU status to medicines before they are authorised and have completed market access procedures provided that they are intended for a serious or rare indication, there is no alternative therapy and the medicine has presumed efficacy and safety in light of available evidence. The ATU status can be conferred to a medicine for a specific identified patient or for a group of (well identified) patients. The benefits of this program are multiple: it provides early access to innovative medicines, it allows developers to collect RWE that complements the clinical trials data and supports market access procedures.

This program provides relevant insights on how tailored pathways can facilitate early market access and support the collection of further evidence.

Source:
Ministère des Solidarités et de la Santé (2022)

European best practice for value-based contracting to unlock wider adoption across Europe

Innovative OMPs bring high value to patients but pose a challenge to national healthcare budgets

Innovative OMPs bring high value to patients, they address unmet needs and present significant advancements to the treatment of rare diseases. Bringing these innovative OMPs to the market commands a high upfront investments during the (often) long development period and the developer bears significant risk of failure during the development and regulatory phases. Estimates show that around 7% of OMP of development projects reach the market.[1] To maintain sufficient level of incentives in the rare disease space, pharma companies need to be able to expect a sufficient reward to compensate their investment including the investments into those development projects that did not succeed in reaching the market. As a result, pricing and reimbursement conditions are a crucial aspect to consider towards meeting unmet needs of rare disease patients.

Currently, the price level required by innovative OMPs to recuperate the investment given the small patient populations, often challenges national budget frameworks and pricing and reimbursement practices. Due to the small patient population and uncertain long-term effects, the level of evidence that can be collected on efficacy for innovative OMPs is often not satisfactory in payers' eyes, as it leaves a certain level of risk on the value actually delivered and the total impact on the healthcare budget. Put simply, the price per patient is perceived too high in the face of uncertainty on effects. This tension around pricing often leads to a situation where too few OMPs are reimbursed for a too small set of patients, thereby hindering patient access.[2]

Other types of barriers may also lead to suboptimal pricing and reimbursement decisions. This is, for instance, the case when budgetary constraints force public healthcare providers to make suboptimal treatment decisions based on one-year time horizons rather than a timespan that reflects the duration of a full care pathway.

Innovative payment models can unlock patient access to medicines

A partnership-based tool to overcome these challenges are innovative payment models which go beyond the upfront cost of the OMP and assess the monetary value of the achieved outcomes. These models can be tailored to the needs and specificities of each healthcare system and revolve around value-based contracting between the OMP developer and national health authorities. Existing experience, including Takeda's, shows how these models can unlock access to medicines for patients, see Box 10.

A key feature is that developers and payers share the risk associated with reimbursement of the OMP such as a lower value delivered in real-life use compared to the clinical settings. This lessens the perceived risk associated with reimbursement by holding OMP developers accountable for the delivery of value to patients, i.e. a specific outcome to which the compensation is linked.

Data, including RWE, plays an important role in innovative payment models as it allows to monitor and measure the outcome or value achieved. It therefore is crucial for the success of these partnerships that actors make clear agreements on what data should be collected and assessed, how and by whom.

An infrastructure for the collection and sharing of data is another success factor for the implementation of these contracts such that they do not create unnecessary burdens on the limited resources for payers.

Only a partnership-based set-up reaps maximum benefits

Innovative payment models range from simpler agreements to more complex ones, see Figure 17. Payers often already have experience with the former, which are more straightforward to implement but offer limited advantages linked to budget containment only (for instance, cost-based tendering). While these payment models have the advantage of ensuring that OMPs fit the limited national healthcare budgets, they do not exploit the full potential of partnerships around innovative payment models. More complex payment models have the advantage of ensuring not only cost containment but also improvements in standard of care for patients. These complex payment models might regard multiple products, additional services and consider the specificities of the disease and the treatment.

1) Average probabilities of success in clinical phases based on Thomas et al. (2016), page 16. Probability of success of market access based on Malinowski et al. (2018) // 2) Malinowski (2018)

European best practice for value-based contracting to unlock wider adoption across Europe

Box 10. Experience with innovative payment models for pricing and reimbursement of OMPs

HAE: managing the cost of personalised treatments

The treatment of HAE involves a prophylactic treatment to prevent attacks. The effectiveness of the prophylactic treatment depends on the patient receiving the right number of vials of treatment, which can vary between patients.[1] Such need for "personalisation" of treatment presents a risk for payers as it is hard to anticipate the number of treatments needed. Takeda therefore concluded an agreement based on vials usage, where additional vials needed per patient are provided without additional charge. This ensures that patients who require more vials receive them without cost-increases for the payer. This in turn allows clinicians to offer the best care to each patient without being constrained by budget considerations.

Source: Takeda's experience

Crohn's disease: pay-for-performance scheme

Crohn's disease patients often suffer from a complication involving perianal fistulas.[2] To mitigate payer concerns around treatment effects for the individual patient for this complication, Takeda set up a pay-per-performance scheme. The scheme splits the payment into two instalments: the first is linked to the prescription of the treatment, the second is linked to the complete remission of the patient. This outcome is reported by the treating clinician based on MRI tests. Through removing a hurdle in the reimbursement process, the scheme allows for patients to access the treatment.

Source: Takeda's experience

CAR-T cell therapies: reimbursement of one-off, high-cost OMPs

Two innovative and potentially transformative cancer treatments were approved in 2018.[3] These therapies posed significant challenges for HTA and payers: uncertainty around the real-world value given the potentially transformative health benefit supported by shorter-term data at launch, combined with high target prices.[4]

These drugs have successfully been through HTA processes and obtained reimbursement in major EU countries. The agreements reached between payers and developers are innovative models centred around monitoring of outcomes and additional collection of evidences. These allow to manage the perceived risks associated with reimbursement through risk-sharing between payers and the developer.

Source: Jørgensen et al. (2020)

Innovative payment models for CAR-T cell therapies

France	Annual reassessments based on longer-term follow-up data from pivotal trials, post-launch data collection in France
Germany	Outcomes-based rebates, linked to individual patient outcomes
Italy	Payments in three instalments linked to individual patient outcomes
Spain	Payments in two instalments linked to individual patient outcomes
UK	Future price reassessment based on longer-term follow-up data from pivotal trials, and post-launch data from use in UK patients

Haematology: agreements for sustainable budgets

The treatment of haemophilia involves episodic care, which is used to stop a patient's bleeding episodes, and prophylactic care, which is used to prevent bleeding episodes from occurring.[5] Takeda has applied a broad range of payment models to fit the characteristics of the disease and the needs of payers and healthcare systems in different countries.

Among these, there are complex outcome-based agreements, which pair budget sustainability with increased standard of care for patients. For instance, these can involve "Product+" arrangements whereby the customer pays a fee for the delivery of the product, associated services, and partnerships needed to jointly deliver healthcare system value to improve patient outcomes, quality, and control total cost of care.

Source: Takeda's experience

1) Abuzakouk et al. (2022), page 4, and NICE (2019), page 6 // 2) Rubbino et al. (2021), page 1 // 3) Jørgensen et al. (2020), page 1 // 4) Jørgensen et al. (2020), page 1 // 5) Makris (2012), page 165

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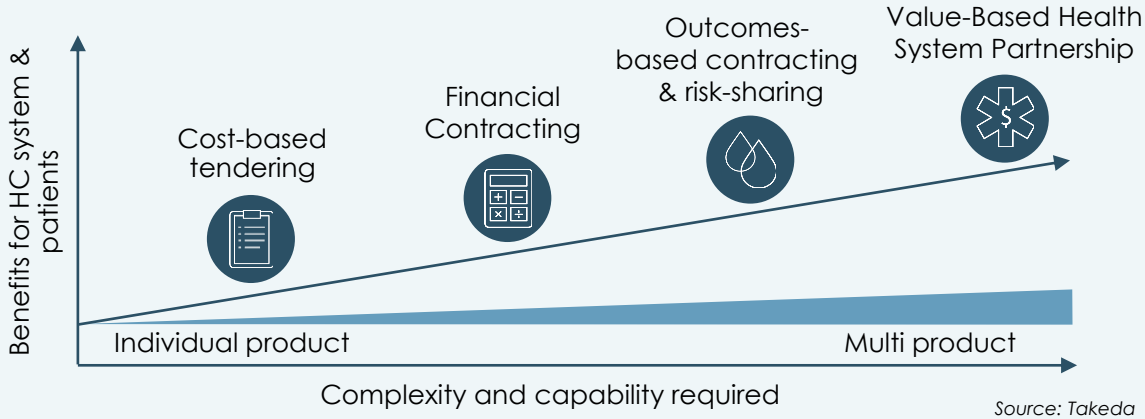
To support more complex payment models, partnerships are needed. This is because the individual actors must be prepared to make occasional sacrifices to reach a mutually beneficial outcome: for the developer this may mean taking increased risk by accepting that a payment is increasingly linked to patient outcomes; for the payer, it may mean accepting remaining uncertainties on measurements of outcomes and value achieved. Moreover the model's require transparency about and interest for the other party's key performance metrics, the challenges they pose to the negotiation, and how they can be met. When confronted with such uncertainties that could become a barrier to the agreement, the sense of mutual trust, collaboration and shared goals prevalent in partnerships allows the actors to go on.

Potential of value-based partnerships is unexploited across Europe

Today, the potential for value-based partnerships is not sufficiently exploited in the European market access landscape and insufficient experience with these models hampers their take-up. Payer stakeholders do recognise the potential benefits of innovative payment models: a survey found that 80% of interviewed payer stakeholders have a positive view on the potential of these models and 85% of them indicated a preference for these models over simple discounts, see Figure 18.

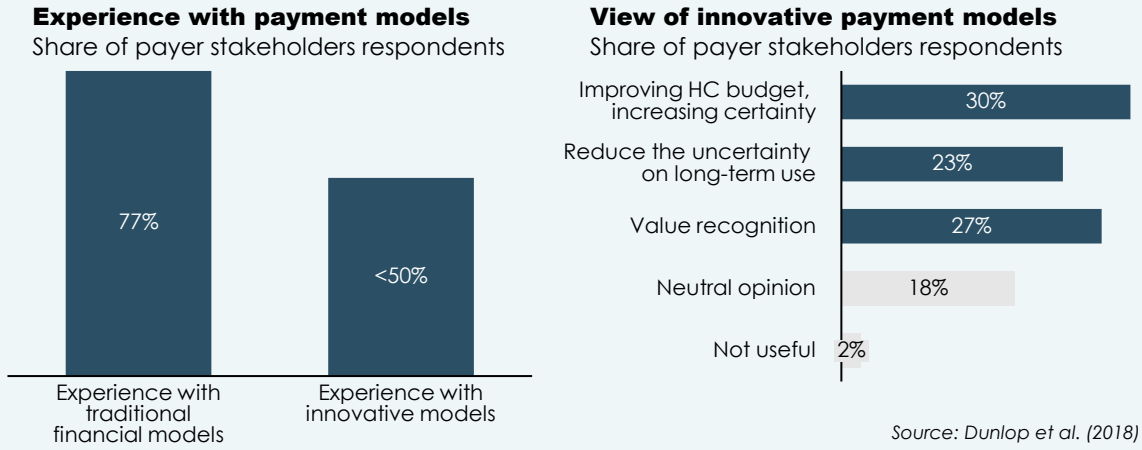
Despite this perceived usefulness and interest, the use of innovative payment models is currently limited. The same survey found that, while 77% of interviewees had experience with traditional financial agreements, half had experience with more complex payment models, see Figure 18.

Figure 17. More complex models bring larger benefits for patients and healthcare systems



Source: Takeda

Figure 18. Use and perception of payment models today (EU4+UK)



Source: Dunlop et al. (2018)

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In addition, there seem to be some limitations in terms of the therapeutic areas of application. In fact, the largest use of innovative payment models is reported in the oncology space[1] where it is easier to identify and track biomarkers and there is a large body of clinical evidence to support the design of such models. This suggests that developing and sharing best practices in the use of innovative payment models has the potential to increase their use in the rare disease space.

What next?

More widespread use of value-based contracting across Europe has the potential to unlock access to medicines for rare disease patients. Policy makers have a role to play in promoting the greater use of value-based partnerships in the pricing and reimbursement of rare diseases. This should go by lowering, as much as possible, the barriers to their use and by giving the actors to such partnerships the tools they need to get started. We therefore propose for EU policy makers to develop, together with payers and industry, best-practice guidebooks for value-based partnerships.

Key enabling factors for value-based contracting

- **Sharing** between the payer and the developer of the **risk** associated with for instance efficacy or treatment cost
- Agreements centred around the **achieved outcomes** for patients and the healthcare system, such as efficacy of the treatment
- Clear agreements on **data including acceptance of RWE**, necessary to assess the treatment outcome/performance
- An efficient, authorised and shared **infrastructure for capturing and assessing new data** to contain the burden on payers' resources.

1) Dunlop et al. (2018)

European forum to develop equity of access solutions

Swift access to treatments is an unmet need across many EU countries

Across Europe, rare disease patients have unequal opportunities to access available therapies depending on where they live. Unequal access results from an interplay of several factors, from budgetary considerations and priorities in individual member states, over challenges posed by national access pathways, to the lack of healthcare system infrastructure[1].

While the use of innovative/ outcomes-based payment models and early evidence dialogues[2] have the potential to support broader and faster access to medicines across Europe, they may not be sufficient to solve access issues is the least wealthy EU countries. Here, lack of access might also be caused by issues around the affordability of treatments for the specific member states as high-value expensive therapies, even if only applicable to few patients, may be considered as a strain on the healthcare budgets in these countries. Moreover, access issues may be rooted in the healthcare system infrastructure where the lack of diagnosis and experts prevent patients from getting the needed treatment on the one hand but may also lead to a lack of recognition of the importance of treating the disease with payers.

To address access inequalities, the Commission has proposed a unidirectional measure, namely, to link the incentives granted under the OMP Regulation to an obligation to launch broadly across all member states immediately after marketing authorisation is received.

A launch obligation creates challenges for developers if it leads to uncertainties about the achievable price in the countries concerned. As a result of an obligation to launch, the price may drop to extremely low levels or even zero in some countries, with spill overs through external reference pricing in other countries, while price negotiations in wealthier states may not make up for the loss in revenue. A resulting drop in revenues may undermined the incentive for some OMP developers to bring products to the market or at least undermine the effect of other incentives (e.g. market exclusivity) on which launch is conditioned.

Moreover, launching in all countries and immediately may become costly especially for small OMP developers that do not have the capacity to launch broadly.

Finally, a launch obligation would put the responsibility of achieving broad access only on one party, the developer. As a consequence, a launch obligation does not as such address one major barrier that prevents patients from accessing medicines in lower-income countries: the lack of a healthcare infrastructure that could sustain diagnosis and treatment of patients with a given rare disease.

Partnerships can enable access

Partnerships between pharma companies and national-level stakeholders are a powerful tool to put the conditions into place that will allow rare disease patients in the least wealthy countries to access treatments. These partnerships need to take systematic approaches to identifying access barriers and planning access – inspiration can for instance be drawn from the company case studies on structured access planning highlighted by the Access to Medicines Index[4], see Box 11 on next page.

Among other things, partnerships need to tackle two key issues:

1. **Affordable solutions in the pricing of OMPs:** Developers and national HTA/reimbursement bodies need to find a clear commitment to reaching affordable solutions in pricing and reimbursement that will safeguard the sustainability of the developer's business. Here, tiered pricing is a way for companies to reflect the socioeconomic status and health system maturity of low and middle income countries while maintaining their long-term business sustainability[3]. Takeda, for instance, uses a four-tiered country system to set its prices based on a set of indicators including GDP per capita and healthcare system maturity. Such pricing can only work if based on the principle of solidarity between EU member states and embedded in a strong framework that prevents counterproductive practices such as external reference pricing and parallel trade.

2. **Building supporting healthcare infrastructure:** Next to affordable pricing, the tackling of barriers in the healthcare system infrastructure that prevent access today is necessary. Without these accompanying measures, true access will not take place.

1) See discussion in chapter 1 // 2) See pages 45-48 // 3) Yadav (2010) // 4) Access to Medicines Foundation (2021)

A European forum to develop equity of access solutions

What next?

European rare disease companies and countries should engage in a forum that has a holistic approach to finding solutions enabling patient access. This means combining two measures into an access partnership for selected countries in Europe: first, to work with tiered pricing that take into account country wealth to remove pricing as a barrier to swift patient access. Second, to combine this with partnerships that strengthen the healthcare and diagnosis infrastructure in the concerned countries.

Such a partnership would need to be accompanied by:

- A selection mechanism for the countries included that separates out the least wealthy countries
- A simplified access pathway, whereby the time to market is minimised
- Accompanying rules that ensure the integrity of pricing from a developer perspective
- Investments in healthcare infrastructure that are at least co-financed by public stakeholders

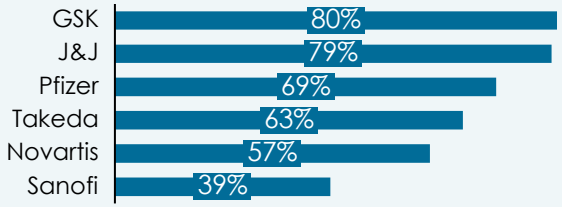
This undertaking needs to be overseen by a central committee, in order to ensure fairness, long-term sustainability, and wider adherence across the pharmaceutical industry and EU member states.

Box 11. Structured access planning by leading companies

According to the Access to Medicines Index, six companies lead in developing structured approaches to access planning, pairing R&D projects with a plan for rapidly ensuring treatments are made available in low-and middle-income countries as soon as possible. These access plan comprise a range of activities, including prioritisation of country launches by disease burden and strengthening supply chains to ensure all populations gain fair access.

Top 6 companies with access plans

Percent of R&D projects with access plans



Source: Access to Medicines Foundation (2021)

Box 12. Diagnosis partnership

The Global Commission to End the Diagnostic Odyssey for Children with a rare disease is a partnership created in collaboration with Takeda, EURORDIS and Microsoft to offer a system-wide solution to the challenge of diagnosing rare diseases. The partnership brings together representatives from multiple sectors to provide diverse perspectives and to develop an actionable roadmap to shorten the multi-year diagnostic journey for rare disease patients, which is considered a key to a longer, healthier life. Moreover, The Global Commission members are committed to continuing to champion the issue of shortening the diagnostic journey and to encourage the rare disease community to act on the Global Commission's recommendations.

Source: The Global Commission to End the Diagnostic Odyssey for Children with a rare disease (2019)

Key enabling factors for European forum

- **Considering broader set of relevant actors,** involving other actors such as medical technology companies, transport services and NGOs
- **Work flexibly and with a long-term vision** to adjust to changing environment and patient needs
- **Establishing an operational framework that** ensures fair prices in countries also outside of the agreements, while maintaining the commercial viability for pharmaceutical companies to develop highly innovative but costly and risky treatments.

Trust in RWE through a European learning network

Data and evidence are a crucial input to medicine development and innovation
Along the value chain, medicine developers use data to shape their R&D plan and clinical trial design and both measure and demonstrate the efficacy, safety and benefits of a treatment.

OMP development is particularly challenged on the data-front, because RCTs are often not feasible for reasons such as small patient populations and inconsistent disease courses. These characteristics challenge the design of classical clinical trial settings, meaning that OMP developers are unable to produce sufficient evidence.

Therefore, in rare diseases, real world data (RWD), or **observational data** not gathered from RCTs, becomes a crucial source of evidence. When RWD is used to demonstrate the usage and potential benefits or risks of a new treatment it becomes **real-world evidence** (RWE). RWE can offer complementary information on the efficacy of rare disease therapies, but also reveal deeper understanding of rare diseases and the disease burden on patients – from the patients themselves. RWE cannot only be used as important input at the regulatory approval stage, when demonstrating safety, efficacy, and significant benefit of a new OMP, but can also serve as important input into R&D programs and inform the decisions of payers and HTA bodies, see Figure 19 below.

Today, RWD is amply collected through various sources, such as public health records, patient-reported outcome surveys, and isolated R&D programs of OMP developers. It allows to understand the lifecycle of a disease over time, explore unmet medical needs and study the effects of different treatment uses by physicians. Hence, it is not surprising that the role of RWE, especially in rare disease research and OMP development, has become progressively more prominent. OMP developers are increasingly adopting tools, directing funds and designing R&D programs around RWE generation, see e.g. Box 13 (following page).

The potential of RWE is underexploited
However, today, the potential of RWE is underexploited. The large variation in the way RWE is collected and used hampers its acceptability and trust towards it as an input in e.g. OMP approval and market access processes.

This is in large part due to a lack of a common framework between developers and regulators that supports common recognition, standards and guidelines to be able to fully utilise the benefits of RWE at the regulatory and market access stage. This includes common approaches on developing fit-for-purpose datasets and clarity on the data methods that allow to solve key scientific or clinical questions.

Figure 19. RWE is a key input along the value chain

To leverage the potential of RWE it is necessary **to provide harmonised guidance, trust and acceptance**. This will allow using RWE in **three steps** of the development path:

Trust in RWE through a European learning network

What next?

Multistakeholder partnerships are a key tool to supporting the greater use of RWE. This has been demonstrated in the past through partnerships set up by companies, see Box 13, or other multi-stakeholder initiatives such as RWE4Decisions that aim at increasing the trust in RWE, see Box 14. Building on these existing initiatives, we therefore propose a European multi-stakeholder learning network for RWE that implements the use of RWE into the policy framework through three steps:

- First, the partnership should develop a clear set of harmonised guidelines at the EU level for the collection of RWE and on the standards that RWE should be able to meet as to provide legal certainty for OMP developers at the approval and market access stages.
- Second, alongside new rules, the partnership should enhance the acceptance and trust for RWE along the OMP lifecycle. This goes mostly be associating all relevant actors to the RWE generation framework .
- Third, the partnership should be accompanied by a clear framework for collaboration in RWE generation and data sharing which will allow a larger set of actors (companies, researchers) to benefit from RWE.

Box 13. RWE generation from the Takeda experience: CARMA-BROS

The Canadian Cancers with Rare Molecular Alterations - Basket Real-world Observational Study (CARMA-BROS), a collaborative research study between Takeda and Princess Margaret Cancer Centre, is the first of its kind to evaluate real-world outcomes in lung cancer patients with rare molecular alterations, such as Anaplastic Lymphoma Kinase (ALK). Takeda is committed to improving care for Canadian patients with lung cancer and has invested CA$ 2.4 million in this initiative. Over a five-year timeline, CARMA-BROS will collect data on the subset of Canadian cancer patients and compare overall treatment outcomes and toxicities in patients. While highlighting the need and feasibility of collaboration between industry and academia in improving clinical outcomes, the results will inform improved care for lung cancer patients with rare molecular alterations and facilitate the market access of innovative, rare cancer treatments.

Source: Takeda, and U. S. National Library of Medicine (2022)

Box 14. RWE4Decisions

The RWE4Decisions initiative is a multi-stakeholder group that brings together policy markers, HTA bodies, payers, regulatory agencies clinicians, patient groups, researchers, industry and academic experts, seeking define a new vision for the use of RWE. Under this initiative, stakeholders work together to agree on what RWE could and should be collected, when, by whom, and how, as to generate relevant and accepted RWE to be used by HTA bodies, payers, clinicians and patients. In September 2020, this group published a paper with recommended actions for stakeholders concerning RWE.

Source: https://rwe4decisions.com/

Key enabling factors for RWE learning network

- **Establish common purpose and objectives**, respecting the goals and interests of all stakeholders, in order to ensure alignment and motivation to stay involved.
- **Create a RWE sharing and generation framework that abides by the FAIR principles[1]**, in order to optimise the full potential, compliance, and use of data. This requires common set of requirements and the standardisation of data as to ensure that RWD can be brought together.
- **Incentivise engagement by all actors**, by considering what the risks of engagement are for each party and what rewards can offset the risk.
- **Define clear and transparent rules and expectations** for collaboration for all stakeholders, in order to foster a culture of trust and responsibility.

1) FAIR principles relate to data that is **f**indable, **a**ccessible, **i**nteroperable and **r**eusable

Source: Takeda internal documents

Integrate patient voices across the OMP lifecycle

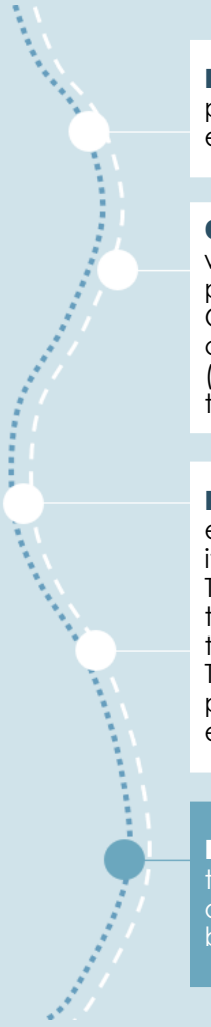
The voice of rare disease patients is vital

Rare disease patients should be at the centre of all development activity in the rare disease space, because they are the ultimate recipients of treatments and an important source of knowledge and data both for the initial development phase of a treatment and for its further development.

Patient engagement can deliver value at all stages of the OMP lifecycle, see Box 15. Although data on the impact of systematic patient involvement is scarce, existing evidence points to substantial benefits. For instance, research by the Economic Intelligence Unit comparing clinical trials with and without significant patient involvement showed that patient-centric trials performed better, with 87% yielding positive results versus 68% in the control group[1]. Research by the Tufts Centre for the Study of Drug Development (CSDD) demonstrated that patient-led improvement of clinical trial design may come at a small added cost but has the potential to substantially increase the value of the medicine under trial.[2]

Importantly, improving patient lives is a goal that all actors involved in the development process (researchers, developers, regulators, payers) share. Therefore, the patient perspective is an important 'common point of departure' and patient involvement can create trust in stakeholder interactions.

Box 15. Value of patient engagement along the development lifecycle



Basic research. Patient engagement offers a better understanding of patients' unmet needs, therefore allowing for better prioritisation of research efforts.

Clinical development. Patient engagement creates vital insights on willingness to engage in clinical trials, how to reduce the burden of clinical trial participation and add the patient perspective to endpoints (Patient Reported Outcomes, PRO, e.g. which symptoms are most important to address).[3] They can therefore improve recruitment into and reduce failure rate in clinical trials (due to patient drop-outs) and allow developers to collect data on outcomes that really matter to patients.

Regulatory approval and market access. Direct patient engagement in early dialogues with regulators and HTA bodies offers valuable insights on what it is like to live with a condition and what they expect from new treatments. They can help shape clinical trial design and agree on primary endpoints. At the market access stage, patients can bring perspectives on the value that a treatment has for them compared to the standard of care.
Thereby, regulators may be more receptive to learning about patients' perspective directly from patient communities rather than from the developer engagement with these communities.[4]

Data creation all along the lifecycle. Patient engagement supported by the use of digital technologies allows the collection of data for the production of RWE instrumental to better understanding the disease burden, treatment burden and the disease impact in real-life settings.

Sources: 1) The Economist Intelligence Unit (2018) // 2) Levitan et al. (2018). // 3) Pharma Board Room (2020) // 4) The Economist Intelligence Unit (2020)

Integrate patient voices across the OMP lifecycle

Today, rare disease patients, especially those with approved therapeutic options on the market, are more informed of their diseases and their therapeutic options than previously. Overall, we have witnessed an increase in the number of rare disease patient associations accompanied by a marked increase in their capability to interact with other stakeholders, such as researchers and regulators. This is at least in part thanks to umbrella organisations or individual companies playing an active role in supporting patients groups in building the necessary knowledge and confidence to engage with regulators and scientists. The EURORDIS Open Academy[1] is one prominent example. Other organisations, such as the European Reference Networks (ERNs) also play an important role in bringing patients together with other stakeholders. Each of the 24 ERNs work closely with patients and health care providers across Europe and facilitate the exchange of knowledge and centralised care and advice for patients living with rare diseases.

Together these initiatives have amplified the voice of rare disease patients and increased the recognition of patients as the central source of disease understanding.

However, patient engagement is not systematic along the lifecycle

Today patient involvement in the OMP lifecycle is not systematic, but rather inconsistent and fragmented. The degree in which patients are involved still depends on the existence and resources of patient advocacy groups, the individual organisational practices by OMP developers and regulators and differs by geography. For instance, among EU ERN's the level of involvement of patients still varies and a culture of partnership with patients does not exist in all 24 networks[2]. Moreover, while a large share of HTA bodies across the world directly involve patients in the HTA process, the modes of engagement vary greatly (from written input over hearings and interviews to advisory groups).[3]

Moreover, even where there is a will to involve patients, meaningful patient engagement can be difficult to achieve. Too often patient involvement is sporadic and transactional without creating opportunities for long-term mutual learning.

These barriers and hurdles mean that, today, patients continue to be a largely underutilised stakeholder group and untapped resource in medicines development.

What next?

Closer and more systematic engagement with rare patients will contribute to bridging the knowledge gap on the patient experience at approval and market access stage. Patient engagement built on a partnership logic, centred around the collection and use of patient-data and insights along the OMP lifecycle can serve to systematically bring the patient experience into all decision-making points. Such a partnership should be designed around a systematic approach to recruitment, a hub for shared patient data, and engagement and dialogue formats that can allow patients to make meaningful contributions to the decisions. In parallel, policy makers should identify the supporting legal framework needed for the shared data infrastructure.

Such measures can pull together existing tools and initiatives from different stakeholders. EURORDIS brings significant expertise for patient engagement, for instance through the Community Advisory Board Programme. In addition, OMP developers have substantial experience from implementing programs and tools for systematically including patients (and physicians) in medicines development and the co-creation of appropriate health systems beyond innovative medicines. For example, Takeda has directed its R&D strategy from developing treatments *for* patients to developing medicines (and improving care infrastructures) *with* patients, from the design of clinical trials over the patient journey mapping efforts and enabling direct data collection from patients through digital technologies, see Box 17.

Finally, a framework and toolbox for enabling a meaningful patient engagement across the OMP lifecycle has already been developed by the PARADIGM programme, see Box 17, in a partnership between patient organizations, medicine developers, not-for profit organizations, regulators and HTA bodies.

1) EURORDIS (2022a) // 2) Finnegan (2021) // 3) Gunn et al. (2021)

Integrate patient voices across the OMP lifecycle

Key enabling factors for patient engagement

- **Find a shared purpose**: identify and agree among stakeholders on the shared purpose of the activity. This requires each stakeholder to be open about the individual goals and interests of their organisation.
- **Outline clear benefits for all actors:** identify the value that the activity creates for all actors involved. In particular, define what is in it for the patients beyond the promise of a new treatment down the line. For instance, patients may want to also benefit from the data and information generated.
- **Ensure representativeness** of involved patients, balancing diversity (geographic, gender etc.) with expertise
- **Address barriers to engagement** on the patient side, e.g. through financial compensation to ensure engagement continuity based on clear policies and metrics[1] and by ensuring accessibility using new technologies.
- **Define clear and transparent rules** of engagement that lay down how particular stakeholders collaborate with each other respecting capacity, resource and other constraints
- **Build capabilities for and a culture of engagement** in the organisations involved. This includes the provision of training and changes to key performance metrics, see example from Takeda in Box 14.
- Through tools employed, **foster a culture of openness to the patient perspectives** and mine for new learnings instead of trying to get confirmation for what we believe we already know
- **Measure impacts and outcomes** to track success.

Box 16. Organisational change to integrate patient engagement

In the past, patient engagement was siloed in pharma companies. Recently, Takeda has deployed a great organizational effort to integrate patient engagement as a routine practice across the entire company and its many functions.

In 2020, Takeda required all programme teams to have a patient engagement plan mapping out how they will partner with patients along the entire development process.

These activities were perceived as valuable, motivational and increased understanding of patients' unmet needs.

1) See US National Health Council (2022) for an example of clear financial compensation policies and metrics for patient engagement activities

Integrate patient voices across the OMP lifecycle

Box 17. PATIENT ENGAGEMENT EXPERIENCES

DESIGNING CLINICAL TRIALS
Friedreich's Ataxia

When Takeda's Global Development Team engaged with patients about the primary endpoint for a clinical trial of a potential new treatment for Friedreich's Ataxia, a rare genetic disorder affecting the brain and the spinal cord, they learned that patients preferred the improvement of fine motor skills over improving their ability to walk. As a result, Takeda suggested to change the primary end point from the traditional walking test to a peg test requiring fine motor skills. The regulator accepted this change after holding a meeting with patients where Takeda was not present.

Source: Wang et al. (2021) and Takeda

COLLECTION DATA & INSIGHTS
MyHAE app

Takeda's MyHAE app allows patients with HAE to systematically report their disease to clinicians all while receiving personalised reminders and report that help them manage their disease and adhere to the treatment. The app allows Takeda to collect real-world data which will help with the generation of real-world evidence. For broad adoption, usability and a clear value for the concerned patients is key.

Source: Apple (2022)

EURORDIS CAB Programme

Patient Community Advisory Boards (CABs) are groups established and operated by patient advocates as part of a programme organised by EURORDIS. A CAB is a group of patients centred around a specific disease to offer expertise to sponsors of clinical research. CABs are an example of how patients can significantly contribute along the OMP development path. Through CABs, patients provide inputs on a variety of topics from patient outreach, clinical studies design and criteria for participation, to clinical endpoints and their measurement, patient relevant outcomes (PROMs), disease registries and their features

Source: EURORDIS (2022b)

PARADIGM

Between 2018 and 2020, the IMI-funded multistakeholder consortium PARADIGM (Patients Active in Research and Dialogues for an Improved Generation of Medicines) worked to provide a framework for structured, effective and ethical patient engagement along the medicine lifecycle with a focus on delivering tools and practices to 'mainstream' the integration of patient perspectives at three key decision-making points: research and priority setting, clinical trial design, early dialogues with regulators and HTA bodies. The tools help with identifying the competences and resources necessary for all involved stakeholders (at individual and organisational level) and gives guidance on rules of engagement.

Source: European Patients' Forum & EFPIA (2022)

THE EUROPEAN PATIENTS' ACADEMY (EUPATI)

The European Patients' Academy (EUPATI) is a pan-European project established in 2012. It is a public-private partnership run by a multi-stakeholder consortium.

EUPATI focuses on education and training of patients to increase their ability to understand and contribute to research and development of medicines, and improve the availability of objective, reliable, patient-friendly information. This project has so far trained over 150 expert patients. EUPATI also provides training on patient engagement for all stakeholders. In addition, it offers and maintains the Toolbox on Medicines R&D, and coordinates a network of National Platforms.

Source: European Patients' Forum (2022)

Sources: Takeda; The Economist Intelligence Unit (2020)

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APPENDIX

Modelling exercise

We modelled a hypothetical orphan OMP development project to estimate the effect of possible revisions of the OMP Regulation on investment incentives.

We modelled a development project for a more average OMP and a very rare OMP through a risk-adjusted NPV (rNPV) model. The rNPV model is a standard valuation tool used in the pharmaceutical sector to assess the profitability of investment projects and therefore guide investment decisions, see box below.

The model covers the lifecycle of the development project, from phase I clinical trials (the assumed time of the investment decision) to the post-market exclusivity period. The inputs to the model are mostly based on literature studies, see next page.

We modelled a baseline scenario reflecting the current situation and incentives provided by the OMP Regulation.

We then modelled different scenarios reflecting possible revisions of the OMP Regulation to assess how these would affect the profitability of the project (i.e. change the rNPV) and therefore investment incentives.
We modelled the following scenarios (i) loss of orphan designation, (ii) 2 additional years of market exclusivity, (iii) early partnership between OMP developer, regulator and HTA/payers focused on evidence. The changes to the modelling assumptions assumed in these scenarios are presented in the main text of the report.

The risk-adjusted NPV model to evaluate incentives to invest in OMP development

Net Present Value (NPV) models are a class of valuation tools commonly used by investors across all industries to inform their decision-making. In the pharma industry, investors and valuation experts commonly use risk-adjusted NPV models (rNPV).

rNPV models allow for a more granular incorporation of the risk specific to the medicine development project. They capture the risk of the investment in (i) the discount rate, which reflects the market risk and company risk, and (ii) the probabilities of success, which reflect the project-specific risk of failure at different stages of the development path:

$$rNPV_0 = -I_0 + \sum_{t=1}^{T} Q_t * \frac{(p_t * q_t) - C_t}{(1+r)^t}$$

where I_0 is the initial investment, p_t is the expected price at time t, q_t is the expected volume sold at time t, C_t is the expected cost at time t, r is the discount rate and Q_t is the probability of success of the project at time t.

The model has to be populated with the investor's best estimate of costs, risks and sales volumes generated by the project. These will often come from the relevant literature and data bases, the investors' experience and from studying the properties of the project in question.

An investor decides to invest in a specific project if its rNPV *at least* positive. In this case, the investment is profitable given the expected costs, risks, market size and timeline of the project.

Modelling exercise

Inputs to the rNPV model		
Parameter	**Input**	
OMP characteristics	NME indicated for a very rare disease with prevalence of 0.2 in 10,000[1] NME indicated for a rare disease with prevalence of 3 in 10,000[1]	
Duration of phases	Phase I: 3.7 years[2] Phase II: 4.5 years[2] Phase III: 4.7 years[2]	Approval: 1.2 years[3] Market access: 0.6 years[4]
Costs[11]	Phase I: EUR 3m[12] Phase II: EUR 19m[12] Phase III: EUR 39.9m[12]	Approval: EUR 12.5m[4] Market access: EUR 2m[1] Post-launch costs: profit margin 24%[10]
Probabilities of success	Phase I: 76%[5] Phase II: 50%[5] Phase III: 73%[5]	Approval: 89%[5] Maintaining ODD: 88%[9]
Discounting	12%[6]	
Revenues	EU revenues estimate based on: • Number of patients: estimated based on assumed prevalence • Treatment cost per patient: median cost of OMPs[7] • Time to peak sales: 7 years from approval[1] US and RoW revenues estimated assumed that EU revenues constitute 24% of global revenues. Revenue erosion after expiry of protection period: probability of generic entry 44%[13] and progressive erosion of revenues starting from 45% in the first year[8]	
Geographic scope	Global	

1) Assumption // 2) Jayasundara et al. (2019), Additional file 2 // 3) Alqahtani et al. (2015) // 4) Assumption based on Takeda's experience // 5) Thomas et al. (2016) // 6) Stasior et al. (2018). and, Villiger and Nielsen (2010) // 7) Chachoua et al. (2018) // 8) van der Schans et al. (2021) // 9) Copenhagen Economics based on Hofer et al. (2018 // 10) Industry average, Damodaran database // 11) We used figures from the literature but we acknowledge that development costs can be substantially higher for specific OMP projects. // 12) Copenhagen Economics based on Jayasundara et al. (2019) in 2020 EUR values based on the average exchange rate in 2013 from the European Central Bank and in the harmonized index of consumer prices (HCIP) in 2013 and 2010 based on data from Eurostat. // 13) European Commission (2019)

Innovating for people living with a rare disease

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