



Breaking the Access Deadlock to Leave No One Behind

A contribution by EURORDIS and its Members
on possibilities for patients' full and equitable access
to rare disease therapies in Europe

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Why this paper?

This paper is a contribution from EURORDIS and its members that offers a synthesis of their analysis, reflections and perspectives on the issue of access to rare disease therapies. This is the final version following a reflection process initiated in February 2017 at the EURORDIS Symposium on “Improving Patient Access to Rare Diseases Therapies”.

During these last months, EURORDIS has listened to feedback, collected new information, and tested ideas, which are now weaved into this collective contribution. **This paper expresses a set of possibilities, strategic orientations and concrete actions that we, as representatives of the rare disease community, believe to be the right approach to ensure better access to adequate care and in particular therapies.**

When it comes to patients’ access, we refuse to take no for an answer. We will not cave under the weaknesses of the current model. We stand up and speak for **patients first**. We, rare disease patients, are not the problem: we are part of the solution.

We believe that viable new models to improve access can only be:

- addressed if elevated to a higher political level within each stakeholder constituency;
- developed through a collective conversation involving all stakeholders, so as to be negotiated and co-constructed in a socially responsible manner; and
- shaped into a comprehensive framework with a global outlook in addition to addressing each technical element and each possibility.

Life-saving and life-improving treatments are sometimes available, but we need them to be affordable for national healthcare systems; we need a sustainable and predictable environment, and most importantly patients must be able to access them.

The ambition of EURORDIS is to have 3 to 5 times more new rare disease therapies approved per year, 3 to 5 times cheaper than today by 2025.

In today’s world, science and technology offer an unprecedented chance to address the unmet medical needs of people living with rare diseases. Before this potential can be translated into actual health benefits, access is creating a deadlock. Our objective is to unlock it with determination so as to leave no one behind.

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1. Executive summary

EURORDIS-Rare Diseases Europe, in the spirit of building on the UN Right to Health, and the UN Sustainable Development Goals of “ensuring healthy lives and promoting the well-being for all at all ages” and of “leaving no one behind”, believes that all people are entitled them to the same quality of care.

Thanks to advancements in science and a favourable legislative environment, the number of therapies for rare diseases has increased dramatically in the past decade and will continue to increase in the foreseeable future. People living with a rare disease must be able to hope for new therapies and to benefit from them rapidly and fully, all across Europe, as soon as they are approved.

Access to Medicines: Overcoming the Weaknesses of the Current Model

The issue of access to medicines in general has gained in recognition over recent years for a number of reasons:

- The persistence of a deteriorating economic context since the 2008 crisis, and its consequences on the labour market and on fiscal revenues, which exert a direct negative impact on the financing of social security institutions;
- The continued ageing of populations, which in turn amplifies the demand for care;
- The very organisation of healthcare systems themselves, which need to be revisited and adapted to the challenges of today;
- The increasing cost of the development of an innovative medicine, all the way from bench to marketing approval;
- The arrival of very innovative medicines for widespread conditions put on the market by their manufacturers at unprecedented high prices;

Faced with the above, payers and health insurers – and even policymakers and the public in general – have found themselves in a challenging situation in which limited resources at their disposal mean difficult choices.

The EU Regulation on Orphan Medicinal Products 1999 continues to be a success in fulfilling its primary purpose - to attract investment to the development of therapies for life-threatening or debilitating diseases for millions of people who today have either no treatment at all or no satisfactory treatment. To date, 143 products have been approved under the EU Orphan Drug Regulation since its adoption, 97 of which are still currently holding orphan status after their period of market exclusivity. This is a genuine success, and one that should be **celebrated proudly by all**.

Contrary to what many believe, the orphan status of a product in Europe is not easy to obtain, is not easy to maintain, and is not meant to last forever. From all orphan designation applications submitted to the Committee for Orphan Medicinal Products at the EMA, **only 72% receive a positive opinion for designation**. Amongst the products designated based on a potential significant benefit over an existing treatment, **27% more will be losing their orphan status at the time of receiving**

their marketing authorisation. This demonstrates the truth that the evaluation of the orphan status is strict and only for therapies addressing unmet medical needs or non-satisfactory treatments.

However, our daily experience provides countless examples of situations when **the price of a new orphan medicine proves to be the stumbling block on which manufacturers and payers fail to agree**, with potentially **dramatic consequences for the patients in need of access to therapies.**

It is fair to acknowledge that orphan medicines have become an attractive destination for investment thanks to the many incentives offered by the legislation – e.g. scientific advice and protocol assistance (with fee exemptions), orphan status, market exclusivity, and so on. It is also important to remember that recent research pointed out that of the **70+ orphan medicines approved by the EMA up to April 2014, 24% of them had an annual cost inferior to £10,000 (€11,000), and only 18% of them an annual cost superior to £100,000 (€111,000).**

There is also a strong body of evidence and literature to demonstrate that orphan medicines continue to represent overall an extremely small fraction of the pharmaceutical budgets of the EU Member States: several robust and independent sources converge to figures well **below 5% of the total pharmaceutical expenditure on average for EU Member States.**

We acknowledge that some “high-price-by-default” policies of certain individual companies, with little or next to no justification other than what the market is perceived to be able to bear, have earned orphan medicine manufacturers a widely negative reputation.

The top three issues that we see having the most impact on access to innovative therapies for people with rare diseases are:

1. **An unsustainable economic model that fuels mistrust between payers and companies:** due to their complexity, orphan medicines pose many different challenges to competent national authorities for pricing and reimbursement, not least as they increasingly tend to arrive at marketing authorisation with higher levels of uncertainty on efficacy and effectiveness.
2. **A vast disconnection between the value of a product and the price claimed:** we see real-life cases of new products for diseases with high unmet medical needs being approved for commercialisation by regulatory authorities but never making it to the patients who need them most because they are deemed too expensive or not seen as presenting sufficient value for national healthcare systems.
3. **The cost of developing new therapies remains too high,** despite advancements in modelling and assessment techniques that could decrease investments dramatically.

It is our view that maintaining such an approach is fundamentally unsustainable, and that industry associations, leading corporate players and also the investor community must take a firm stance towards a fairer pricing strategy and business model.

A framework of possibilities for a comprehensive approach to patient access

We believe the current access framework, certainly in Europe, to be unproductive and outdated. The quest for ways to improve and widen access for patients to orphan medicines must begin farther upstream, at the very moment when medicines are being researched and developed.

For each new orphan medicine coming to market, it will be key to ascertain:

1. what the right budget impact should be based on the therapeutic indication rather than the prevalence of the condition
 - a. for a given level of price for a well-defined patient population
 - b. for a given level of uncertainty over the clinical efficacy and effectiveness based on scientific data related to the product.

We must remember that the majority of people living with a rare disease at this very moment have delayed or no access at all to the medicine they need, or that there is no existing medicine.

If a therapy is approved but does not reach those who need it, it has failed in its primary purpose. We need to close the gap between innovation and access, which is primarily due to the discrepancy between authorisation granted at EU level for a market fragmented across 28 different countries.

We strongly believe that overall, the current access decision framework, which focuses disproportionately on the financial dimension rather than on improving patient outcomes based on the generation of additional clinical data, needs to be majorly overhauled.

All stakeholders have an urgent collective responsibility to shape a new approach that will accelerate the transfer of major scientific advancements into new therapies in a predictable and sustainable way for society. The ambition of EURORDIS with this approach is to have 3 to 5 times more new rare disease therapies approved per year, 3 to 5 times cheaper than today by 2025.

This approach should encompass the following four-pillar proposal:

1) A new blueprint to cut costs and fast-track R&D (Chapter 4.1):

Several existing tools, techniques or methodologies allow medicines to come to market in greater numbers and for lower investments. There is good reason to believe that they would dramatically reduce the cost of R&D for rare disease therapies, reduce the number of patients who need to be involved in clinical research and also reduce the overall time necessary for full development.

[Read our recommendations](#) (p.28)

2) Early dialogue and cooperation between healthcare systems on the determination of value and on patient access (Chapter 4.2):

A new, more sustainable approach for tomorrow must rest on a more systematic and effective practice of collaboration for a seamless and ongoing dialogue on value with product developers, from the very earliest stages of assessment and decision-making onwards, and across all levels of responsibility, with the due involvement of clinical experts and patient representatives.

[Read our recommendations](#) (p.33)

3) A European transparent cooperation framework between national healthcare systems for the determination of fair prices and of sustainable healthcare budget impacts (Chapter 4.3):

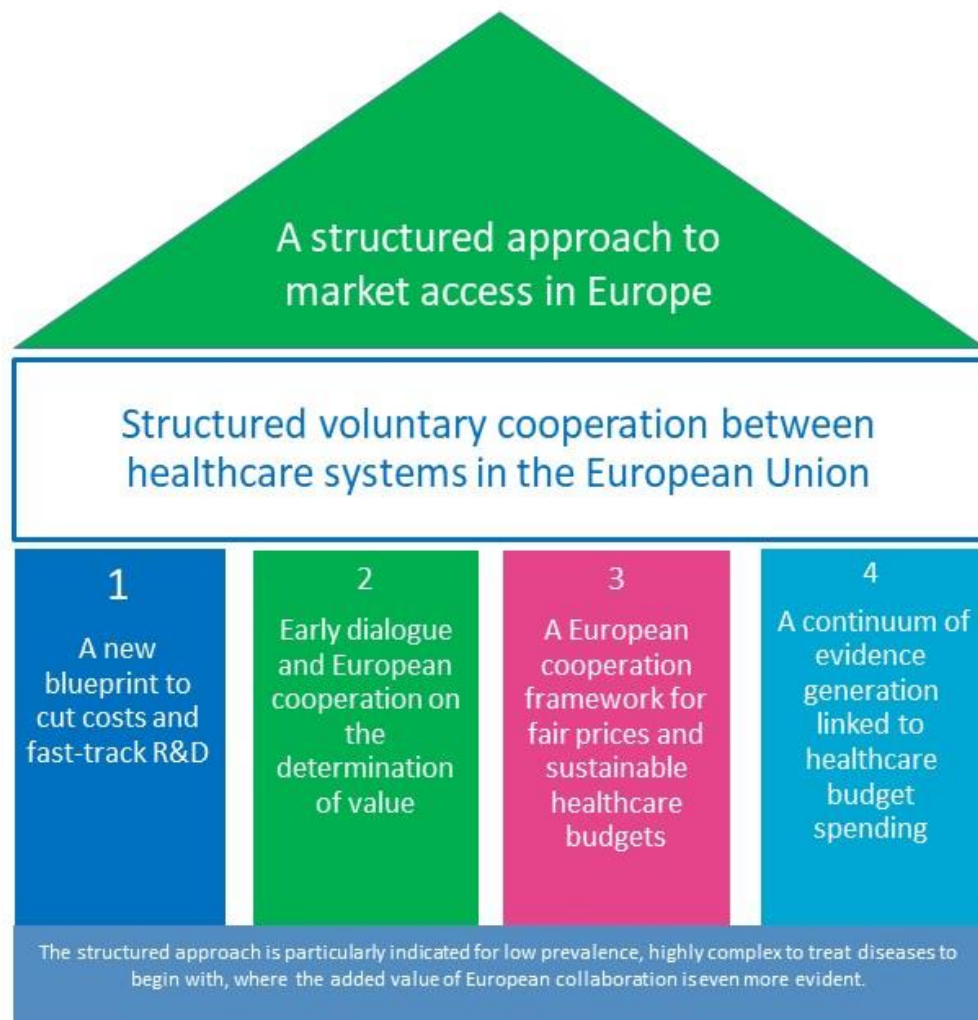
A transparent framework for the determination of prices based on costs, value and policy-defined priorities, supported by a set of well-defined and well-accepted criteria, will help ensure a better and more evident linkage of medicines' prices to the fundamental components of their value.

[Read our recommendations](#) (p.42)

4) A continuum approach to evidence generation linked to healthcare budget spending (Chapter 4.4):

The proper assessment of an innovative technology must not be *ex ante* only, but also *formative* (i.e. at the very moment when the innovation is being rolled out or implemented in real clinical practice) and even later *summative* (i.e. offering a 360° view of the full impacts of the innovation under study).

[Read our recommendations](#) (p.56)



The time for radical action is now

Our motivation behind this position paper is to ensure greater recognition and understanding of the major problems that people living with a rare disease in Europe today face all too often, and to create and feed a genuinely constructive dialogue on the basis of the proposals the formulated above.

It is our view that this debate remains fundamentally a political one. Are we ready to agree that, from a social justice perspective, it is right and just to give all people living with a rare disease the treatments they so urgently need, as soon as these treatments exist and are available?

Indifference is not an option. We want all parties in this debate to take the time to express their respective interests and to reflect on the possibilities expressed in our paper. We call on national competent authorities for pricing and reimbursement and pharmaceutical manufacturers to indicate where they stand on each of our proposals – what they would be ready and willing to take up, and what they would be more reluctant to accept.

We believe that a new ecosystem is possible, a framework based on a global approach to innovation for unmet medical needs and on sustainability for healthcare systems as well as financial attractiveness to industry and investors. And we do not believe that this is a “futuristic” dream: a structured approach can be built with practical solutions and methods that have already been put in practice at varying levels and on different scales.

While an overwhelming proportion of recent debates on access tend to focus solely on innovation in products, we trust that innovation matters too in processes and behaviours. Today's challenges will not be solved by applying yesterday's mindsets. If risks must be taken to deliver scientific breakthroughs and genuine innovation, risks must also be taken to make sure that tomorrow's processes and policies are more adequate and also fairer than today's.

Today's challenges will not
be solved by applying
yesterday's mindsets

Access to and the affordability of medicines, particularly for minority populations as in the case of rare diseases, is today a major point of tension in our societies. The people living with a rare disease that EURORDIS represents are not approaching this debate with a view to demanding special rights carved out from the norm as a disadvantaged community.

On the contrary, since this paper has been developed in collaboration with our membership, it clearly demonstrates that we are positioning ourselves as responsible citizens eager to find fair and balanced solutions that respect the humanistic values at the core of our European society model, and that allow all of us to fully take part in the life of our societies in an inclusive approach. We also believe that the call for more structured access that underpins this paper will, if fulfilled, reinforce the attractiveness and competitiveness of Europe on the global marketplace.

Ultimately, we, the rare disease community, and more broadly all stakeholders having an individual responsibility in developing new therapies and providing them to patients, have an urgent collective responsibility to shape a new approach which will accelerate the transfer of major scientific advancements into new therapies, in a predictable and sustainable way for society.

2. Access to medicines: Overcoming weaknesses of the current model

The issue of access to medicines¹ has gained recognition over recent years, particularly as **national healthcare systems have come under increased financial pressure as a consequence of several factors** including, but not exclusively:

- The persistence of a deteriorating economic context since the 2008 crisis, and its consequences on the labour market and on fiscal revenues, which exert a direct negative impact on the financing of social security institutions;
- The continued ageing of populations, which in turn amplifies the demand for care;
- The very organisation of healthcare systems themselves, largely inherited from more affluent times in our history, and which need to be revisited and adapted to the challenges of today, e.g. through a greater focus on prevention rather than treatment, on improved management of chronic conditions, and on greater efficiencies at all stages in the chain of care;
- The increasing cost of the development of an innovative medicine, all the way from bench to marketing approval, today estimated at USD 2.6 billion ^{a b}.

Against that backdrop, pharmaceutical products have naturally come under the spotlight as a substantial item within the total healthcare expenditure of a country. **The extent of the actual contribution of pharmaceutical products to the worsening of the sustainability of healthcare systems is, however, debatable.** While voices have arisen to note a perceivable increase in the prices of medicines over years, often described as questionable², it must still be noted that in many

European countries the percentage of budget spent on pharmaceuticals within the total healthcare expenditure has either remained stable *or even decreased* between the 1970s and the present time^c, while in parallel healthcare expenditure itself has sharply increased in every single country over the same period^d. The very latest figures available from the OECD show indeed that, "*between 2009 and 2014, expenditure on pharmaceuticals dropped by 1.1% in real terms on average in the European Union*"^e, an evolution which needs to be put into perspective with the demonstrated increase in

¹ Although various definitions are often used, we lend support in this paper to that formulated by the United Nations Development Group in 2003 as part of its "Indicators for Monitoring the Millennium Development Goals (MDG)", which puts to the fore the notions of *continuity in availability and affordability* at public or private health facilities *within reasonable distance* from the homes of the population. In the same spirit, *sustainable access* is seen as dependent on four elements: (1) the possibility for patients to receive *appropriate* medicines *in the correct dosages and within the required time frames*; (2) the ability of governments and individuals to *afford* the medicines essential to maintaining health; (3) *the continuous availability of funds* to pay for treatments; and (4) the existence of health and supply systems that ensure that medicines are available when required.

² Such criticisms have been going particularly strong in past years with the arrival of new innovative medicines with prices well into the 5- to 6-digit range, e.g. the latest generation of direct acting antivirals against hepatitis C (one of which being the well-known Sovaldi by Gilead). Even more recently, a number of cases of so-called "price gouging" by individual companies (e.g. Turing, Valeant, to name but the most prominent ones) were exposed and garnered substantial attention both from the general public and from policymakers. "Price gouging" is defined as an increase in the price of a given medicine, up to a level much higher than may be considered reasonable, fair or even ethical.

longevity and reduction in premature cancer mortality attributable to pharmaceutical innovation over the same period of time.^f



8 November 2017

Figure 1 - The success of the Regulation on orphan medicinal products is proved by the numbers.

2.1. Orphan medicines: framed as the perfect culprit

In that context, orphan medicines have received particular attention. Orphan medicines are pharmaceutical products designed for the treatment of rare diseases, a family of more than 6,000 medical conditions, each of which shares the common feature of affecting a small to ultra-small population of patients – typically less than 1 in 2,000 people. Many of them are of genetic origin and manifest from early childhood onwards. They are frequently chronic, degenerative and disabling, and often cut short the life expectancy of affected individuals.

These very characteristics of rare diseases raise a number of questions, for instance in terms of the level of prioritisation and resources public healthcare systems should dedicate to them as opposed to more widespread diseases affecting much larger populations. Should people living with a rare disease be entitled to the same level of care?

A proper, unbiased answer to these questions must take its roots in the essential principles of social justice, equality and solidarity that form the cornerstone of our societies, and that have long been recognised as such by the Member States of the European Union – most recently in the Council Conclusions of the Maltese Presidency of the EU of 16 June 2017, which reiterated that *“health systems deliver a wider social benefit that goes beyond human health protection and make a major contribution to social cohesion, social justice and economic growth”*.⁹

1/4 of persons living with a rare disease in Europe report that the treatment they need has not been available in their country over the previous 12 months

[« Access to treatment: Unequal care for European rare disease patients » A Rare Barometer Survey \(February 2017\)](#)

The European Union has very clearly chosen to follow that path as early as December 1999, when the groundbreaking **EU Regulation (EC) No 141/2000 on orphan medicinal products** stated that *“patients suffering from rare conditions should be entitled to the same quality of treatment as other patients”*. The June 2009 **Council Recommendation on action in the field of rare diseases** went even farther, by emphasizing that *“the principles and overarching values of universality, access to good quality care, equity and solidarity, as endorsed in the Council conclusions on common values and principles in EU health systems of 2 June 2006, are of paramount importance for patients with rare diseases”*.

These statements found substantial ramifications at the national level as EU Member States strived all through the years 2000 to 2015 to develop national action plans for rare diseases and translate into actual policy the ambition for social justice and greater assistance to individuals whose rare conditions generate an overwhelming accumulation of medical, social, financial vulnerabilities.

This approach has also found immense resonance at the global level, as we observed in recent years the emergence of a more structured global agenda around the notions of “Right to Health” and “Universal Health Coverage”. Amongst the 17 Sustainable Development Goals (SDGs) outlined by the United Nations as of late 2015, the third – entitled “Good Health and Well-Being” – enshrines the objective of *“ensuring healthy lives and promoting the well-being for all at all ages”* as essential to achieve any progress towards sustainable development. Even more so, the underlying ambition of all SDGs as a whole is, as spelled out by the UN itself, to *“leave no one behind”* – or in other words to reach first and foremost the populations who are furthest behind and have the greatest needs.

2.2. The pricing issue

Traditionally, orphan medicines often bear price tags well in excess of the prices of medicines for more common conditions, not least because of the challenges intrinsic to the development of often very complex therapies for no less complex diseases, and of the small to ultra-small size of the total population of patients which mechanically puts a firm limit on the size of the market from which a manufacturer can look to recoup its original research and development investment. In turn, that last element also explains why, historically, payers and health insurers have generally not shied away from covering the cost of orphan medicines and caring for persons living with a rare disease – precisely because, despite significantly high unitary prices, the low numbers of patients due to receive the said medicines meant that the overall budget impact and financial exposure to be incurred was ultimately of a reasonable order of magnitude compared, for instance, to that of chronic diseases which may be more widespread in the general population.

But, recently, that equilibrium itself has come under question for several reasons.

One of them is that healthcare systems have found themselves under a new, tremendous pressure because of the arrival of very innovative – and sometimes even breakthrough – medicines for widespread conditions such as HIV-AIDS, hepatitis C or various types of cancers (e.g. breast cancer, metastatic melanoma, or non-small-cell lung cancer, to name but a few)^h.

These medicines have been put on the market by their manufacturers at unprecedented high prices presented as a reflection of their genuine value, in particular when these new medicines offer a promise for cure or, at least, a shorter duration of treatment with far less negative side effects compared to older existing therapies. This watershed moment has led payers and health insurers to develop grave concerns that such prices, when put in relation to the much wider populations of patients suffering from these diseases, would lead to an inordinate budget impact well beyond what national healthcare systems are currently able to withstand.

There is in essence good reason to question and challenge such concerns, especially as it is a proven fact that competition between several products developed by different marketing authorisation holders has led in several cases to a significant decrease over time in both the prices and the budget impact on healthcare systems – thus showing that, for common diseases, economic regulation through fair market competition actually can work. However, little reassurance has been provided by current forecasts, according to which even more innovative medicines should see the light of day in the near future, particularly for very widespread conditions for which no treatment exists today (e.g. Alzheimer's as one major example) and at price levels which could not reasonably be expected to be any lower.

Faced with the above, payers and health insurers – but policymakers and even the public opinion in general – have found themselves pulled in a challenging situation where the limited resources available at their disposal mean exacting choices and prioritisation decisions have to be made. In such a context, **it is little surprising that the prices of orphan medicines have come under renewed scrutiny or even that questions have arisen as to whether it is more fair and just to cater for the needs of the very few or to those of the many.**

On top of this, a number of decisions or practices by manufacturers of orphan medicines have also, over time, raised questions in the minds of public health decision-makers and patient advocates alike as to whether the high price of a given orphan medicine should always be accepted as legitimate. Three obvious types of situations can be outlined.

- **It is reasonable to wonder whether there is any real justification in repurposing an existing, well established, and inexpensive hospital preparation for which there is no safety concern into a product subject to marketing authorisation, and whether that new product should then come at a price hundreds of times higher than that of the original preparation** when the approval remains based on a limited clinical data set, good manufacturing processes and toxicology studies. As we observed in all too frequent cases, while hospitals are obliged to prescribe the said products after approval, the steeply increased price means that decision-makers have to think twice and that, in many countries, either the treatment ceases to be provided or hospitals continue to provide the original hospital preparation in full breach of the European legislation. In such a situation, where is the clinically relevant advantage for patients and for the healthcare systems?
- **Another classic example is the extension of indications for a previously commercialised product, which is often accompanied today by a price increase, supposedly to recoup additional investments into clinical studies in the new condition under consideration.** But it is fair to challenge this: we should actually see much more contrasted situations according to the extent of the studies performed and to the size of the targeted population. For instance, in the case of an orphan medicinal product for which the different small target populations associated with each individual indication do add up to form a much less small population overall, why would it not be legitimate to actually open a discussion on the link between volume and price?
- And even in the case when a new orphan medicine represents a genuine, unquestioned scientific breakthrough, the value of which may then be reflected in a higher class of price, what is the unchallengeable rationale why its price should be set at a 6- or even 7-digit figure rather than a 4- to 5-digit one? Very little evidence is provided by companies and investors to justify this approach. **The fundamental question remains: who should ultimately pay for the next developments in the pipeline of a company? Should it be its shareholders through their investment of funds based on the capital value of the company? Or should it be the public healthcare system based on the value of the first product(s) approved and reimbursed for this company?**



Thaïs and Matthieu, mucopolysaccharidosis type 1, France.

2.3. Getting the facts straight

The situations described above are directly inspired by real developments, and raise no less genuine questions. **However, it would be a fallacy to infer from a few well identified cases that the prices of *all* orphan medicines are questionable, and that *all* orphan medicines are contributing to undermining the sustainability of our ailing healthcare systems.**

In truth, there also is a vast majority of orphan medicines approved and commercialised to date, the prices of which have fueled no controversy, such as the many approved treatments over the last 15 years for pulmonary arterial hypertension or multiple myeloma. As a matter of fact, recent research pointed out that the annual costs of 70+ orphan medicines approved by the EMA up to April 2014 ranged between £726 (€805) and £378,000 (€420,000) and that, while figures in the upper range are indeed significant, **the median cost was much more reasonable at £30,000 (€33,000) per annum.** In addition, the study showed that 24% of all orphan drugs considered in that review had an annual cost inferior to £10,000 (€11,000), and only 18% of them an annual cost superior to £100,000 (€111,000).ⁱ

« The annual cost ranged between £726 and £378,000 (median: £30,000). 24% of the drugs cost less than £10,000 annually [and only] 18% cost [above] £100,000 annually. »

[Onakpoya JJ, Spencer EA, Thompson MJ and Heneghan CJ. \(2015\)](#)

It is possible, and actually highly necessary, to have a more accurate and granular understanding of what appears to be a very diverse reality:

- **Hospital preparations** which have been approved as orphan medicinal products have prompted a heated debate around their high price tags in view of their sometimes very limited added value.³
- For medicines against **rare cancers**, which have significantly improved patients' hopes for survival for many such conditions, the debate has been dominated in the first 10 years following the adoption of the EU regulation on orphan medicines by the Gleevec/Glivec case, as that particular medicine went through several extensions of indication to different types of cancers, hence leading to a substantial enlargement of the product's target population and, de facto, to the creation of a commercial "blockbuster".⁴ In truth, some of these medicines must be recognised as transformative, while some others have come to the time of marketing authorisation with much higher uncertainty about their actual effectiveness. Nevertheless, the situation in the field of rare cancers is not fundamentally different from what can be observed with frequent cancers, in the sense that public healthcare systems do accept the notion that therapeutic progresses in the fight against cancer tend to be incremental, with marked advances through the use of combination therapies.

³ Recent cases which have garnered public attention include, to name but a few: hydroxycarbamide for the treatment of sickle cell disease; carglumic acid for the treatment of high blood ammonia levels due to NAGS deficiency; or arsenic trioxide for the treatment of relapsed/refractory acute promyelocytic leukemia.

⁴ For further reference, read in particular <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4190613/> and <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4598066/>

- If one looks now at the clusters of approved medicines which have changed the course of rare conditions such as **pulmonary arterial hypertension or multiple myeloma**, clearly their levels of uncertainty on clinical effectiveness have often represented an issue at the time of marketing approval – hence the loss of their orphan status at the time of marketing authorisation in the absence of convincing data on significant benefit. But in turn, the orphan medicines indicated for these conditions which kept their status should indeed be seen as providing an additional significant benefit compared to existing treatments, and their clinical value should not be questioned. In addition, in several well documented cases (e.g. pulmonary arterial hypertension, multiple myeloma, haemophilia), EU market exclusivity has not hindered fair competition between several rare disease therapy products developed by different marketing authorisation holders, and has actually led to bring prices down and help absorb the overall budget impact.
- The field of **metabolic lysosomal storage disorders** has been dominated by enzyme replacement therapies and other highly sophisticated biotechnology treatments, which have shown to be usually very effective, but also long-term, *life-long* chronic treatments and expensive ones at that. It is a fact that several rapidly growing companies specialized in orphan medicines have built their success on such products, and that – as there often is only one treatment available for a specific disease or for a specific population subset in a given condition – competition has been less fierce in that niche, thus leading to stronger benchmarking in the determination of ex-factory prices. While these therapies tend to come to market in the same high price range, they also present a good safety and efficacy profile for undisputed unmet medical needs. This being said, they are also generally associated with high uncertainty about their effectiveness, about the varying level of response from patient to patient, or still about the different regimens to apply. The fact that such uncertainties can subsist even 10 years after market entry is a serious issue to address. Three, five or seven years after approval, has the value for money increased?
- Most of the other existing orphan medicines today form a very diverse and mixed group – some with high uncertainty over their effectiveness, while others not; some with high prices, while others are far more reasonable. It is in this category of products **that the “high-price-by-default” policy of certain individual companies, with little or next to no justification other than what the market is perceived to be able to bear, has earned orphan medicine manufacturers as a whole a widely negative reputation.** It is our view that maintaining such an approach is fundamentally unsustainable, and that industry associations, leading corporate players and also the investor community must take a firm stance towards a more fair pricing strategy and business model – failing that, the gust of scathing criticisms and the general distrust of policymakers and the general public alike will only become stronger

2.4. Is the EU Orphan Regulation the problem?

What can we take away from this brief categorisation?

Contrary to the received opinion, the real problem is not actually one of budget impact in absolute terms. Despite the overwhelming attention and criticism garnered by the very high prices of a few individual products, there is a strong body of evidence and literature to demonstrate that **orphan medicines continue to represent overall an extremely small fraction of the pharmaceutical budgets of the EU Member States: several robust and independent sources converge to figures well below 5% of the total pharmaceutical expenditure on average for EU Member States offering at present the widest possible access!**

- A comprehensive 2011 study looking at modelling the total cost of orphan medicines in Europe between 2010 and 2020 as a percentage of total European pharmaceutical expenditure found that, while rising from 3.3% in 2010 to 4.6% in 2016, **the share of the total expenditure represented by orphan medicines would then reach a plateau and stabilise between 4% and 5% up to 2020.**^j
- A 2013 comparative study focused on Sweden and France concluded that **the budget impact of orphan medicines in these two countries would plateau between 4% and 5% of the total national pharmaceutical expenditure in 2020**, and would sustainably remain set at a small proportion of it despite payer concerns about growing designation rates.^k
- A similar 2014 study in the Netherlands concluded that **“the individual budget impact of orphan drugs is often limited, although exceptions exist”** and that, while firmly on the rise, the proportion of pharmaceutical expenditure spent on orphan medicines reached only 4.2% in 2012, with *“the relative growth rate decreas[ing] over time”*.^l
- An even more recent study in Latvia in 2016 showed that **the annual expenditure on orphan medicines still represented a tiny fraction of both the total pharmaceutical market in the country (0.84%) and the total drug reimbursement budget (2.14%),** with one particular product accounting for 34% of that expenditure.^m

With this firmly in mind, can orphan medicines continue to be seriously described as the crux of the problem, and to be assimilated to the proverbial “last straw” that will irremediably break “the camel’s back” and lead our already tense national healthcare systems’ budgets to complete bankruptcy? We believe that such a claim is largely exaggerated and fails to reflect the reality we are observing daily.

In our view, the real problem is rather, for each new orphan medicine coming to market, to ascertain **what the right budget impact should be for a given level of price; for a well-defined patient population based on the therapeutic indication rather than the prevalence of the condition; and**

for a given level of uncertainty over the clinical efficacy and effectiveness based on scientific data related to the product.

And this, in turn, is the reason why we strongly believe that **the current decision framework, which focuses disproportionately on the financial dimension rather than on improving patient outcomes based on the generation of additional clinical data, needs to be overhauled in depth, and with courage.** We must collectively find new ways and agree on new solutions to ensure that the prices of future orphan medicines are determined in a decisively fairer manner. We must ensure that patient outcomes become once again the single most important factor in the decision, and that patients are not exposed to unjustifiable access delays or restrictions.⁵ **We must achieve a more acceptable balance between the conflicting demands of a scientific uncertainty that is here to stay, and of a financial sustainability that more than ever needs to be restored.**

This paper aims to spur such a debate by laying out a set of possibilities on how a new approach could be structured that better meets the need of rare disease patients for full access to orphan medicines, but also helps restore transparency and trust between payers and pharmaceutical companies by paving the way for fair pricing and ensuring that the value of new medicines is optimised for society.



Wojciech, Stanislaw and Katarzyna, spinal muscular atrophy 1, Poland.

⁵ A recent (March 2017) research report by the Office of Health Economics thus illustrates that, while a large majority of the 143 orphan medicines with a valid marketing authorisation in the EU today is available and accessible in countries like Germany and France, that proportion may fall as low as 30% to 60% only in many other European countries. In England, less than 50% of approved orphan medicines are routinely funded by the NHS. What is more, while the shortest time from authorisation to reimbursement is observed in France and Italy (with an average of 19 months – more than 1 year and a half!) that time can rise up to 23 months in Spain and pass well over the 2-year mark in the United Kingdom. For further details:

<https://www.ohe.org/publications/comparing-access-orphan-medicinal-products-omps-united-kingdom-and-other-european>



What we are calling for

- i. People living with a rare disease must be able to hope for new therapies and to benefit them rapidly and fully, all across Europe, as soon as they are approved, so as to live their personal and social life to their full potential.
- ii. In full keeping with the letter and spirit of building on the UN Right to Health and the UN Sustainable Development Goals of “ensuring healthy lives and promoting the well-being for all at all ages” and “leaving no one behind”, and with the firm aspiration to hold on to the EU Regulation on Orphan Medicinal Products, the Council Recommendation on Action in the Field of Rare Diseases, Art. 13 of the EU Directive on Patients’ Right to Cross-Border Health Care and to the essential orientations outlined in the Council Conclusions of the Maltese Presidency of the EU of 16 June 2017, we contend that the human dignity common to all people – including those living with a rare disease - entitles them to the same quality of care.
- iii. We, the rare disease community, and more broadly all stakeholders having an individual responsibility in developing new therapies and providing them to patients, have an urgent collective responsibility to shape a new approach which will accelerate the transfer of major scientific advancements into new therapies, in a predictable and sustainable way for society.

3. The need for clarity about orphan medicines: Reiterating facts, dispelling common misunderstandings

As longstanding contributors to the public debate on rare diseases and orphan medicines, we have recently noticed a marked increase in the number of negative comments or interpretations directed at the EU Orphan Drug Regulation of 1999 and at certain of its provisions – e.g. with regard to the EU market exclusivity.

It is therefore only timely to ask: is the EU Orphan Drug Regulation be at the origin of all access and affordability problems observed today?

Our view is that this is a profound misunderstanding of the legislation and of its provisions.

3.1. Challenging common misperceptions about orphan medicines

We base our analysis on several undisputable facts:

- The EU Orphan Drug Regulation has played, and continues to play, its one main role – i.e. **to attract investment in the development of therapies** for diseases which have today either no treatment at all or no satisfactory treatment.ⁿ The Regulation addresses in a proper fashion what remains a major public health issue, i.e. the needs of millions of people living with life-threatening or debilitating diseases.
- **For a company, and for the investors lending their financial support to it, financing the development of an orphan medicine for a rare to ultra-rare disease is still far from being an easy or obvious business choice.** The costs and difficulties associated with bringing an orphan medicine from the bench to the patient are very substantial, not least in relation to the innovative mechanisms of action or vectors employed (e.g. gene and cell therapies). A key characteristic of rare diseases is also that the knowledge base available is very limited or even sometimes non-existent – be it in terms of understanding the natural history of a given disease, of the relevant and validated endpoints to retain, of having access to the best experts and investigation centers or to robust registries, and also of the higher risk of late-stage failure. This characteristic, in turn, translates into barriers to development that any company willing to enter this field of medicine must inevitably tackle, very often at a much increased cost. As a result, many of the smaller industry players entirely focused on orphan to ultra-orphan medicines are often still non-profitable today, despite being in business for years.
- To date, 143 products have been approved under the EU Orphan Drug Regulation since its adoption, 97 of which are still currently holding orphan status.^o This is a genuine success, and one that should be celebrated proudly by all – the European institutions, the Member States,

the companies developing orphan medicines, the clinicians, and most importantly the patients and their families.

- It is fair to acknowledge that orphan medicines have become an attractive destination for investment thanks to the main incentives offered by the legislation⁶ – e.g. the scientific advice and protocol assistance (with fees' exemption), the orphan status, the market exclusivity, etc. It is no less fair, however, to acknowledge that, **without such incentives, these investments would have most likely been channeled to other segments of the economy offering high returns, rather than health and pharmaceutical research.** The attractive effect of the said incentives should be seen for what it is – a fragile and transient ecosystem – and we encourage ardent critics of the legislation to think twice and carefully about the long-term consequences of public messages and positions which could very swiftly create sufficient concern or unpredictability to deter financial analysts, investors and corporations from investing their resources into the research and discovery of new medicines.
- **The current situation in Europe cannot be properly analysed and understood in complete disconnection from that in the United States.** Historically, it is the United States that has taken the first major political steps to accelerate the development of rare diseases therapies, as early as 1982, with a U.S. Orphan Drug Act that led to a sharp increase in the number of designations and approved medicines. A particularity of the U.S. Orphan Drug Act – unlike the EU Orphan Drug Regulation – was that it did not include any provision related to the “significant benefit” of new orphan medicines⁶, hence in the United States almost all products have ended up receiving marketing authorisation and retaining their orphan status later on. While it would be wishful thinking to pretend that Europe is not a player amongst others in a global competitive marketplace today, we must also realise – and accept – that legislations do not stand alone as “statements of virtue”, but *are instruments by which a country or a region may secure an advantage in that economic competition.* In that light, and in a context in which the existing U.S. legislation is seen by investors or companies today as more attractive *de facto* than its European counterpart, we must ask ourselves in honesty what the effect of a repeal of the EU Orphan Drug Regulation overall, or even of a mere restriction of the scope of its incentives, will be. And there is good reason to believe that, far from having the virtuous impact that some candidly expect, this would only send the signal that the EU is giving up on attracting investment and clinical developments to its territory. Similarly, it is not far-fetched to expect that the second impact of such a move would be to channel a large part of today's and tomorrow's R&D investments back to the United States, where companies and the financial community would be able to secure higher returns on

⁶ EU Orphan Drug Regulation No 141/2000 stipulates in its Article 3 “*Criteria for designation*” that a medicinal product shall be designated as an orphan medicine on the basis of two criteria only – one of which being the absence of another satisfactory method of diagnosis, prevention or treatment for a given condition or, should such a method exist, the **significant benefit** delivered by the medicine under consideration over such existing method. The said “significant benefit” is defined in Article 3(2) of Regulation (EC) No 847/2000 as “*a clinically relevant advantage or a major contribution to patient care*”. The purpose of the legislation is thus to encourage and reward innovative treatments that can bring meaningful advantages for patients in addition to showing all necessary evidence on quality, safety, efficacy and prevalence. For further reference, please consult the European Commission's Notice on the application of Articles 3, 5 and 7 of Regulation (EC) No 141/2000 on orphan medicinal products (2016/C 424/03) accessible here: http://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=OJ:JOC_2016_424_R_0003&from=EN

their investments, with the concrete outcome of seeing many more generations of orphan medicines come to commercialisation first in the United States and then, only much later, in Europe. Could we – and all European citizens living with a rare disease and in dire need for a therapy – seriously view such a situation as a vast improvement over what exists today?

- Contrary to what may be believed, **the orphan status of a product in Europe is not easy to obtain, is not easy to maintain, and is not meant to last forever.** It has value for the drug developer; it should be better understood and valued by the healthcare provider. From all orphan designation applications submitted to the COMP at the EMA, only 72% receive a positive opinion for designation. Amongst the products designated based on a potential significant benefit over an existing treatment, 27% more will be losing their orphan status at the time of receiving their marketing authorisation.⁹ And for the ones that may still have retained their orphan status, it must be borne in mind that that status lasts only for 10 years, not forever. It is a fact today that, after 18 years that the EU Orphan Drug Regulation has been in place, there are only 91 medicinal products still with active market exclusivity, vs. a total of 130 medicinal products approved and indicated for rare conditions, which no longer have orphan status. This clearly does not vindicate nor support the concept of an overwhelming orphan medicine “tsunami”, as described or denounced by some commentators.
- **The EU market exclusivity enshrined in the EU Orphan Drug Regulation is not a monopoly.** This is a profound misconception, and the fact that this misconception is regularly repeated by many does not suddenly make it a truth. The principle of market exclusivity is simply and only meant to offer, when applicable, a temporary protection against the entry onto the market of a similar product during the said period of exclusivity. This incentive was created and added to the legislation in order to enable a company to recoup its successful investment over a period of time. Contrary to what many seem to believe, market exclusivity does not prevent in the least the entry onto the market of other medicinal products for the same condition. Quite the opposite, actually: over the past few years, an accurate and neutral observer could notice the emergence of clusters of orphan designations and approvals⁷, because companies do happen consider there is less risk and uncertainty for them in entering a clinical field where there is already a higher level of scientific and medical knowledge as well as more experienced regulators and health assessors.
- **Market exclusivity does not automatically and univocally lead to high prices for orphan medicines.** This is another profound misconception, which completely ignores the fact that the prices of many orphan medicines are usually considered to be reasonable. A high price is not directly engendered by the market exclusivity – it is rather determined by the price that a marketing authorisation holder decides to claim, according to their strategy, and by the negotiation that follows between the marketing authorisation holder and the payers.
- Furthermore, **the “price” – be it the ex-factory price or the European Reference Price – is not what payers actually end up paying.** What is effectively paid in real life is a factor of all

The EU market exclusivity enshrined in the EU Orphan Drug Regulation is not a monopoly.

ensuing negotiations, which are generally associated with all sorts of mutually agreed financial arrangements ranging from rebates, price caps, clawbacks, payments based on outcomes, provision of free quantities of a given product, etc. Focusing only on a nominal price ex ante offers only a distorted view of the reality, and tends to underestimate the instruments and bargaining power at the hands of payers.



Daniil, Williams syndrome, Russia

3.2. The weakness:

The persisting fragmentation of Europe's market

More fundamentally, all stakeholders in Europe should recognise that **the major limitation of the EU Orphan Drug Regulation is that it was directly inspired by the U.S. Orphan Drug Act** (which, originally in the 1980s, was developed, adopted and implemented for a liberal market environment with over 300 private health insurance companies and a marginal public coverage), **while Europe is on the contrary a highly regulated market environment**, with medicines paid first and foremost from public budgets fed by social security systems, and with payers negotiating on behalf of society at the level of 28 individual Member States.

This disjointedness between the original spirit of the EU market exclusivity and the reality of a fragmented regulated market creates an imbalance. A large majority of Member States, except maybe the most populated such as France, Germany or the United Kingdom, are largely *disempowered* and unable to have sufficient critical mass to negotiate on their own when it comes to rare disease therapies. Even when they do, it is still on the basis of a small to very small number of patients. As always in rare diseases, it all has to do with the numbers – and with the small number of patients first and foremost. **This imbalance of negotiating power between the marketing authorisation holder, which holds a medicine for an unmet medical need, and the payers at the level of the national healthcare systems is the fundamental issue.** It exists for all medicinal products intended for small populations, with or without orphan status, and it is not an issue that can be addressed solely in the remit of the EU Orphan Drug Regulation. **The solution, if any, is firmly in the hands of EU Member States themselves if they wish to regulate the EU market exclusivity. By organising proactively their cooperation and better coordinating their national healthcare systems, Member States can regain power to become real partners in commercial negotiations with manufacturers to achieve better value for money and better medicines for patients.**

In that respect, it is comforting and encouraging that **this concept seems to be increasingly understood by national governments**, as exemplified in the recent Council conclusions of June 2017 on , paragraph 20 of which *“notes that tackling the specific characteristics and challenges arising in the healthcare market for therapeutic innovations, in particular in the field of rare diseases, [...] may benefit from voluntary cooperation so as to ensure a balance between access, quality, affordability and sustainability of health systems”*.⁵ However, the need to translate that understanding into action and actual policy initiatives remains pressing. EURORDIS-Rare Diseases Europe welcomes steps taken by many different individual EU Member States to enable greater cooperation – e.g. Belgium, Netherlands, Luxembourg and Austria within the BeNeLuxA platform, or more recently even the several Member States (Romania, Greece, Cyprus, Malta, Italy, Spain, Portugal and Ireland) that undersigned the Valletta Declaration – but we call on them and on others not involved yet to do more and particularly to explore how these new collective processes could apply in the first place to orphan to ultra-orphan medicines.

For all of the above reasons, it is frankly a staggering paradox that the EU market exclusivity should be so widely depicted by many as a strong advantage – especially as in truth this “EU market” to which exclusivity is granted is **extremely fragmented between 28 countries**, sometimes even regions within countries, and sometimes even more individual counties or individual hospitals locally.

If the EU is really serious about its objective to bring greater completion to the Single Market in an effort towards more competitiveness, growth and jobs, then one immediate, logical step should be to encourage the Member States, with the European Commission acting as a facilitator, to put in place a true Europe-wide collaboration for a structured approach to this EU market as a whole so as to unify it much more than it is today.

A few closing considerations, all grounded in the reality of the Treaty on the European Union:

- **The EU pharmaceutical regulatory framework applicable to orphan medicines cannot go beyond a core set of components**, such as: the compulsory European centralised orphan designation; European scientific advice and protocol assistance; the compulsory centralised marketing authorisation to assess the quality, safety, efficacy of the product (and significant benefit when relevant); or the post-marketing safety and efficacy research activities agreed through centralised procedures.
- **The European HTA Network, based on the ongoing consultation on scenarios for the future of HTA in the European Union, could provide in coming years a platform for a compulsory European centralised scientific advice and rapid assessment of clinical effectiveness**, based on shared scientific and medical information. To come to life, this could require the adoption of a new EU Regulation in order to become a mandatory pathway for all rare disease therapies at the very least; and to ensure that the common assessment report is automatically re-used at the national level by national competent authorities so as to avoid two layers of assessment, potential divergences of opinions, and overall an unnecessary duplication of efforts and waste of scarce resources.
- An EU Regulation alone cannot unilaterally impose collaboration on price and market access as the new standard practice between Member States. **But a Council Recommendation, adopted by the Council of the European Union and by all Member States within it, in full respect of its indicative and non-compulsory value, could nevertheless provide the much needed spark** – the political support and organisational support – to put in place a more effective European collaboration between national healthcare systems to better govern and regulate the economic advantage linked to the main incentive granted in the existing legislation – i.e. the EU market exclusivity – and to offer a more structured approach to the EU market to which exclusivity is granted.

3.3. In summary

As we draw this reflection to a close, we hope that our readers will remember, and agree upon, a handful of important notions.

The first one is that the nominal price of an orphan medicine, no matter its level (very often reasonable, sometimes high, and occasionally indeed very high) is nothing more than a weak indicator of what public healthcare systems and payers actually disburse and of the overall budget impact that particular orphan medicine will bear on public resources.

The second one is that current criticisms solely directed at the EU Orphan Drug Regulation as if it were the one and only mother of all access and affordability issues (and as if tearing it apart would suffice to solve all of the said issues), need to be immensely nuanced and mitigated. A careful analysis of the legislation and facts reveals that, while certainly imperfect, it does not deserve to become a scapegoat.

The third and last one is that, in our view, the one and only virtuous way out of this conundrum in order to link the science with the economy and the real therapeutic added value in clinical use with value for money, will lie not in challenging the EU Orphan Drug Regulation, but rather in realizing what is missing beyond it in terms of European collaboration between national healthcare systems to reinforce and complete it.

To this end, EURORDIS-Rare Diseases Europe is putting forward the following proposals as opportunities to improve patient access.



Sunna (right) with her brother, alternating hemiplegia of childhood, Iceland

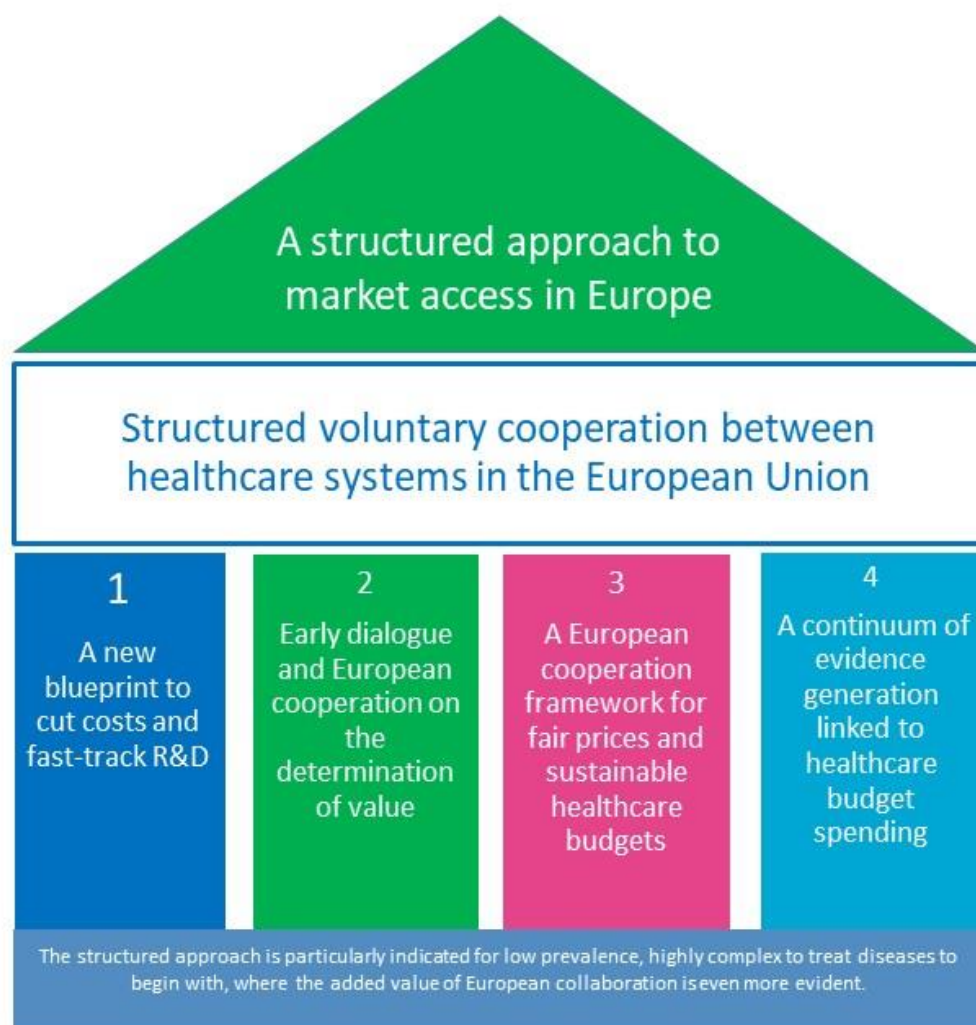


Our recommendations

European collaboration between national healthcare systems is the single immediate pragmatic transformative way forward to address the lack of completeness of the EU pharmaceutical regulation framework on orphan medicines, and to generate a structured, predictable, sustainable and equitable patient access across the entire European Union.

- We must reaffirm, and society as a whole must acknowledge, that rare disease patients deserve the same level of quality of care as any other citizen. That principle was proclaimed as a fundamental choice consciously made by society when the EU Orphan Drug Regulation, the European Commission's Communication and Council Recommendation on Rare Diseases, or still the EU Directive on Patients' Rights to Cross-Border Health Care were adopted. We must not forget. We must not backtrack on this. And we need to act accordingly. Our common ambition should be to leave no one behind.
- We must recognise that rare disease therapies – because their very specific characteristics (small patient populations, scattered medical expertise...) set them aside from more common medicines – do require a "continuum of evidence generation", all through their life cycle, from scientific guidance and assessments until well after the moment of marketing authorisation, as well as early patient access to address the unmet needs of conditions which are frequently life-threatening and debilitating. And we must accept the logical consequence: that the required level of expertise, of debate and of decision to support such a new approach can only be found at the European level – not nationally.
- We must link the economy with the science and, consequently, we must also link any discussion on the price of orphan medicines with the level of evidence provided at the time of the negotiation and with clear post-marketing research activities towards the reduction of the uncertainties associated to these medicines.

4. A framework of possibilities for a comprehensive approach to patient access: A visual interpretation



4.1. Pillar 1:

A new blueprint to cut costs and fast-track R&D

1

A new
blueprint to
cut costs
and fast-
track R&D

Access issues tend to gather much attention when a medicine nears market entry, as tensions may start to polarise between its manufacturer and national competent authorities for pricing and reimbursement over the interpretation of that medicine's value and benefit for patients, or still the adequation between these elements and the price requested by the manufacturer for that medicine.

EURORDIS-Rare Diseases Europe believes, however, that access issues find their true roots much earlier in time. **The quest for ways to improve and widen access for patients to the orphan medicines they need must begin farther upstream, at the very moment when medicines are being researched and developed.**

4.1.1. Companies need to be much bolder innovators in their R&D strategy and processes

Several tools, techniques or methodologies exist today that can allow medicines to come to market in greater numbers and for lower investments, by accelerating development timeframes but also reducing the costs incurred by companies from early designs to approval. These innovative approaches, which increasingly find their way into common practice with robust levels of reliability, offer new avenues to design and execute clinical trials, and feature *inter alia*:

- **Clinical trials designs in small populations (e.g. cross-over clinical trials, sequential trials, multi-arm studies) and innovative statistical methods (e.g. Bayesian methods)** are accepted by the EMA since 2006 and based on experience gained, are now encouraged by the EMA and recommended by IRDiRC. We believe that they should now be **the design and method of preference for the development of rare disease therapies**. Due priority should be given to exploring the feasibility of clinical studies which require less patients to be recruited, which allow faster trials, and ultimately which lower the threshold of investment required while still maintaining high standards on the robustness of data. Quite unusually, we observe that the case for conservatism and over cautiousness is today more on the side of the industry and less on that of the regulators, and this is why we call on product developers to be far more audacious. For companies developing new orphan medicines, seeking from the earliest stages of development the EMA's Scientific Advice and Protocol Assistance is the right and wise approach to discuss its clinical trial designs and methods in a way that fully meets the expectations of the regulators.
- **Patient-relevant outcome measures (PROMs)** are essential in rare disease therapy development and consensus has emerged in recent years on the need to develop them more consistently. Additionally, experience on that front has been rapidly growing, both in the USA and in Europe. To support this important trend, the International Rare Disease Research Consortium (IRDiRC) has developed recommendations involving all stakeholders from

- regulators and HTA authorities to patient advocates, clinicians and companies.[†] The EMA has also been encouraging the development of PROMs at an early stage of the product development so as to integrate them as much as possible into clinical trials as secondary endpoints, and it is now possible to obtain a qualification of a PROM by the EMA⁷ through a specific part of the scientific advice procedure. A more extensive use of PROMs has helped, and could have helped even more products, to present more convincing data at time of the marketing authorisation. As the CHMP can only base its scientific opinion on available evidence, PROMs contribute to create a set of evidence relevant to patients which translate into clinical benefits (or risks) perceived by them as meaningful. In addition, PROMs have been proving useful to support the preparation of a product's core value dossier ahead of HTA assessment. PROMs are generally specific to a disease, or to a sub-type of a disease, rather than product-specific, and they should be systematically devised in the earliest stages of clinical development, by the company, in good collaboration with medical experts and patient representatives for the disease targeted by a given product.
- **Biomarkers and their qualification** are encouraged both by the EMA, by HTA authorities and by payers as long as there is robust evidence that the surrogate endpoint measured with a biomarker actually translates into a clinical benefit.
- **Alternatives to animal models** are currently not so widespread, although we observe an increasing use of in-vivo cellular models or in-silico models. The science and technology is rapidly progressing and needs to be further supported through funding from private and public sectors alike. Alternatives to animal models, whenever they exist and attain a high level of reliability, can help save years of research and massive investments in often complex animal studies.
- **Patient registration**, inclusive of biological and clinical data, can be a major driver to design advanced clinical trials in rare diseases and accelerate patients' recruitment for these clinical trials. The recently established European Reference Networks (ERN)^u offer a new opportunity which is nothing less than a change of paradigm for research on rare diseases in Europe – i.e. the opportunity to register all patients consulting a medical expert in a centre of expertise, be it a full or affiliated member of an ERN, with a minimum common dataset baseline, standard operating procedures, and full interoperability between national centres of expertise within an ERN as well as between ERNs for all 24 therapeutic areas covered. The common dataset at the cornerstone of this project should include the OrphaCode, the genotype, the phenotype based on the Human Phenotype Ontology^v and the functional abilities or disabilities based on the International Classification of Functioning, Disability and Health (ICF)^w.^x We support the inclusion of these elements into the IT Platform provided by the European Commission to ERNs, based on the experience of previous projects such as Epirare^y, PARENT^z and RD-Connect^{aa}. The persons affected or potentially affected by a rare disease are the category of the population which will most benefit from genome and exome sequencing and other future advanced technologies: they are at the forefront of new models of research. Combined with the rapidly growing possibilities of bioinformatics, together they will drive major changes on how future clinical trials will be conducted faster, better and cheaper.
 - **Disease registries** should be created for each rare disease as early as possible to support the development of new therapies and monitor their impact. Such should even more so be the

⁷ One such recent example being the May 2016 Letter of Support undersigned by the European Medicines Agency to inform the Dravet Syndrome Foundation Spain of the approval of the qualification of the "Patient Data Platform" as an electronic tool for capturing patient reported outcomes in paediatric epilepsies. More details here:

http://www.ema.europa.eu/docs/en_GB/document_library/Other/2016/05/WC500206671.pdf

case when several products are under development for the same disease, forming a cluster of development. These registries should be developed according to common standards, as has already been recommended by IRDiRC at the international level, and in keeping with the work already conducted by the European Commission's Joint Research Centre (JRC)^{bb} for the EU Platform on Rare Disease Patient Registration.^{cc}

- **Natural history studies** are crucial, often missing or started at too late a stage when a product development is already very advanced. Natural history studies are essential to build the knowledge base when developing a rare disease therapy or when trying to stimulate therapy development in a disease area. Natural history studies provide a better knowledge on the course of the disease as well as its multiple and complex features, and they also enable a more rapid identification of relevant clinical endpoints, as well as a validation of adequate methods to measure them or a better anticipation of how such methods can be developed.
- **Clinical Research Networks on Rare Diseases** can offer a structured approach to clinical research, can help “de-risk” investment and, ultimately, can generate a greater development of therapies for rare diseases with fully unmet needs. Now that the 24 ERNs involving almost 1 000 high-level centres of expertise exist, EURORDIS-Rare Diseases Europe, the clinical leaders coordinating these 24 ERNs, the European Commission's Expert Group on Rare Diseases (which includes representatives from the 28 Member States as well as industry, academic and patient representatives) are all calling for an integration of EU research infrastructures with these ERNs. EURORDIS, the clinical leaders of the ERNs and IRDiRC^{dd} (which will launch in 2017 a Task Force on Rare Diseases Clinical Research Networks) are jointly calling for funding of clinical research networks embedded within the ERNs, per disease or per group of diseases. A shared platform, set of methods and tools, as well as a standard or minimum common dataset (inclusive of genotype and phenotype data) fed by life-long data collection would be a major enabler in speeding up patient identification and recruitment, but also upstream research on new clinical endpoints and biomarkers, as well as their validation at the international level. They would also greatly accelerate the scaling up of the training of hospital clinicians (who can often be very highly specialised in rare diseases, but far less so in clinical trials, quality data collection and validation, regulatory affairs and health technology assessments).
- **The involvement of patient advocates in the lifecycle of the product**, from the very early stages of development onwards, and based on proven good practices, is a method increasingly recommended by regulators, both the EMA and the FDA alike^{ee}, to help shape research questions and base them on patients' needs and preferred treatment options. Structured and transparent conversations upstream (e.g. through patient groups' established Community Advisory Boards) offer a reliable vehicle to better anticipate natural history studies, to form a much more accurate understanding of what it means to live with the disease, or still to lay the groundwork for an initial disease registry, for the identification of expert centres or for the elaboration of PROMs. According to the experience of companies and patient advocates collected to date, a greater participation of patients contributes in no small measure to “de-risk” the development of the product and to reduce the number of possible mistakes the company can make.

These tools are all the more important in our field, which is characterised by small to ultra-small patient populations, in which the genetic expression of the disease can be very heterogeneous, even between individuals supposedly affected by the same sub-type of diseases. This, in turn, raises questions as to the possibility, or even simply the relevance, of randomised placebo-controlled trials, and underlines the dire need for new methodologies more attuned to the reality experienced by the patients we represent and defend.

The following dilemma should be more starkly recognised at long last: **double-blinded randomised clinical trials are a great and essential source of medical knowledge, but the knowledge they provide is only formulated in averages, and is merely a reflection of the statistical sample of individual patients enrolled in the trials – nothing more, nothing less. It is a fallacy to pretend that they are offering the fullest possible level of understanding of how a medicine works inside the patient: an uncertainty always remains**

These limitations become only more exposed when an attempt is made to apply that methodology to rare diseases, as the scarcity of patients decreases even further the statistical relevance of any such trials.

The non-conventional designs, and innovative methods or tools presented hereabove, as well as the more structured approach bringing care and research closer together for rare diseases, are profound “game changers”. They can transform the current model of product development and mutually reinforce one another. If put into practice, there is good reason to believe that **they would dramatically reduce the cost of R&D for rare disease therapies**, reduce the number of patients who need to be involved in clinical studies (which is a fair objective from an ethical perspective, but also an important one to maintain a sufficiently large number of naive patients for future clinical trials), and also reduce the overall time necessary for full product development from proof of concept to approval. **As such, they can best meet the expectations of patients (more and better-quality medicines), of companies (faster and more predictable approvals), and of national competent authorities for pricing and reimbursement (less uncertainty and lower development costs).**

It is also our conviction that embracing these new advances will actually empower European clinical researchers to develop and run many more trials in Europe for rare and ultra-rare diseases compared to today.

4.1.2. Innovative changes in R&D can help solving the access conundrum.

We urge companies to embrace these scientific advances as of today – not doing so is simply laying the ground for difficulties, misunderstandings, tensions and ultimately delayed access.

But we also urge governments and payers to be equally fair and to make the effort to analyse and understand how new techniques as the ones outlined here above – clearly a departure from more classic development pathways – are acutely relevant and needed in the case of rare disease therapies. Governments and payers must also be consistent in their appreciation. All too often we still observe that, in a given country, **the medical regulatory authority can be fairly open to these innovative methods while the HTA authority may be far more reluctant and doubtful of the validity of a new study method, hence viewing the regulatory assessment with lesser confidence, if not outright distrust.** This lack of alignment has no scientific, economic or policy rationale to justify its continuation.



Our recommendations

- Product developers should consider the specific methods of clinical trials in small populations as the first and preferred approach while seeking early on, the parallel European scientific advice of EMA and HTA; they should anticipate the development of PROMs, natural history studies, initial steps in disease registry development, biomarkers and alternatives to animal models, with the primary objectives of reducing the number of patients involved in clinical studies, reducing the overall time of studies from proof-of-concept to regulatory approval, and reducing dramatically the financial investment in R&D.
- Patient organisations should create Community Advisory Boards composed of trained patient advocates, per disease or per group of diseases, in order to enable a structured, high quality, and transparent dialogue with product developers from academia or industry.
- With the IT Platform for the ERNs, the European Commission should aim at registering all patients who consult at any point of an ERN, with a minimum common dataset including phenotype, genotype and functions, in order to accelerate patient identification and clinical trial recruitment but also to offer a “building block” to initiate more disease registries and facilitate more upstream therapy development.
- Public funders, the European Commission and the Member States’ competent authorities in research policy should all support a much greater integration of care and research – one essential feature of which could be European research infrastructure servicing across all ERNs, and clinical research networks per disease or per group of diseases embedded within the ERN, so as to accelerate the identification and recruitment of patients in clinical trials, to produce more natural history studies and longitudinal studies, and provide solid economies of scale in a structured, high performance research environment for product development in a more competitive Europe.
- EU Member States need to ensure greater understanding and consistent appreciation of these innovative methods with an alignment across their medicines’ regulators, health technology assessors and experts responsible for pricing negotiation and reimbursement decisions.

4.2. Pillar 2:

Early dialogue and European cooperation between healthcare systems on the determination of value and on patient access

2 Early dialogue and European cooperation on the determination of value

The reality we observe today abounds with real-life cases of new products for diseases with high unmet medical needs being approved for commercialisation by regulatory authorities but never making it to the patients who need them most because, at the end of the chain, they are deemed too expensive or not seen as presenting sufficient value for national healthcare systems.

Such deadlocks are dangerously unsustainable for all stakeholders – not only for patients, of course, but also:

- For *regulators* (whose European centralised opinions and decisions made by the 28 national regulatory agencies on the quality, safety and efficacy of medicines may eventually appear inexplicably challenged and overturned by national authorities for pricing and reimbursement);
- For *health technology assessment bodies* (whose expert appraisals of the effectiveness or relative effectiveness of the said medicines may also appear as disregarded);
- For *national competent authorities for pricing and reimbursement* (who may come under criticism for denying access to an approved and much needed medicine on economic grounds only, but also make the conscious decision of leaving patients' unmet medical needs unaddressed, thus running the risk of degraded health outcomes and possibly extra public health costs); and
- For *pharmaceutical manufacturers* (whose products end up not being commercialised, and whose needs for a predictable market environment and return on investment for their innovation are completely ignored in such a context).

At the cornerstone of this situation, we see **absurd disjointedness**, not only between EU Member States that have in so many instances taken divergent or even completely opposite access decisions on one same medicine; but just as worryingly between all the main constituents of the public health decision-making chain at national level. The three main types of national competent authorities – regulators, HTA, and payers – are far too often working in silos at their local level. And while Member States happen to collaborate increasingly strongly with one another at the regulatory level with common assessments and decisions, and to be also more collaborative than ever at the health technology assessment level, they turn out to remain completely disorganised and uninterested in any form of European cooperation at the payer level.

Highly complex new medicines coming at potentially high prices do call for a more intelligent form of European cooperation between Member States.

We believe that **a genuine European collaboration between national healthcare systems should intervene at all levels, involving all three types of national competent authorities**. And our firm view is that this is even more important in the field of rare diseases for which patients and medical expertise are scarce, hence requiring a Europe-wide approach, and for which highly complex new medicines coming at potentially high prices do call for a more intelligent form of European cooperation between Member States.

This notion has been captured in principle in the recent Council conclusions of June 2017 on *'Encouraging Member States-driven Voluntary Cooperation between Health Systems'*, which were approved by the Health Ministers of all 28 EU Member States. **It must be now translated into reality.**

EURORDIS-Rare Diseases Europe strongly believes that a new, more sustainable approach for tomorrow – and one that can better fulfil the needs of all parties – must rest on **a more systematic and effective practice of European collaboration for a seamless and ongoing dialogue on value with product developers, from the very earliest stages of assessment and decision-making onwards, and across all levels of responsibility, from regulators to HTA authorities and up to payers, with the due involvement of clinical experts and patient representatives.**

The notion of early dialogue is not one-faceted but covers many different realities, all of which can be, and have been, explored and applied at different levels and to different extents:

1. **Horizon-scanning** – i.e. a systematic, forward-looking review of which new therapies are likely to enter a national healthcare system and when – can help better substantiate the implications of new medicines in terms of the possible evolutions to be applied to clinical practice or service design (e.g. when a new therapy offers a marked progress vs. the standard of care accepted until then) but also in terms of budget impact, funding modalities and potential disinvestments or re-prioritisations of resources that may need to affect other therapy areas. Experiences in that field are already building up robustly based on the advanced collaboration in place between EU Member States in Scandinavia, in BeneluxA^{ff}, in the Valletta Declaration countries (Malta, Portugal, Cyprus, Greece, Spain, Italy, Ireland and Romania), on the EUnetHTA^{gg} 3rd Joint Action^{hh} (which has a dedicated plan in its Work Package 4 "Joint Production"⁸), and on the EMA's advisory functions in regulatory science⁹.
2. **Early dialogue at a very early stage, on a specific disease, in a multi-stakeholder format including patients representatives, clinicians from the European Reference Networks on rare diseases, regulators, HTA experts and payers** can help to refine existing assumptions on unmet needs, to review the feasibility of specific clinical or natural history studies, to discuss the relevant endpoints to be considered, the inclusion of patient-relevant outcomes measures, the need for registries ... but also to consider the economic assumptions, the potential positive spin-off for given countries (e.g. new production sites, centers of expertise) or the possibility to bundle other products of the same manufacturer in a wider negotiation. The EMA has already gained significant experience through workshops organised for certain diseases (e.g. Duchenne, spinal muscular atrophy, haemophilia¹⁰) with the productions of "Points to

⁸ <http://www.eunetha.eu/activities/eunetha-joint-action-3-2016-20/work-package-4-joint-production>

⁹ http://www.ema.europa.eu/ema/index.jsp?curl=pages/about_us/q_and_a/q_and_a_detail_000141.jsp&mid=WC0b01ac05805040fc

¹⁰ References to previous workshops on Duchenne can be retrieved here: [http://www.nmd-journal.com/article/S0969-8966\(10\)00110-0/pdf](http://www.nmd-journal.com/article/S0969-8966(10)00110-0/pdf) (2009) and here: <http://exonskipping.eu/meetings-and-events/stakeholder-workshop-2015/> (2015). For spinal muscular atrophy, see:

Consider” or “Guidelines”. In the United States, the FDA is gathering a different kind of experience with its Patient Focus Groups per disease.

3. **Early dialogue at a very early stage on a specific product**, either triggered by a company, by a payer or by a patient advocacy group, can help to inform and support major investment decisions on whether the clinical development of a given compound should be continued (“go/no-go”) and the expected relevant outcomes, but also an opportunity to clarify to payers the genuine drivers behind a company’s views on the price of a new product (e.g. past and future investment plans, portfolio decisions, anticipations of a future indication, etc).
4. **Scientific advice and protocol assistance at the EMA** is today a firm reality and a very regular procedure. And there is a growing body of evidence to show that products which have gone through such a process tend on average to “de-risk” the future course of their clinical development, with higher rates of CHMP approvals further downstream.¹¹
5. Building on the achievements of many pilots in recent years (e.g. in the 2nd EUnetHTA Joint Action and in the SEED project in particularⁱⁱ), **the translation of new early dialogue concepts into standard practice has vastly accelerated**. The recent HTA Network Reflection Paper on Synergies between Regulators and HTA Issues in Pharmaceuticals from November 2016^{jj} sets out a clear and ambitious path, stating that ***“it is planned that the cross-European processes for parallel advice will become a single common model at the latest by the end of EUnetHTA JA3”***. EUnetHTA is today advanced, developing the concepts of Early Dialogue, Late Dialogue, and Evidence Generation Plan.
6. Similarly, **the EU Mechanism of Coordinated Access to Orphan Medicinal Products (MoCA)^{kk}** has gone a long way since its inception in 2010 to facilitate **a voluntary dialogue between national payers and pharmaceutical manufacturers, with the active participation of patients, on specific orphan medicines in development with a view to addressing identified challenges to effective market access**. Today, MoCA can look back at a track record of more than 10 pilots, each focused on a real product, and many of which are still active at the time of completion of this paper.

http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/events/2016/07/event_detail_001310.jsp&mid=WCob01ac058004d5c3 (2016). Similar workshops were also organised on endpoints for cystic fibrosis clinical trials in 2012: http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/events/2012/07/event_detail_000609.jsp&mid=WCob01ac058004d5c3 and on haemophilia registries in 2015: http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/events/2015/04/event_detail_001150.jsp&mid=WCob01ac058004d5c3 Another example worth mentioning is the ongoing collaboration between the FDA and the EMA on Gaucher’s Disease: http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2014/05/WC500166587.pdf

¹¹ Please refer in particular to “Regulatory watch: Impact of scientific advice from the European Medicines Agency” by Hofer MP, Jakobsson C, Zafiroopoulos N, Vamvakas S, Vetter T, Regnstrom J and Hemmings RJ, in *Nature Reviews Drug Discovery* 14, 302–303 (2015) doi:10.1038/nrd4621, accessible here: <http://www.nature.com/nrd/journal/v14/n5/full/nrd4621.html>, with additional data of interest from the European Medicines Agency also accessible here: http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2015/04/news_detail_002308.jsp&mid=WCob01ac058004d5c1

What these operational examples underline is two-fold:

1. **The necessary “building blocks” are all there**, and have been extensively tried and tested in many different settings. A total system change is not needed to put them into action tomorrow – what is, is only the willingness to draw all the logical consequences from the work completed to date.
2. We must veer away from segmented, fragmented decisions which taken together, do not add up to produce a positive outcome for society. **Access must be and remain the one central objective for all parties involved**, not just by the time of marketing authorisation but even much earlier, from the very initial stages of clinical development and early dialogues.

We believe that increased cooperation crossways between the European Medicines Agency, HTA bodies and payers can help fertilise a more constructive and continuous dialogue on value, and prevent “dead end” situations in which an approved medicine is denied access on economic grounds

To do so, we believe that **increased cooperation crossways between the European Medicines Agency, HTA bodies and payers can help fertilise a more constructive and continuous dialogue on value, and prevent “dead end” situations in which an approved medicine is denied access on economic grounds¹²**. We strongly recommend that all current mechanisms of coordination between stakeholders – PRIME, cross-committee working groups at the EMA and Community Advisory Boards within the patient community, scientific advice and protocol assistance at the EMA, parallel EMA-HTA scientific advice, early scientific dialogue at EUnetHTA, MoCA, etc) be over time more closely articulated with one another in order to avoid duplication of effort and to offer a more seamless, logical, and easy-to-navigate path – which, in turn, would only enhance the unity, consistency and predictability of the entire system for all.

In order to support that increased coordination and ensure greater consistency in decisions on the value of an orphan medicine, we believe that **common principles** can offer a much needed shared benchmark.

In that respect, the findings of **the European Working Group for Value Assessment and Funding Processes in Rare Diseases (ORPH-VAL)** – a group of 15 rare disease experts across 7 European countries, including HTA practitioners, physicians, patient representatives, academics, politicians and industry representatives¹¹ – can lend interesting insights. Over slightly more than a year, the Working Group led an iterative assessment of existing orphan medicine guidelines and frameworks at the national level, backed up all through the course of the initiative by extensive public debate during the 1st EURORDIS Multi-Stakeholder Symposium of February 2016, by a public consultation supported by both EURORDIS and OrphaNews in March 2016 and by further discussions with MoCA in September 2016. Ultimately, the Working Group collated all of the received input to formulate 9 overarching principles to help improve the consistency of the pricing and reimbursement of orphan medicines in Europe, in a manner that properly reflects the inherent characteristics of rare diseases.

¹² ... or even on scientific grounds if an HTA body disagrees with the previous assessment.

These principles range from aspects related to value assessment, pricing, reimbursement or still funding processes for orphan medicines, **focusing on 4 different steps – decision criteria, decision processes, sustainable funding and European coordination.**

Principles on OMP decision criteria

Principle 1: OMP assessment should consider all relevant elements of product value for OMPs in an appropriate multi-dimensional framework

Principle 2: Pricing and reimbursement decisions should be founded on the assessment of OMP value and adjusted to reflect other considerations beyond product value

Principles on OMP decision process

Principle 3: Those making P&R decisions about OMPs at a national level should take account of all official regulatory and health technology assessments of OMPs undertaken at the European level

Principle 4: The assessment and appraisal of OMPs to inform national P&R decisions should incorporate rare disease expertise including both the healthcare professionals' and patients' perspectives

Principle 5: To accommodate uncertainty, value assessment and pricing and reimbursement decisions should be adaptive subject to the need and availability of information over time.

Principle 6: All eligible patients within the authorised label of an OMP should be considered in the national P&R decision although different decisions on access may apply to different sub-populations

Principles on OMP sustainable funding systems

Principle 7: Funding should be provided at the national level to ensure patient access to OMPs

Principle 8: Evidence-based funding mechanisms should be developed to guarantee long-term sustainability

Principles on OMP European co-ordination

Principle 9: In the future there should be greater co-ordination of OMP value assessment processes at a European level

Figure 1: The nine principles defined by ORPH-VAL

In parallel, ORPH-VAL also led a systematic review of elements of value retained for orphan medicines across all of the national frameworks under study, and condensed them in a single coherent set as shown below:

	OMP Value	
	Impact of Disease on	Impact of Treatment on
Patient level	Survival/Life expectancy Morbidity Patient experience and health-related quality of life Patient economic burden	
	Existing treatment options	Side effects Treatment convenience
Healthcare system level	Healthcare system resources and budget Healthcare system organisation	
Societal level	Family/carer health-related quality of life Family/carer economic burden Societal economic burden	
Considerations beyond OMP Value		
Rarity <ul style="list-style-type: none">□ Budget impact□ Sustainability of innovation in rare diseases Societal preferences		
Uncertainty of OMP Value		
Quality of evidence Uncertainty around OMP value parameters		} Considered within the context of disease rarity, existing evidence base

Figure 2: Core elements of value for orphan medicines as recommended by ORPH-VAL

In this table, elements of value proposed in the literature were sorted by frequency of occurrence and grouped by theme (e.g. disease-related, clinical, and economic) and by perspective (patient, healthcare system, society). While there was a definite acknowledgement within the Working Group that the choice of value elements to be used to assess an orphan medicine should be country-specific, **there was also a fundamental agreement that the core elements outlined above should be common to all health systems**, and that both HTA authorities and payers should strive to make more explicit which elements of value they use or prioritise in any discussion on a given orphan medicine, how the rarity of a disease may influence their assessment, and how societal preferences are incorporated into their decisions, if at all.

EURORDIS believes in the relevance of, and need for, a streamlined coordinated European approach extending all the way from orphan designation, through parallel EMA-HTA scientific advice and marketing authorisation (EMA) all the way down to value assessment (EUnetHTA Joint Action 3) with joint rapid assessment reports and joint full assessment reports based on the Common Principles on Value, and ultimately to pricing and reimbursement negotiations.

Such an approach could also make space for new processes to be tested to a more advanced degree – e.g. **“formative” HTA**, which would pursue the objective of not delaying patients’ access to a major therapeutic innovation by giving immediate access through a provisional rapid effectiveness assessment report focused on scientific and medical data, recognising the high level of uncertainty, but consenting to give sufficient time for more evidence to be collected ahead of a more proper full assessment. Such a “deferred” HTA assessment would be proposed and implemented on a case-by-case basis and only on the condition of an agreed plan of research questions, of a strong plan for evidence generation and of a clear time point for re-evaluation.



Lily and Tristan, mitochondrial cardiomyopathy, France.



Our recommendations

- The practice of horizon scanning should be extended and supported – from the research funders through IRDiRC and partners such as eRare, to EMA and HTA authorities and all the way up to payers, all of whom should collaborate regarding their methods and exchange their analysis. It is only by doing so that the current/future gaps and real unmet therapeutic needs in rare diseases will be better understood and addressed.
- However, the proliferation of various types of, and methods for, horizon-scanning in Europe today on the part of individual countries, regional agencies or networks, or even international organisations, raises a question. The optimization of limited resources and time calls for clarity and coordination between all partners as to what analysis and what methods are being performed, or what types of information can be fruitfully exchanged and harmonised. Very early dialogue with all relevant stakeholders for the development of therapies for a given rare disease or group of rare diseases, or for a specific product or group of products, should strongly be encouraged. The possibility should be offered for such dialogue to be triggered by any stakeholder, and it should involve by default patient representatives, clinical experts from ERNs, relevant researchers, regulators, HTA experts and payers.
- EMA scientific advice and protocol assistance is today a very strong asset to build upon. It should now be more proactively promoted to the attention of developers of designated drugs, in an open dialogue on all non-conventional and adaptive methods.
- Parallel EMA-HTA scientific advice should become as soon as possible the preferred procedure for all product developers in the field of rare diseases. This is our single best chance to optimise clinical development plans in compliance with the level of evidence expected by regulators and HTA assessors in the specific context of a given disease, product and healthcare system.
- Early dialogue between payers and product developers at the European level (MOCA pilots) should be encouraged for a much greater number of rare disease therapies under development. Such dialogue, with the due involvement of patients and possibly medical specialists, can go a long way to enable a comprehensive discussion of all aspects of patient access, including but not limited to economic considerations (e.g. pricing scheme, potential budget impact, managed entry agreements), also covering specific issues related to diagnosis, healthcare system organisation, registries, real-world evidence collection, as well as research questions to further reduce uncertainties on efficacy, effectiveness, extent of clinical effect, population size, budget impact, etc. Scaling up the experiments that have taken place to date requires political encouragement and financial support to lead to a truly European collaborative effort.
- All existing platforms for early dialogue can, and should, be coordinated with one another in much greater “lockstep”, and in a seamless manner. For instance, payers should participate more directly as observers into EUnetHTA early scientific dialogue or into EMA-HTA parallel scientific advice in order to better capture the content of

discussions with regulators and HTA assessors, but also to receive the opportunity to raise their own concerns ahead of time for future well-informed discussions.

- The ORPH-VAL Common Principles on Value should be acknowledged as a credible and legitimate basis for discussion and consensus amongst all stakeholders. A third round of consultations, involving EFPIA and EuropaBio beyond EUCOPE, all possible payers members of MEDEV and members of EUnetHTA, could be launched in partnership with EURORDIS to explore how such elements of value could be more consistently used in value and pricing discussion related to future orphan medicines.



Juniper, chromosomal anomaly Xp11.23-11.22, USA.

4.3. Pillar 3:

A European transparent cooperation framework between national healthcare systems for the determination of fair prices

3

A European cooperation framework for fair prices and sustainable healthcare budgets

As highlighted earlier in this document, our daily experience provides countless examples of situations when the price of a new orphan medicine proves to be the stumbling block on which manufacturers and payers fail to agree, with potentially dramatic consequences for the patients in need. **This must change.**

Besides being all too often a “red rag” in discussions between manufacturers and payers, the price in itself is just an illustration of **the different points of view in play**. Companies expect the price to be set as a reflection of the value of a medicine but also of other parameters (e.g. past research failures that may have directly contributed to the development of that one successful medicine, portfolio investment decisions, anticipations of future indications or new developments, etc). In comparison, payers tend to focus more on the high level of uncertainty often associated with a new orphan medicine (thus opposing resistance to consenting a high price as the prospect of positive and tangible health outcomes may not be absolutely guaranteed), on the overall budget impact of the said medicine, or on its “value for money”.

4.3.1. The illusion of value-based pricing

One solution proposed to break that conundrum has been the notion of “**value-based pricing**”, supposedly thought to offer a better and fairer deal by setting a price according to, and in proportion with, the perceived or estimated value of a medicine. However, years of experience are showing that **value-based pricing as a one-size-fits-all concept does not work, in particular for rare diseases:**

- In most cases, **there is no available information about the current burden of the disease on the healthcare system**, nor on the human losses for society.
- **An assessment of the value of a given medicine does not automatically induce an accurate and indisputable figure at which to set the price of that medicine.**

Experience shows on the contrary that a product assessed by HTA as having a high therapeutic added value can eventually be priced high or low – and the same largely applies to products assessed as having a moderate therapeutic added value.

In reality, price discussions do not take as a starting point a value assessment: they rather, and much more simply, start from the price that the marketing authorisation holder claims to the payer. And while value does come indeed as a factor in that price-setting discussion, we observe that many other elements do enter into account too in any such discussion between companies and payers, e.g. the R&D investment consented for that product, the cost of failure associated with other

products which did not make it to commercialisation, the cost of investment in innovation towards new products, the development strategy of the company, the return-on-investment expected by investors or the target assigned to the company in terms of shareholder value creation, etc. Furthermore, it would be wishful thinking to deny that price benchmarking is common practice – not only throughout the pharmaceutical industry, but even in rare therapeutic areas where market knowledge and company experience are very low by default. **As a result, when applied to the particular context of rare diseases, it is fair to say that the notion of value based pricing only translates into what the market is perceived to be able to bear.**

This is not in the least to say that discussion on the value of rare diseases therapies should be disregarded or avoided. Indeed, EURORDIS-Rare Diseases Europe does encourage and support efforts to better define the principles and determinants based on which the value of a rare disease therapy should be debated and assessed. Our point, however, is to highlight that while all stakeholders have spent, and continue to spend, considerable time and resources to refine such principles and methods on value, **a vast disconnection continues to exist in real life between the value of a product and the price claimed.**

Furthermore, when applied to rare diseases, the notion of value-based pricing runs into several methodological difficulties that ultimately invalidate it, and that have to do with:

- the high level of uncertainty at the time of the initial assessment of the value of an orphan medicine, and the limited knowledge about the disease;
- the uncertainty about the capacity to collect the additional data needed after market authorization.

Our point, however, is to highlight that while all stakeholders have spent, and continue to spend, considerable time and resources to refine such principles and methods on value, a vast disconnection continues to exist in real life between the value of a product and the price claimed.

Recent debates and developments since February 2017¹³, when a first version of this paper was published, have only continued to underline the need for a step change in approach – and one that finally recognises that **the notions of value and price are not as unilaterally linked as all too often presented.**

4.3.2. Greater transparency of the price, or of the process to set the price?

Even more radically, many voices have arisen to call for **greater transparency of prices, or of what is actually being paid by each national healthcare system**, as the be-all and end-all solution, which would lift the veil on the real, unambiguous “value” of a medicine and instantly solve affordability challenges.

We believe this to be a simplistic misconception, which will only lead to adverse results. As the practice of **international reference pricing** has extensively shown over the years, it is difficult from a

¹³ Not least of which the Fair Pricing Forum organised jointly by the World Health Organisation and the Dutch Ministry of Health in Amsterdam on 10 and 11 May 2017: www.fairpricingforum2017.nl, and also see here for the resulting official meeting report: http://www.who.int/medicines/access/fair_pricing/FairPricingForum2017MeetingReport.pdf?ua=1

methodological point of view to define what to compare in the first place (e.g. name, form, strength or presentation of a given product) but also to adjust the approach to differences in per capita income between countries or any other factors that may actually justify price differences from one country to another.

More fundamentally, in our view, **the calls for transparency of prices mistake the symptom for the cause.** It is because there are divergences of views on the value and uncertainty of an orphan medicine that its price comes into question – **focusing on the price only in a near-sighted manner will do very little to advance a better, shared understanding of the value, nor to remove the said areas of uncertainty, and indeed does not help to discuss value for money.** On a similar note, the practice of international reference pricing has so far encouraged EU Member States only in looking for a price lower than the price their neighbours are paying – not in pursuing approaches for a meaningful and effective cooperation between themselves, nor in putting in place a more stringent framework to encourage the generation of data from the use of medicines in real-life settings and to improve medical practice (or even to simply have a better idea of the value received for the money they paid).

If national healthcare systems are serious about achieving the twin objectives of (a) trying to provide as fast as possible new treatments to patients and as early as possible, in order to assess clinical use evidence to reduce uncertainties, and (b) to pay lower prices than today and to reduce the budget impact for each new product...

... and **if pharmaceutical and biotech companies are serious** about the twin objectives of (a) trying to get their treatments as fast as possible to the wider possible relevant patient populations in the scope of the indication of their new medicine and to collect quality evidence from post-marketing research activities, and (b) to generate revenues as fast as possible during their period of market exclusivity...

... then, we should all surrender to the fact that the current trend, or calls, for a mere transparency of prices is a very limited approach as it will ultimately not deliver on any these objectives.

In order to break the current practice of price setting as a competitive “tug-of-war” between the conflicting interests of manufacturers and payers, and in order to ultimately offer access to all patients in need, a new approach will necessitate the definition of commonly agreed ways in which the price of an innovative medicine can be set, taking into account all relevant parameters.

The calls for transparency of prices also ignore in no small measure **the macroeconomic impact** that such a generalised approach could have – i.e. the fact that the savings payers could reasonably expect to secure on the very short term would be offset, over time, by the de-incentivising effect this would have on the private sector and by the aura of increased unpredictability it would convey about Europe as a marketplace for investment in pharmaceutical research. **If this were to lead eventually to a decrease in the pace of pharmaceutical discovery and commercialisation in Europe, and to patients being deprived of the medicines they need, how could this ever be a good thing?**

We all know that this strategy has already been applied to different medical areas, with a negative impact on financial investments and R&D, and with the only outcome of killing innovation. **The**

classic example is antibiotics: within few years of the implementation of public purchasing policies focused solely on prices, prices went down indeed, but investment turned away, knowledge vanished in just a few years, innovation halted... and today, we are now left to fight the enormous challenge of multi-resistant bacteria and to incur the massive costs of re-launching scientific research and re-attracting investments.

We must be lucid. The same could very well happen within a few years' time for rare disease therapies, and orphan medicines in particular. A similar narrow-minded, short-termist approach would assuredly lead to a complete public health disaster and to more social injustice.

Instead, EURORDIS-Rare Diseases Europe believes that the proper way forward is to explore how to bring greater transparency to the determination of prices¹⁴ and to the negotiation, in a process trusted by companies and payers as much as by society.

Ultimately, the radical evolution towards fair and often significantly lower prices, in exchange of wider and faster patient access to treatments, must be based on well-negotiated, reliable and mutual commitments.



Paulius, spina bifida, Lithuania

¹⁴ A position which EURORDIS has been upholding since years now, as we were already calling for greater transparency in the price structure back in 2012 during the debate on the revision of the EU Transparency Directive.

This approach, in our view, should rest on a number of major components:

A) A European Table of Negotiation for all volunteering payers from EU Member States¹⁵

The first essential component is to establish a “European Table for Negotiation”. This is not a new concept per se, as it has been proposed by EURORDIS-Rare Diseases Europe and by the European Patients’ Forum (EPF) as early as 2015. That proposal was welcomed at the time by many Member States, and has been gaining strong momentum under the Dutch Presidency of the European Union in the first half of 2016 and still afterwards.

Far from being an artificial or slightly aloof notion, this “European Table for Negotiation” and the idea that EU Member States could pool themselves together is actually firmly rooted in reality – and, to begin with, in the current demographic and economic state of play of the European Union.

1	Germany	France	GER + FRA	
Population (latest official figures available, in 1000s)	82 800	66 991	149 791	
GDP (2016, in billion USD)	3 495	2 488	5 983	
2	Italy	Spain	Poland	ITA + SPA + POL
Population (latest official figures available, in 1000s)	60 789	46 449	38 484	145 722
GDP (2016, in billion USD)	1 852	1 252	473	3 577
3	Other EU (excl UK)	Differential		
Population (latest official figures available, in 1000s)	151 495	Population (between 3 and 2) 3.96%		
GDP (2016, in billion USD)	4 231	GDP (between 1 and 2) 67.26%		

The above table captures the latest population and GDP figures available to this day for EU Member States. A simple look at population figures shows that, from a purely demographic point of view, it would be possible to categorise all EU Member States (to the exception of the UK) in three groupings or tiers of relatively homogeneous size – one with France and Germany alone as the two most populated countries in the EU; one with Italy, Spain and Poland as the next three most populated; and a last one with all remaining EU Member States. Each group would represent close to 150 million

¹⁵ This proposed component, which EURORDIS-Rare Diseases Europe has proposed years ago already, also finds its reason-to-be as an extension of ORPH-VAL principle no. 9 (“In the future, there should be greater co-ordination of OMP value assessment processes at a European level.”)

citizens, and the variation between the smallest and the largest of these three groupings would not exceed 4%.

From an economic perspective, the groupings as described above are of slightly lesser relevance as the GDP gap stretches to almost 70%. However, from a GDP per capita perspective (see table below), a number of coherent “clusters” or “arcs” of countries start to re-emerge and paint the picture of a region in which, oftentimes, neighbouring countries do happen to share not only similarities in the organisation of their healthcare systems but also convergent macroeconomic fundamentals.

An attempt at grouping EU Member States from an economic point of view:

Tiers of nominal GDP per capita (in USD; World Bank, 2016)

7,000 to 15,000	15,000 to 25,000	25,000 to 40,000	40,000 to 50,000	Above 50,000
Bulgaria Romania Croatia Poland Hungary Latvia Lithuania	Slovakia Estonia Greece Czech Republic Portugal Slovenia Cyprus	Malta Spain Italy France	Belgium Germany Finland Austria Netherlands	Sweden Denmark Ireland Luxembourg
↕	↕	↕	↕	↕
"Eastern and Southeastern Europe"?	"Central and Southern Europe"?	"Mediterranean Europe"?	"Germanic Europe"?	"Northwestern Europe"?

The preceding considerations must be comprehended in conjunction with existing data on the prevalence distribution of rare diseases (see chart above), which point beyond doubt at a limited number of rare diseases having a sharply higher prevalence while the immense majority of them has extremely small prevalences (the “tail” part of the curve).

For all rare diseases the prevalences of which are the smallest (e.g. under 1/10,000 or even under 1/50,000), this means that the total numbers of patients to be found across Europe are accordingly extremely limited.

If EU Member States are not that dissimilar in demographic or economic terms, then why would they reasonably continue to privilege an individualistic approach narrowly focused on their national prerogatives when it comes to addressing the needs of special citizens who may be extremely few at the local level, but certainly less few at the regional level?

Ideally, this “table” should be structured around three pillars:

- **A stronger European collaboration between the national competent authorities of several EU Member States**, as the wide divergences in access often observed today from one Member State to another must come to an end.
- **A trusted space for a well-informed dialogue**, helping these participating authorities to engage with the industry, as the absence of constructive exchange is ultimately detrimental to all – not least patients. Medical experts and patient representatives

participate today in many such platforms – at the EMA, with HTA experts, at the national or European levels, or in MoCA pilot – and, with the value of their input widely recognised by all parties, they would also have a role to play in the “European Table of Negotiation”, in order to reinforce its legitimacy and transparency.

- **A commitment to approaching pricing and reimbursement decisions based not solely on the price claimed by the marketing authorisation holder of a given medicine, but rather on a balance of three factors: value, volume, and evidence generation** – i.e. its estimated value, the volume of patients who should receive access to it over time, and plans for the continuous generation of real-world evidence post-approval to reduce uncertainties.

These principles are increasingly being accepted by most EU Member States.

Cooperation between EU Member States has been gaining in strength over the last few years with the emergence of multi-country platforms such as the one between **Belgium, the Netherlands, Luxembourg** and most recently **Austria**, which attract growing interest from several other Member States. Similar initiatives are now emerging in **southeastern Europe**, in the **Western Balkans** or still in the **Baltic region**.

Platforms for early dialogue between payers in the industry have also been steadily developing, as exemplified by the **Mechanism of Coordinated Access to Orphan Medicinal Products (MoCA)^{mm}**, a platform initiated under the auspices of the European Commission in 2010 and still active today, which offers a relevant prefiguration. MoCA, if strengthened appropriately, can become the cornerstone of an overall ‘table of negotiations’, building up on the experience gained with the pilots already concluded or in progress, and developing new pilots on ultra-rare conditions, where European collaboration makes even bigger sense.

Now is the time to consolidate and unify these efforts, rather than to re-create a new fragmentation around various “tiers” of Member States based on their GDP per capita. Only by coming together shall the Member States of the European Union also consolidate and further increase their bargaining power.

B) A “fair price” beyond value-based pricing¹⁶

The second essential component would be **new methodologies** through which the price of a medicine can be defined in firm accordance with a number of legitimate and well accepted elements, going beyond value-based pricing.

These new methodologies should better reflect the reality of the investments and of the costs which, contrary to a number of claims frequently heard, are significantly *below* those for a medicine indicated for a much more common disease. As a matter of fact, the overall R&D process for an orphan medicine is costly because of the current specific hurdles of small populations and limited knowledge but certainly not as costly as in frequent diseases for which clinical trials do involve thousands of patients from all around the world and up to the end of phase 3 studies. Similarly, the commercialisation of an orphan medicine itself does not or should not require a large investment in extensive marketing and commercial teams as orphan medicines generally tend to be hospital specialties in niche therapeutic areas and with small numbers of prescribing doctors.

Several methodologies are being proposed in publications and reports by health economists. The question of fair prices encompasses all innovations – medical devices, vaccines, diagnostic tools as much as medicines. And the notion of fair price is being debated today well beyond the European Union only but rather at the global level, both at the OECD and within the UN system. At the UN, it has emerged as a burning issue both within the WHO, in particular with regard to essential medicines, and even higher up with the recent publication of the final report by the UN Secretary-General’s High-Level Panel on Access to Medicines.ⁿⁿ

We venture in this reflection paper into proposing two possibilities which we see as more promising:

One could be **a fair price based on a “justification of the price”**, in an approach aiming at opening a conversation between the manufacturer and the competent authority for pricing and reimbursement on the very elements that the company invokes to justify its price. The conversation would be intended to be very open, not prescriptive nor set in a narrow framework, but rather open to all justifications e.g. (but not limited to): the company’s investment in other innovations; the company’s investment in other therapeutic indications with the same product or technology; the company’s place of location for R&D or manufacturing within the EU; the specificity of a very small to ultra-small population of patients; the specificity of a very complex treatment with a high set of constraints for the delivery of treatment procedures (e.g. in the case of a gene therapy to be administered only in a limited number of highly specialised centers in Europe); etc... The bottom line of this approach would be to overcome the disconnection between the determined value and the price claimed, and to embed the conversation within explicit and tangible elements.

Another could be **a fair price based on a dynamic, mutually constructed approach to incentivise value and healthcare priorities**, starting from **a cost-based price**, which would then be adjusted as a

“A low price is not necessarily a fair price”

Martin van Rijn, Dutch State Secretary for Health, Welfare and Sport, Fair Pricing Forum, 10-11 May 2017

¹⁶ In full alignment with ORPH-VAL principle no. 2, see page 35 (“Pricing and reimbursement decisions should be founded on the assessment of OMP value and adjusted to reflect other considerations beyond product value.”)

factor of **the agreed determination of the value of the product** (as per the notions outlined in the previous section of this paper, with a view to rewarding high-risk investments as much as genuine healthcare innovation), and of **bonus/malus to incentivise private investments** in the specific directions called for by healthcare systems.

The base price should be a cost-based price would include all structural costs incurred by the developer for R&D, approval, market entry and commercialisation, planned post-marketing research activities, patient access schemes such as early access programmes, etc. Other elements could be incorporated on a case by case basis e.g. the cost of failures of previous developments when relevant to the new therapy or disease area, or relevant investments; the initial investment to lay the ground before repurposing a compound. That baseline price would be compounded by **a 20% profit margin** corresponding to the average in the pharmaceutical and biotech sector.¹⁷

This base price – or “bedrock” – could then be **multiplied by a factor of 10% to 100% according to the agreed determination of the value of the product**, based on common principles and criteria as outlined in the previous section of this paper. “Value” would thus be taken into account as one element in the determination of price and its negotiation, but not as the sole element.

The resulting figure could then be adjusted with a number of **premiums encouraging investment in areas of particular importance** as prioritised by national healthcare systems themselves.¹⁸ Premiums ranging from 0% up to an extra 10% could be granted for each of the following:

- **A premium for being the first medicine for a disease that has no treatment at all;**
- **A premium for medicines commercialised first in Europe** before other regions of the world;
- **A premium for medicines developed from R&D of higher productivity with high cost reduction impact** on clinical development, manufacturing and delivery, including unconventional methods, scientific or technological innovations;
- **A malus for medicines, the clinical trials of which were not conducted in Europe**, at least for part;
- **A malus for medicines not having an early access programme** to patients via compassionate use in the case of diseases without any other therapeutic option available thus far.

¹⁷ While individual methodologies may differ, a great number of converging sources point at a ballpark figure of 20% as a realistic indicator of the average profit margin experienced in the pharmaceutical and biotech sector today (see for instance <http://www.businessinsider.com/sector-profit-margins-sp-500-2012-8?IR=T>). Interestingly enough, this figure is far from being abnormally high compared to other industry sectors – and is actually even lower than what is for instance observed in the food and beverage, software or automotive sectors.

¹⁸ Again, in full alignment with ORPH-VAL principle no. 2, see page 35 (“Pricing and reimbursement decisions should be founded on the assessment of OMP value and adjusted to reflect other considerations beyond product value.”)

The above-described mechanism of premiums and discounts would not only help offer more targeted rewards to real value and real innovation – **it would also constitute a new instrument or lever in the hands of policymakers and payers to steer future research investments** by private manufacturers in the direction of areas or needs which society considers as most critical to be met – this could be part of a new proactive approach to shape the horizon, not just to scan it.

What you get is
what you
incentivise

C) Shifting towards a European Transactional Price and Differential Pricing in lieu of a European Reference Price

Today, the practice of European reference pricing is recognised as a substantial barrier to accelerating decisions by national competent authorities, but also to accelerating patient access across Europe. It has also been roundly criticised by many commentators as having unwanted effects – e.g. creating a bias for companies to release their products first in certain countries where they are likely to have more freedom to set their prices at a higher desired level (hence generating access inequalities for patients in other countries), and therefore “gaming” the reference pricing system as that higher price will then be taken as baseline. In other words, a system meant to contain prices may lead to paradoxically inflationary tendencies.^{oo}

To overcome this hurdle, we introduce the possibility of resorting rather to a **European Transactional Price** – defined as the price negotiated, according to the methodology described as step 2 above, between a marketing authorisation holder and the voluntary Member States participating in the “European Table for Negotiation” (as per step 1 above). De facto, this European Transactional Price would serve as a benchmark – a new European reference price of sorts – inasmuch as a pre-condition for participation in the European Table for Negotiation would be the full commitment of Member States to use as a baseline that price which they would have directly contributed to negotiating.

We are also introducing the possibility that such a European Transactional Price could then be adjusted via a **differential pricing** mechanism in order to match the different purchasing power or “abilities to pay” of different EU Member States, measured according to the most appropriate criteria. Such a mechanism would naturally need to be tailored to the operational recommendations outlined by the European Commission in its December 2015 study on enhanced cross-country collaboration in the area of pharmaceutical product pricing^{pp}. The need, however, is real and urgent: as well captured in the European Patients’ Forum’s June 2016 Core Principles from the Patients’ Perspective on the Value and Pricing of Innovative Medicines^{qq}, differential pricing as a **“political strategy driven by collaboration between Member States with the aim of improving equity of access”** has still not been satisfactorily explored to date.

However, the notion of differential pricing may not be viable if not coupled with **an exemption on parallel trade**, so that the wide differences in GDP (and, therefore, in adjusted prices) do not distort the market even more and so that any attempt is prevented at taking advantage of a price difference between two or more markets. We recognise that opinions on this aspect diverge.

D) New Approaches to Funding: Managed Entry Agreements, Joint Purchasing, Discount for Uncertainties, Payment Based on Outcomes

While the previous steps focused on the determination of a fair price, the proposed approach would not be complete without also considering the sustainability of the overall impact on healthcare budgets – which touches upon the issue of funding schemes and ways in which necessary budgets can be freed up and allocated to enable access to the orphan medicines that rare disease patients need.

We believe that a number of innovative solutions and mechanisms exist, which should be more comprehensively put into practice as national authorities see fit. Such mechanisms may include:

- **Managed Entry Agreements (MEAs)** are an adequate instrument to capture in a contractual setting the parameters and conditions at which a medicine shall be put onto the market following the European Joint Negotiation, and the commitments to be met by all parties in return for the determined European Transactional Price – both in terms of patient access (on the payers' side) and in terms of data still to be gathered or generated post-approval, studies to be run or target populations to be refined (on the manufacturers' side). Nevertheless, recent research⁷⁷ highlights the paucity of any managed entry agreements relative to orphan medicines and, whenever they exist, their tendency to be more financial-based (e.g. price-volume agreements, utilisation cap, payback agreements) rather than outcomes-based – one reason for this being that this report focuses on product approved under exceptional circumstances or conditional approval, which obviously grasps only part of the MEAs concluded in rare disease therapies. Experience also points at performance-based agreements being more difficult to implement as it may prove more difficult to agree ex ante on what should be measured – or even on what is actually measurable – and as collecting and validating the required evidence to even discuss outcomes can be a stumbling block (for further thoughts on this, please refer to section 3.4 below). **We see in the European Table for Negotiation an ideal platform to establish a concrete dialogue on how to further extend the practice of MEAs for orphan medicines or other rare disease therapies, as another tool towards accelerated patient access.**
- **A discount on uncertainty**, for the time needed to generate robust evidence, could be another such mechanism. The discount would be consented by the manufacturer in proportion of the level of uncertainty associated with the medicine at the time of initial price determination. This mechanism would offer the twin benefit of being completely relevant in light of the situations and difficulties frequently observed with orphan medicines (i.e. coming to the time of marketing authorisation with many question marks still left about their effectiveness, about the varying level of response from patient to patient, or still about the different regimens to apply), and of being rather simple to put into practice. That discount could be temporary, over a period of 3 to 5 years approximately, until the developer can provide required evidence to refine knowledge of the actual patient population size, patients' levels of response to the

medicine, real-life effectiveness benefits, etc. Once such evidence would be provided to clear areas of pre-existing uncertainty in a compelling way, the said discounts could also be lifted and the price of the product could be corrected to a higher level reflective of its revised and increased value – or in the contrary case, the discount could be maintained or even increased.

- **Outcomes-based payment systems** are a sub-category of MEAs that allow the price and reimbursement status of medicines to change over time as a function of follow up data of the original trials or observed health and financial outcomes in daily practice. In effect, this means that, after a price and coverage level has been agreed upon at initial submission, that price and coverage may be revised at later time points, based on a verification of the predicted outcomes. Such a system can encompass a broad range of variations, based on whether the resulting reevaluation of the pricing and reimbursement conditions occurs only after verification of collected evidence at a defined time point (coverage upon evidence development) or even retroactively before that (performance-linked reimbursement) paving the way for paybacks by the manufacturer, should the actual outcomes be inferior to the predicted ones. The one feature common to all these mechanisms is the fact that the decision-making process on pricing and reimbursement becomes a dynamic and continuously evolving one – not a static one.

EURORDIS-Rare Diseases Europe believes that outcomes-based payment systems are an option requiring careful study and, to support this, we have contributed to a collaborative reflection under the auspices of **think tank FIPRA**, resulting in a discussion paper and in a set of **10 principles** which, if adhered to, can help achieve more efficiency and consistency in the outcomes based

assessment of new health technologies and avoid duplication of efforts.⁵⁵

Payment based on outcomes as a system may be more suited for innovative medicines in general, rather than for orphan medicines for which the process for real-world evidence generation may at the moment still present added complexities. However, **such a system may already be applicable for certain well-defined rare diseases for which the collection of real-life clinical use data or of real-world evidence is already an established practice**. Furthermore, the European Reference Networks are likely to profoundly change the current state of play and to open up new perspectives for a broader use of performance-based payments even in rare diseases.

- **Joint purchasing**, intended as the **collective effort by a group of countries to join forces for the common sourcing, price negotiation and eventual procurement of all or certain medicines, are another important policy concept currently under consideration, which has gained in interest lately in Europe thanks to the renewed attention paid by successive Presidencies of the Council of the EU to the need for reinforced voluntary cooperation between Member States on the issue of access to and affordability of pharmaceuticals**. The 2016 Dutch Presidency of the EU played a very important role in that regard, with such a possibility being clearly outlined as a next step in the Council Conclusions of 17 June 2016 on *"Strengthening the balance in the pharmaceutical systems in the EU and its Member States"*^{tt}, but the notion remains more present than ever as the **2017 Maltese Presidency** of the EU endeavored to make further progress towards *"mechanisms of voluntary structured cooperation between health systems driven by Member States, to further support*

Member States and provide tangible benefits for health professionals and patients”¹⁹. In our view, the move towards a joint purchasing system is a natural evolution and outlet of the diverse multi-country cooperation platforms that have started to emerge to date (in various parts of Europe e.g. between Belgium, the Netherlands, Luxembourg and Austria, between Scandinavian countries, between Baltic countries, in the Balkan region or along the

Southern European arc). This can be supported by the recent update in the European regulation on Joint Procurement. It is also, ultimately, an objective of the European Table for Negotiation that we are calling for, and with this in mind **we urge all EU Member States to explore how such a system could become a more widespread reality in Europe within a not so distant future.**

A transparent framework for the determination of prices based on costs, value and policy-defined priorities, supported by a set of well-defined and well-accepted criteria, will help **ensure a better and more evident linkage of medicines’ prices to the fundamental components of their value**. In turn, such an improved framework will offer ample justification of why the prices of certain medicines may deserve to be set at a higher level than others. **If the terms for it are jointly agreed by payers and the industry, price in itself can no longer pose a sufficient obstacle to access.**



Jacob, MCT8 mutation, USA

¹⁹ As per its official programme, accessible here: https://www.eu2017.mt/en/Documents/NationalProgramme_EN.pdf



Our recommendations

- All EU Member States already engaged in multi-country cooperation platforms should accept to join voluntarily to establish the “European Table of Negotiation”. If not all EU27, a significant number will create a population critical mass enabling to address the challenge of rarity, hence immediately becoming the pivotal partner for negotiations and launching a dynamic.
- All EU Member States on board the “European Table of Negotiation” should commit to examining, in an open multi-stakeholder format, the innovative approach to lay out a more transparent pathway to the construction of prices (based on costs, compounded by a determination of the value of the product, and adjusted by premiums and discounts as relevant).
- All EU Member States on board the “European Table of Negotiation” should commit to entering into Joint Price Negotiations or Joint Purchasing as the next step – if only for orphan medicines at the beginning – and to formalising the outcomes of these negotiations into Managed Entry Agreements with manufacturers.
- All EU Member States on board the “European Table of Negotiation” should commit to exploring much further the feasibility of applying differential pricing mechanisms to the agreed “European Transactional Price”, as a means to tailor the said price to their respective levels of purchasing power and domestic wealth.
- All EU Member States on board the “European Table of Negotiation” should commit to considering discounts for uncertainties, payments based on outcomes, formative HTA assessments and all other appropriate modalities or techniques so as to provide early patient access to medicines approved under exceptional circumstances, under conditional approval, at the end of stage 2, or in any other situation when uncertainties are high or significant

4.4. Pillar 4:

A continuum approach to evidence generation linked to healthcare budget spending

4

A continuum of evidence generation linked to healthcare budget spending

The reduction of uncertainties is an essential need, not only for national healthcare systems but also – and to a no less important extent – for patients and clinicians.

Orphan medicines pose many different challenges to competent national authorities for pricing and reimbursement, not least as they increasingly tend to arrive to the time-point of marketing authorisation with higher levels of uncertainty on efficacy and effectiveness. This is particularly true, but not exclusively, when a product is approved with a conditional marketing authorisation, or an approval under exceptional circumstances, or a marketing authorisation at the end of phase 2 studies. These earliest possible approvals

are generally based on risk-benefit assessments: the patients' unmet medical needs are high, the product has a good safety profile and sufficient evidence on efficacy to go ahead for approval and often enough evidence to support significant benefit over existing treatments if any. This approach of early access, seeking the right trade-off between risks and benefits, and in line with patients' treatment preferences is to the benefit of patients to speed up access to new therapies and address their medical needs. But the level of evidence available is often not sufficient for health technology assessors to perform a stringent effectiveness assessment and for national competent authorities on pricing and reimbursement to make a well-informed decision. And, as noted before in this document, this situation means that price very easily becomes the stumbling block: if the price of the medicine is low, a higher level of uncertainty can more easily be accepted; however, with a high price, the level of uncertainty becomes a barrier to a positive decision.

This level of uncertainty is linked to many different elements: the nature of the therapy itself (e.g. in the case of a new class of products with a new mechanism of action or a gene therapy), the heterogeneity of the patient populations in what is generally assumed to be a same family of rare diseases (the natural history of rare diseases always offers a large range of patient courses of the disease, with phenotype-genotype links not always so well defined in each sub-population), or still the difficulty – or even impossibility – to conduct a clinical trial on broader patient populations and therefore the impossibility to fully predict how the new medicine shall perform in real life.

In the current framework, the price of a new medicine is normally set at the timepoint of marketing authorisation, based on an *ex ante* appraisal of its value – an appraisal that is generally not revised *ex post* – hence paving the way to what can be very acute tensions further downstream between the manufacturer of that medicine and payers, tensions which are usually resolved through fierce negotiations and commercial deals (e.g. clawbacks, extra rebates, caps, etc) focusing solely on the price and budget impact of the said medicine.

4.4.1. Formative and summative assessment methods for robust health technology assessment without delaying patient access to therapeutic innovation

We believe the current framework to be unproductive and outdated: it is a waste of resource for the national healthcare systems and detrimental to the quality of care that patients have a fundamental right to enjoy.

A growing body of research is pointing at the fact that the proper assessment of an innovative technology must not be *ex ante* only, at a very narrow moment in time – but also **formative** (i.e. at the very moment when the innovation is being rolled out or implemented in real clinical practice, to identify ways in which that implementation can be improved) and even later **summative** (i.e. offering a 360° view of the full impacts of the innovation under study, but also advancing reflections as to how observed obstacles may be overcome).

4.4.2. Evidence generation, value re-assessment and price revision

The new approach we are calling for should rather be based on the conscious recognition of the uncertainty associated with a new medicine, and particularly orphan ones, at the time of marketing authorisation, as well as on the concept that the price of that medicine – the European Transactional Price as defined above – can and must fluctuate according to the re-assessment of the value of the product based on additional evidence in order to reflect both that uncertainty and, later on, the progress made to address it.²⁰

The new approach we are calling for should rather be based on the price of that medicine – the European Transactional Price as defined above – can and must fluctuate according to the re-assessment of the value of the product based on additional evidence

The concept is simple. In case a new medicine presents a certain level of uncertainty as to its therapeutic benefit for a given patient population and its ability to deliver the expected health outcomes, the price at marketing authorisation should be kept at a discounted level to reflect that uncertainty in the very short term. An agreement could then be found between the manufacturer and payers to **link any future evolution of the price – upwards or downwards – to the generation and provision of fresh evidence from the actual clinical use of the medicine in real life**. In other words, if the medicine delivers on its promise and the expected positive health outcomes are observed in patients' clinical use, hence demonstrating the real-life value of the medicine, then its price should be revised upwards to reflect it. Conversely, if the therapeutic benefit is never delivered, or not to the desired extent, then the price may either be kept to its existing level or taken a few pegs downwards, or in the worst cases the product may be taken off the market altogether.

²⁰This position has also been extensively affirmed by ORPH-VAL, as per principle no. 5 ("To accommodate uncertainty, value assessment and pricing and reimbursement decisions should be adaptive subject to the need and availability of information over time.") but also principle no. 8 ("Evidence-based funding mechanisms should be developed to guarantee long-term sustainability."). See above on page 35.

Decisions as to how the price of the medicine should fluctuate would be taken on the basis of real world data to be gathered from the real-life clinical use of the medicine in order to demonstrate its actual therapeutic benefit. As pointed at the end of the previous section, these data could be part of a managed entry agreement, which could outline from the outset which data or information are missing and need to be obtained either through further studies or observations.



Anton, Stickler syndrome, Spain

4.4.3. European Reference Networks as a “game changer” to enable a continuum of quality and validated evidence generation

When it comes to the generation, collection and analysis of real-world data, many voices have arisen in recent years to underline the difficulty of implementing such processes in a thorough and effective manner. **We believe that such comments, while inspired in their time by real difficulties and challenges faced on the ground as often happens with any major innovation, are increasingly a view of the past.** We are confident that, if all stakeholders agree to address this core issue, several new initiatives will contribute to making the collection of such data, the development of new registries and an optimal linkage with healthcare systems become a reality.

One major driver for change will be the **European Reference Networks**, which are no longer a concept but, as of 1st March 2017, are set up as recognised entities by the European Union and become a reality firmly entrenched at the national and local level. With more than 1,000 centers of reference within 370 hospitals, distributed amongst 24 networks by groups of rare diseases, the membership of which will continue to develop in coming years, they will provide for the first time a unique opportunity for a new and significant critical mass of highly specialised clinicians and researchers to share expertise, knowledge and resources across borders.

Another major driver is the new information technologies, their higher capacities, their lower cost. The ERNs have the authority to adopt common standards with regard to data collection and interoperability and shall build in no small measure on existing IT tools and platforms to deliver their mission. In coming months and years, the ERNs will endeavour to develop a host of new services – virtual clinical consultations for rare disease patients across the EU, the elaboration of best practices in diagnosis and care, the collection of shared common datasets, the constitution of disease patient registries, etc.

Going one step farther, it is today reasonable to envisage a new reality in which the European Reference Networks could enter in contractual agreements both with the national healthcare systems and authorities and with manufacturers to execute agreed data collection strategies. As this new reality gets off the ground, we must appreciate that **these new resources will also demultiply and accelerate our current capabilities to generate, collect and analyse real-world data.** For that reason, it is nothing less than essential that all stakeholders take full stock today already of what is to come, and act accordingly when planning or implementing decisions related to evidence generation and the optimal use of current and future therapies.

4.4.4. Disease patient registries: The pivotal instrument to reduce uncertainties

The work of the ERNs will be particularly important in the field of **registries and patient data collection.** Registries are at the core of the evidence generation process and have an important role to play to underpin major decisions at all stages in the lifecycle of the product, with regard to post-marketing authorisation activities, access and funding for instance.

To be of the highest value and relevance, a registry must be disease-focused and not solely product-focused (a preference long upheld by the patient community but also by public decision-makers e.g. the Commission Expert Group on Rare Diseases and the EMA) and based on a public-private dialogue with clinical experts, patient representatives, regulators, HTA experts, payers and the company (or companies).

We trust, and so do many clinical leads and company leads with us, that is in the best interest of a company to fund the creation of such a registry and to start far upstream, when the product is starting to be developed, as generated data will come in support of regulatory and HTA requirements. The ERNs have the potential to offer common methods, standards and tools to produce quality validated data, and could generate new opportunities as well if supported with adequate human and financial resources in a public-private partnership framework. It is worth noting that, in Europe, the European Organisation for Research and Treatment of Cancers (EORTC) has three decades of similar experience which can be immediately applied. AIFA, the Italian Agency for Medicines – which covers the full spectrum from regulatory decisions to HTA and pricing negotiations – has also developed a programme of post-approval registries supported with public funding, from which lessons could be drawn.

The upcoming discussions between the European Commission, the Board of Member States for ERNs and the Joint Action for Rare Diseases, with a view to developing and adopting a framework for the partnership between ERNs and companies, will offer a unique opportunity not to be missed to put in place a scientifically and economically sound and meaningful process which could be scaled up in the future.

The most appropriate time points for discussions on registries are occasions for very early dialogue between all stakeholders in a disease area, e.g. the scientific advice at EMA and HTA, MoCA early dialogues with payers and, following that, the CHMP post-marketing requirements, and in our proposed scheme, the agreement on post-marketing key research questions and data collection for later re-assessment.

4.4.5. A European Fund to co-fund the post-marketing evidence generation as a research activity?

Similarly, ideas ventured by some leading stakeholders in recent years about a **“European Fund”** could be usefully linked to the issue of real-world data generation. One such option could be to set up a fund that would support the generation of evidence from the moment of the marketing authorisation of a medicine up to the time point of the first reassessment of its value, e.g. 3 years later.

The interest of such a fund would be to **“shift the risk”** – i.e. to lift the financial pressure on EU Member States and support them in ensuring full access to the medicine while the required data are being collected, up to the point when a more clear-cut view of the value of the medicine is available to guide Member States’ decisions. This approach is used already in the Netherlands, a country which is funding several orphan medicines out of its research budget during the time needed to generate additional evidence. Such an approach would make much more sense if rolled out on a European scale. And such a European Fund could be financed from the EU budget directly, or based on individual contributions from each Member State or from several volunteering ones of them, or still a combination of both options.

The Fund could support a proportion of the cost of treatment for a standard duration of 3 years (with possibility of variations between 2 to 5 years) in a co-funding scheme with the Member States which could be covered as part of a Managed Entry Agreement. In exchange, the benefiting Member States would agree to provide immediate access after the grant of marketing authorisation and to apply the common European agreement for post-approval research activities.

4.4.6. Towards “horizon-shaping”?

Most, if not all of the previous reflections in this paper have focused on how to optimise the interactions by which a private developer of a new orphan medicine and a public entity agree on the conditions and parameters at which the said medicine shall be priced and reimbursed – and at which it will ultimately reach the patients who need it.

This being said, as this paper draws to a close, it may well be time to shift that perspective rather radically.

While much attention has been given to the widespread practice of “horizon-scanning” (see for instance section 3.2 above), this approach presents a fundamental flaw in that it is much more *passive and reactive* than proactive – i.e. in that governments and other public institutions that apply it today measure and define their actions by the yardstick of which new treatments pharmaceutical manufacturers are placing on the market, rather than which new treatments are needed and should be developed by pharmaceutical manufacturers to eventually come to the market.

EURORDIS-Rare Diseases Europe strongly believes that the time is right to place a greater emphasis on this latter dimension. How could governments and public institutions take action to shape the horizon of what we need – and want – to see coming? How can we encourage to a much greater extent the development of therapies for the disproportionate number of rare diseases repertoried today for which no satisfactory treatment exists yet? How can we also use such new approaches to encourage, wherever treatments may already exist today, the development of less expensive or less invasive treatment options? We believe that it is not intellectually possible to de-couple and silo the two debates – i.e. that of the sustainability of existing healthcare solutions on the one hand, and that of how public resources and funds could be used to steer research and development in a direction which is most critically needed by society at a given moment in time. The virtuous model of tomorrow could be one of a public-private partnership going all the way from the bench (public or public-funded private research) to clinical trials and approval across a pre-defined pathway, and resulting in a medicine that offers a real and recognised therapeutic solution to a clear unmet need at a price seen and accepted as fair.

EURORDIS-Rare Diseases Europe further believes that the European Union, thanks to its existing body of legislation on public procurement, should be playing a vanguard role in this conversation. The concept described hereabove could for instance be materialised in the form of public calls for tenders run jointly by the European Commission and interested Member States with a view to incentivising the development of new orphan medicines in specific therapeutic areas and at a specific range of prices, with either one developer or a group of them ultimately being selected to deliver the agreed work.



Our recommendations

- We call on HTA authorities and experts from all EU Member States to more openly consider new approaches for the health technology assessment of orphan medicines – e.g. formative and summative assessments – particularly in application to innovative therapies with a high level of uncertainty at the time of marketing authorisation.
- We call on national HTA bodies and national competent authorities for pricing and reimbursement to more openly consider modalities according to which the price of a medicine coming to marketing authorisation with a high level of uncertainty should not remain fixed and “set in stone”, but rather fluctuate upwards or downwards according to the evidence collected from real-life use.
- We ask the governments and public authorities from all EU Member States to lend their full support and commitment to the European Reference Networks, so that the ERNs may demonstrate over time their capability to generate, collect and analyse the real-world data that are very much needed today.
- We ask the European Commission, the Board of Member States for ERNs and the Joint Action for Rare Diseases to adopt a sound and meaningful framework for partnerships between ERNs and pharmaceutical manufacturers, whom we urge in turn to strengthen their involvement in the development of more numerous and more consistent disease patient registries, and beyond, a robust framework for the production of quality and validated data fulfilling the needs of the drug developers as of the regulators or competent authorities.
- We encourage the European Commission and all EU Member States to consider proposals for a dedicated “European Fund”, as part of the FP9 EU Research Programme, and the resources of which could help finance the generation of evidence for high-uncertainty orphan medicines from the time point of marketing authorisation up to the first reassessment of their value. This would be in the interest of Member States (which would **be subject to** less financial pressure in the early days of the commercialisation of a new orphan medicine); of pharmaceutical manufacturers (lesser short-term unpredictability about access, plus better chances of generating valuable real-world evidence); and above all of rare disease patients, who would be able to receive rapid and full access to the medicines they need.

5. Conclusion: The time for radical action is now

Getting 3 to 5 time more new rare disease therapies, 3 to 5 times cheaper

Our motivation behind this paper is to ensure greater recognition and understanding of the major problems that persons living with a rare disease in Europe today face all too often, and to create and feed a genuinely constructive dialogue on the basis of the proposals formulated here above.

It is a profound misunderstanding and a misleading approach to believe that the debate on access to medicines can be summarised and reduced to a merely technical discussion in which greater affordability and lower prices would be the only solution to insurmountable budget limitations and financial constraints.

Instead, **it is our view that this debate remains fundamentally and stubbornly a political one**, the cornerstone of which is our direct responsibility in deciding today what we collectively want our societies to stand for, and in creating therefrom a political framework aligned on that vision and from which technical aspects can later be derived.

Are we ready to agree that, from a social justice perspective, it is right and just to give all persons living with a rare disease the treatments they so urgently need, as soon as these treatments exist and are available?

In the same line of thinking, are we ready to agree that it is no less an end in itself to improve the health of a small fraction of the population with dire unmet medical needs, than to address the needs of the multitude?

Are we ready to agree that, from a social justice perspective, it is right and just to give all persons living with a rare disease the treatments they so urgently need, as soon as these treatments exist and are available?

Indifference is not an option. We want all parties to this debate to take the time to express their respective interests and to reflect on the possibilities expressed in this contribution and beyond. Expressions of support are welcome, differing views even more so. National authorities competent for pricing and reimbursement and pharmaceutical manufacturers must indicate in an unambiguous way where they stand on each of our proposals – what they would be ready and willing to take up, and what they would be more reluctant to accept.

We believe that a new ecosystem is possible, a framework based on a global approach to innovation for unmet medical needs and on sustainability for healthcare systems as well as financial attractiveness to industry and investors. And we do not believe that this is a “futuristic” dream: a structured approach can be built with **practical solutions and methods that have already been put in practice at varying levels and on different scales.** We have mentioned and referred to concepts and initiatives that have gone in recent years from theory to practice, and that have reached today an operational critical mass. For these that have delivered robust proof of their functionality and value-added, the question worth asking now is: what are we waiting for to extend them into standard practice? What are we waiting for to muster the political willingness to do so?

While an overwhelming proportion of recent debates on access tends to focus solely on innovation in products, we trust that innovation matters too in processes and behaviours.

Today's challenges will not be solved by applying yesterday's conservative mindsets and judgmental patterns. If risks must be taken to deliver scientific breakthroughs and genuine innovation, risks must also be taken to make sure that tomorrow's processes and policies are better, more adequate and also more fair than today's.

Access to and the affordability of medicines, particularly for minority populations as in the case of rare diseases, is today a major point of tension in our societies. The persons living with a rare disease, whom EURORDIS represents, are not approaching this debate with a view to demanding special rights carved out from the norm as a disadvantaged community, or in an "affirmative action" manner.

The persons living with a rare disease, whom EURORDIS represents, are not approaching this debate with a view to demanding special rights carved out from the norm as a disadvantaged community, or in an "affirmative action" manner

On the contrary, since this paper has been developed in collaboration with our membership, it clearly demonstrates that we are positioning ourselves as responsible citizens eager to find fair and balanced solutions that respect the humanistic values at the core of our European society model, and that allow all of us to fully take part in the life of our societies in an inclusive approach.

Similarly, far from pretending that our point of view is the only right way to approach this debate, or that our legitimacy should exceed that of other stakeholders around us, we call for what, according to us, is a fair and equitable right shared by all, and consequently take pride in representing all persons who fight every single day with their serious conditions.

The possibilities contained in our proposals are not a set-in-stone, "take it or leave it" package. They can be combined together or adapted to different situations or challenges. What remains, however, is that **they are in our opinion the only constructive, "win-win" way in which the current tensions between payers, the industry and patients on access to medicines can be resolved and overcome, and in which the promises of "fair pricing", "affordability", "sustainability" and "predictability" can be delivered.**

On a final note, we also believe that **the call for more structured access that underpins this paper is of a nature, if fulfilled, to reinforce the attractiveness and competitiveness of Europe on the global marketplace.** By laying out the four-pillar approach described in this paper, we believe we can achieve a more rapid development of innovative medicines, faster access of patients to them, a faster and more predictable return on investment for manufacturers, and also better and more reliable processes for the generation of real-world data and evidence post-marketing authorisation.

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Breaking the Access Deadlock to Leave No One Behind

A Position Paper by EURORDIS and its Members

*“ The ambition of **EURORDIS** is to have
3 to 5 times more new rare disease therapies approved per year,
3 to 5 times cheaper than today by 2025 ”*



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