Access to Affordable Medicines for Rare Diseases – Towards an Equitable European Ecosystem

Reflection paper for the initiation of a flagship initiative

for a rapid patients' access to innovative therapies for very rare diseases

Introduction

In today's world, science and technology offer an unprecedented chance to address the unmet medical needs of people living with a rare disease. This potential is currently not translated into actual health benefits for the large majority of people living with a rare disease due to issues concerning availability, accessibility and affordability of treatments.

The **French Presidency of the Council of the European Union**, together with Czech Republic and Sweden in their Trio, intends to put a clear focus on rare diseases, recognising its long-standing national focus and **the added value of collaborative action at European level to drive change in the accessibility, affordability and sustainability of the lifecycle of medicines for rare diseases.**

France follows a series of **EU Council Presidencies** calling for greater solidarity and innovation in ensuring availability and affordability of therapies across Europe (e.g., Belgium - 2010, Italy – 2014, The Netherlands – 2016, Malta – 2017, Portugal - 2021). However, whilst those Council Conclusions have provided focus and attention to the issues, **much remains to be done, particularly to address the persisting fragmentation of regulatory and access frameworks at the national level, which only results in delaying patients' access to medicines that have been approved**.

The COVID19 pandemic has accentuated rare diseases' challenges, i.e., scarcity of data, uncertainty and vulnerability of the patient population, access inequalities, and shown even further the importance of pulling together resources, expertise and efforts at EU level to fight common challenges[i]. For example, **the pandemic showed that procurement to match innovation with unmet need(s), in particular joint procurement and advanced purchase agreements (at least at European level) are now possible and should be extended to rare diseases therapies** under the right conditions.

Coordinated, more **strategic policies are required to address these shortcomings and inequalities and ultimately improve the health outcomes and quality of life of people living with a rare disease,** where the added value of European action has never been in doubt, but that now needs **a transition from incremental improvement to success by design**.

Problem definition

The Regulation on Orphan Medicinal Products (OMPs) was implemented since 2000 by the European Commission to stimulate investment in the development of medicinal products for rare diseases by creating incentives for manufacturers. Orphan market exclusivity, distinct regulatory processes, as well as scientific and financial assistance for research and development (R&D) were instituted. The Regulation proved to be a great success,

progressing care in many overlooked conditions. Despite this progress, concerns about remaining unmet needs, patient access, affordability, and sustainability of pharmaceutical spending have risen in the past few years.

In particular, **there are concerns about the appropriateness of the current regulatory framework to attain the societal goal of reducing unmet needs while ensuring value-for-money**. As a result, the European Commission is examining the strengths and shortcomings of the OMP Regulation, with the view to recalibrate this policy. European Commission publications have highlighted that 95% of the 6,000-7,000 identified rare diseases are without approved therapeutic options[ii]. This lack of treatment in most rare diseases is interpreted as a major unmet medical need and a failure of the OMP Regulation to address these diseases. While it is true that most rare diseases remain improperly addressed, the full picture is more complicated when it comes to availability and accessibility.

Rare diseases are not uniformly spread across prevalence: **only 4% of diseases sit in the 1-5 in 10,000 prevalence bracket, while 84% affect fewer than 1 in 1,000,000 patients**. While the more prevalent diseases are less frequent, the size of the populations suffering from each of these diseases is significantly higher, meaning that 80% of all rare disease patients fall in the 150 diseases with the highest prevalence[iii].

In very small populations and/or Advanced Therapeutic Medicinal Products (ATMPs), evidence at time of pricing and reimbursement (P&R) is often immature. **A very unique problem to rare diseases is that** because of the small population affected and the small number of patients included in clinical trials, **there is a high level of uncertainties at time of Marketing Authorisation which makes clinical value assessment very challenging for all EU Member States.**

This leads to delays in Health Technology Assessment (HTA) processes and results in delayed and incomplete access[iv]. On average, with the notable exception of a couple of larger EU countries, it takes approximately 2 years from marketing authorisation to patient access, and in many smaller countries, patients may not gain access at all[v]. **Costs are often high, threatening affordability and increasing uncertainty around value for money, and the lack of uptake reduces manufacturer revenue meaning prices have remained high whilst access remains uneven and unequitable**.

Goals

A **European level flagship initiative** should support more global discussions, which are essential to improve access to medicines and therapies for very rare conditions for all patients who need them, **leaving nobody behind**: the momentum created by the COVID-19 crisis should be leveraged, as an example of feasibility and collective strength of cross-country negotiations and collaborations for the greater good of citizens.

A workable system for very rare disease medicines should be developed at European level to economically regulate the relationship between public buyers and companies[vi] - providing a structured market access as a collateral to the incentive of the market exclusivity granted – as much as to generate the post-marketing Real World Evidence which are essential to assess the clinical effectiveness value and the value for money: this is particularly urgent in order to ensure access to advanced therapies such as gene and cell therapies.

Now, it is the time for a **true European equitable ecosystem for therapies for people living with very rare diseases**. This would integrate **early dialogues, joint scientific assessment, structured collaboration in price negotiations**, and the **use of joint procurement**, post-marketing **European evidence generation plan**, and **real-world data in decision-making**. It would **build upon the clinical infrastructure created with the European Reference Networks (ERNs)** in order to encourage earlier and wider access to transformative therapies for very rare diseases such as **ATMP**s and cement the role of **Europe as a leader in innovation** for rare diseases.

Principles

This flagship initiative would steer and support Member States in addressing inequities in access across countries and in maintaining the sustainability of their healthcare systems. It should be structured around three pillars:

1. **A stronger European collaboration between the national competent authorities** of several EU Member States based on **solidarity** principles, as the wide divergences in access often observed from one Member State to another must come to an end.

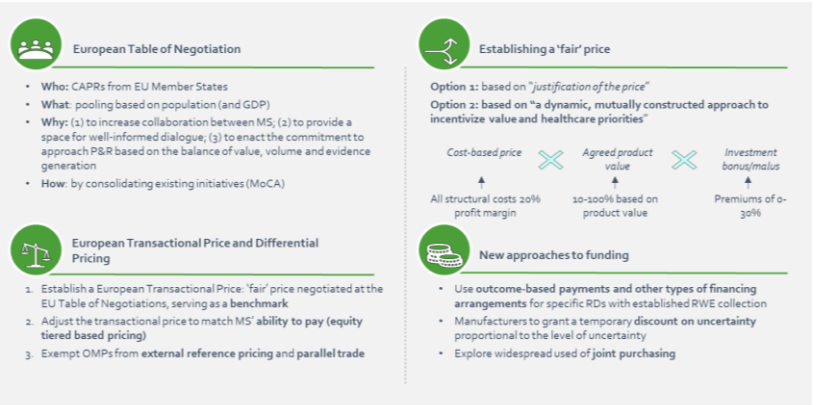
2. **A trusted space for a well-informed dialogue**, helping these participating authorities to engage with the industry, as the absence of constructive exchange is ultimately detrimental to all – not least patients.

3. **A commitment to approaching pricing and reimbursement decisions based on a balance of three factors: value, volume, and evidence generation** – i.e., the medicine's 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.

An **EU-Fund** should be established to help finance **access to the transformative and potentially curative gene and cell therapies for very rare diseases** and co-**finance the generation of post-marketing authorisation evidence** across Member States **during the years initially following approval**, in order to reduce impact of uncertainties whilst at the same time allowing for timely access to life saving therapies.

Governance and operations

The EU and associated EEA countries can lead a flagship initiative to allow for **greater consolidation at EU level for very-rare disease therapies (those with a prevalence of less than 1 in 10,000 people)** through the development **a EU Fund to cover evidence generation across countries** and **early uptake of promising therapies**, immediately after EC Marketing Authorisation (MA), **as pilot project.**



Access to this fund should be granted by a voluntary (to begin with) negotiating alliance between Member States, such as a **Table of Negotiations**, building on existing regional (BENELUXAI, FINOSA)[vii] and European initiatives (the payer-led Mechanism of Coordinated Access – MoCA)[viii]. The management of the Fund should be ensured via a cooperation with the EU institutions, whilst respecting current Treaty competences.

Any joint price negotiations by Member States or led by the European Commission must build on a joint assessment of the value of the product, which is binding to all participating Member States, and needs to be the basis of any pricing discussions. Moreover, any joint negotiation effort has to take account of the unique legal, political and economic challenges it brings about, owing to the differences between national health systems in terms of policy goals, clinical practice, patterns of medicine usage, as well as medicine pricing and reimbursement.

Immediately from EC approval, the Fund would guarantee at least one year of full coverage of the medicines, or enough time to secure a successful agreement between the marketing holder and MSs on a transactional price (see table 1), the discount for uncertainties, the tiered differential pricing approach, the modalities of payment (per capita, per performance or outcomes, and also over time, etc).

Furthermore, **key research questions to address the main uncertainties should be defined resulting in a pan-European real world evidence generation plan,** building on and consistent with the EMA qualified registry, the Post Approval safety studies, the post approval efficacy studies, and the HTA requirements based on their common clinical assessment.

Contractual specifications between companies and healthcare providers, linked to treatment delivery and data collection, should be defined contractually ahead of time. These specifications are sometime already reviewed by the CHMP, it could become systematic, and reviewed by the Table of Negotiation for a full alignment on data requirements (RWE), pushing up safety and quality, while enabling to have clarity on what is being paid.

Financially it means that **during the first year, 100% of the medicine is covered by the EU Fund, at the price claimed by the company; after negotiation, the company pay back the difference to the Fund.** In this respect the fund would have some similarities to the Autorisation Temporaire d'Utilisation (ATU) programme that is successfully in place in France, or to the measure successfully put in place in Germany with an immediate patient access for all products representing less than 50 M€ annual revenue and postponing the HTA assessment by one year or more.

Scope and budgetary requirements

As stated above, the Fund should cover very promising yet complex treatments such as gene and cell therapies (ATMP), addressing very rare disease with a prevalence of less than 1 in 10,000.

Disease	Estimated Prevalence	Product	Type	Estimated patient / year	List price
Leber's Congenital Amaurosis	Less than 1 in 10,000	Luxturna (voretigene neparvovec)	Gene therapy	105	EUR 360,000*
Early cerebral adrenoleukodystrophy (CALD)	Less than 1 in 10,000	Skysona (elivaldogene autotemcel)	Gene therapy	424	N/A
B-lymphoblastic leukaemia/lymphoma	1.2 in 10,000	Kymriah (tisagenlecleucel)	Cell therapy	N/A	EUR 320,000*
Severe combined immunodeficiency due to adenosine deaminase deficiency (ADA-SCID)	Less than 1 /100,000	Strimvelis	Gene therapy	5 - 20	EUR 594,000*
Metachromatic leukodystrophy (MLD)	Less than 1/100,000	Libmeldy	Gene therapy	86	EUR 2,500,000**
Spinal muscular atrophy	Less than 1/10,000	Zolgensma (Onasemnogene abeparvovec)	Gene therapy	580	EUR 2,155,000*
TDT Beta-thalassemia	Less than 1/10,000	Zynteglo	Gene therapy	N/A	EUR 1,580,000

*Table 1. List of selected ATMPs approved in the past 5 years, with a prevalence less than 1/10 000. Sources: European Medicines Agency (EMA), Orphanet. *List prices as indicated in the Italian Gazzetta Ufficiale **NICE*

Based on the average revenues reported by the study to support the evaluation of the EU Orphan Regulation[ix], we estimate that 3 to 5 medicines per year would be eligible for the Fund, with revenues on average ~€100M. If the Fund covered

a) 100% of the cost of treatment during the first year, while negotiations are taking place and the European real world evidence generation plan is being designed, it means a cost of 300 to 500 M€ for the first year. Over 6 years the total would be 3 B€. From which an estimated average of 50% will be paid back by the marketing holder to the fund, after negotiation, 1,5 B€. (Table based on maximum 5 products 500 M€)

b) for the 3 to 5 following years, part of the therapy's cost plus the cost of data collection, at a level of co-funding varying between 20% and 50% according to the level of uncertainties, it might therefore need to be ~€150M – €250M per year. (Table based on average 200 M€, with maximum 5 additional years of all products)

Over a period of 6 years, the Fund will need 0.5 B€ on Year 1, 0,7 B€ in Year 2, 0,9 B€ in Year 3, 1.1 B€ in Year 4, 1.3 B€ in Year 5 and 1.5 B€ in Year 6. **A total of 6 B€ over 6 years would probably be a conservative yet realistic total. For the following year, with the same scope the Fund will need 1.5 B€ per Year**.

Five products / year	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6	Total
100% coverage	500 EUR Million	500 EUR Million	500 EUR Million	500 EUR Million	500 EUR Million	500 EUR Million	3 EUR Billion
30% to 50% over 5 years ; 160 to 250 EUR Million / year (average 200 EUR Million / year)		200 EUR Million	200 EUR Million	200 EUR Million	200 EUR Million	200 EUR Million	
			200 EUR Million	200 EUR Million	200 EUR Million	200 EUR Million	
				200 EUR Million	200 EUR Million	200 EUR Million	
					200 EUR Million	200 EUR Million	
						200 EUR Million	
Total	0.5 EUR Billion	0.7 EUR Billion	0.9 EUR Billion	1.1 EUR Billion	1.3 EUR Billion	1.5 EUR Billion	6 EUR Billion
Payback of 50% of year 1		250 EUR Million	250 EUR Million	250 EUR Million	250 EUR Million	250 EUR Million	1.25 EUR Billion

The three variables on which to adjust the use of funds are

a) the level of co-funding for the evidence generation, which could be reduced to 10 to 30% -instead of 20 to 50% when the system is more mature and as more medicines will be approved every year;

b) the level of funding during the 1st year.

c) the prevalence level

Expected benefits

The Fund should lead to earlier and broader access as well as enhanced data collection and better value for money, by financing 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 Fund would be beneficial to:

- Member States, which would be subject to much less financial pressure in the first years of the commercialisation of a new orphan medicine, which is the period where uncertainties still remains, and will obtain real world evidence based re-assessments in a much shorter period of time, hence having better value for the public money; a new solidarity between EU Members states.
- Pharmaceutical manufacturers, with a good predictability of EU consolidated revenues for the 3 to 5 years after approval and launch; lesser short-term unpredictability about access and a huge reduction of the burden and useless cost of navigating the fragmented HTA and payers environment across Europe; plus, better chances of generating valuable real-world evidence.
- The alignment with the Regulation on HTA Cooperation in Europe (to be implemented by 2024), plus potential integration of key elements of the revised Regulation on Orphan Medicinal Products and general Pharmaceutical legislation.
- The overall attractiveness of the European ecosystem for investment in research and development of transformative, life saving treatments, contributing to a highly skilled and value based European economy

and above all to highly vulnerable and neglected people living with a very rare disease across Europe, who would be able to receive rapid and full access to the medicines they need.

[i] EURORDIS Rare Barometer survey on COVID-19 (2020) available at https://download2.eurordis.org/rbv/covid19survey/covid_infographics_final.pdf

[ii] European Commission. Commission Staff Working Document Evaluation. Joint evaluation of Regulation (EC) No 1901/2006 of the European Parliament and of the Council of 12 December 2006 on medicinal products for paediatric use and Regulation (EC) No 141/2000 of the European Parliament and of the Council of 16 December 1999 on orphan medicinal products. (2020) [online] Available at: https://ec.europa.eu/health/sites/default/files/files/paediatrics/docs/orphanregulation_eval_swd_2020-163_part1.pdf

[iii] Nguengang Wakap, S., Lambert, D.M., Olry, A. et al. Estimating cumulative point prevalence of rare diseases: analysis of the Orphanet database. Eur J Hum Genet 28, 165–173 (2020).

[iv] Detiček A, Locatelli I, Kos M. Patient Access to Medicines for Rare Diseases in European Countries. Value Health. 2018 May;21(5):553-560. doi: 10.1016/j.jval.2018.01.007. Epub 2018 Mar 16. PMID: 29753352. https://pubmed.ncbi.nlm.nih.gov/29753352/

[v] EFPIA Patients W.A.I.T. indicators 2021: https://www.efpia.eu/media/602652/efpia-patient-wait-indicatorfinal-250521.pdf

[vi] EURORDIS Breaking the Access Deadlock to Leave No One Behind (2018) A contribution by EURORDIS and its Members on possibilities for patients' full and equitable access to rare disease therapies in Europe available at http://download2.eurordis.org.s3.amazonaws.com/positionpapers/eurordis_access_position_paper_final_4122017.pdf

[vii] https://beneluxa.org/ ; https://www.tlv.se/in-english/international-collaboration/finose---a-nordic-cooperation.html

[viii] https://www.eurordis.org/content/moca ; https://www.medev-com.eu/

[ix] European Commission. Commission Staff Working Document Evaluation. Joint evaluation of Regulation (EC) No 1901/2006 of the European Parliament and of the Council of 12 December 2006 on medicinal products for paediatric use and Regulation (EC) No 141/2000 of the European Parliament and of the Council of 16 December 1999 on orphan medicinal products. (2020) [online] Available at: https://ec.europa.eu/health/sites/default/files/files/paediatrics/docs/orphanregulation_eval_swd_2020-163_part1.pdf