The 20 million people living with a rare disease in the European Union, and the 30 million in Europe, highly anticipate the Revision of the Orphan Medicinal Products and Paediatric Regulations at the end of this year. The EU Regulation on Orphan Medicinal Products has helped transform the lives of many people living with rare diseases and continues to be successful in fulfilling its primary purpose – attracting investment to the development of therapies for life-threatening or debilitating diseases for millions of people who today live without any, or without satisfactory treatment options. Yet major difficulties in accessing approved treatments still exist.

EURORDIS-Rare Diseases Europe and our 1000 patient organisations have become experts in this field, not by choice, but by necessity. Our population still has vast unmet needs, and access to treatments and therapies was identified as the top priority for people living with a rare disease by 2030.

According to a Rare Barometer survey in 2019[1]:

- Only 5% had received a transformative treatment approved for the entire European Union, with 69% of rare disease patients having received only symptomatic treatment for their rare disease.
- 22% of people with rare diseases could not get the treatments they needed because it was not available where they live, reflective of the fragmentation of the market across the 27 Member States.

[1] Results unpublished but available upon request.
In 2018 EURORDIS and its 1000 member organisations in Europe, set out, in the Position Paper “Breaking the Access Deadlock to Leave No One Behind”, our ambition to see three to five times more new rare disease therapies per year, three to five times cheaper than today. This was reinforced by consensus through the participatory Rare 2030 Foresight Study, which also set the ambition for 1000 new therapies to be available by 2030, in line with the IRDiRC vision.

Our driving principle remains the same: how can we have more and better treatments that are available, accessible and affordable for people living with rare diseases?

We are looking to the European Union to take the opportunity of the revision of the Orphan Medicinal Products and Paediatrics Regulations to create a robust regulatory framework that will drive innovation and improve access to transformative treatments for this population in the years to come. We have two decades to learn from, and the potential to set the direction for the two decades to come. We also have the opportunity to situate Europe as a global leader in drug development and access, as such decisions on clinical research and investment are taken on a global level.

The rare disease community has also been calling for a European Action Plan on rare diseases - a coordinated, goal-oriented strategy - of which the OMP Regulation would be a crucial pillar.

EURORDIS remains available to provide further information to support these points.
To transform the European Research & Development for the rare disease ecosystem building upon advances of the past 20 years, for the next 20 years

This must reflect and connect developments across science, technology and policy, such as the European Reference Networks for Rare Diseases, the future Clinical Research Network on Rare Diseases planned under the Rare Diseases Partnership, the European Health Data Space, and the current strong acceleration of ATMPs, as well as the progress the OMP and Paediatric regulations themselves have driven.

To situate Europe as a global leader in research, development and access, through a regulation that is attractive for developers, and competitive globally.

Reflections should be made in aligning with and maintaining competitiveness with the USA’s FDA system.
To define a model that is centered on the unmet needs of people living with a rare disease, and includes patient participation in its establishment and implementation.

To establish a European pathway, from development to access, to ensure innovation coupled with affordability and to gain that crucial strategic autonomy in research and development.

To ensure convergence and coherence between different relevant legislation

This includes the HTA Regulation, the General Pharmaceutical Legislation, the Regulation on Paediatric Medicines, the Regulation on ATMPs, the Cross Border Healthcare Directive, the Blood, Tissue and Cells Regulation and the European Health Data Space.

This proposal is a contribution from EURORDIS-Rare Diseases Europe and its members that offers concrete recommendations for the upcoming revision of the Orphan Medicinal Products Regulation.

With 20 years of experience following the lifecycle of orphan medicinal products through the Orphan Medicinal Products Regulation in the EU and of the US FDA Drug Act, it is most importantly based on the experiences of people living with a rare disease in Europe.

The proposals have been socialised progressively since 2018 through European Commission public consultations, evaluations, events and conferences.

Thank you to all who have contributed to these proposals, including the Therapeutics Advisory Group, the Drug Information, Transparency and Access (DITA) Task Force, the Council of National Alliances and the Council of European Federations.
TOWARDS AN EVOLUTION
OF THE REGULATION

To achieve these objectives, our key ask for revision in the regulation is to evolve the incentives framework to maintain predictability for sponsors while enhancing Europe’s competitiveness. This could be achieved through specific, concrete revisions to the regulation:

01. Maintain the prevalence threshold to leave no disease behind, while including an incidence threshold

Maintaining the prevalence threshold allows general alignment with the US regulation in the field and some of its provisions. We strongly believe that lowering the current threshold would disincentive the investment and research field, weakening the global approach to product development.

In addition, incidence criteria should be introduced, as is already used in rare cancers, 6 per 100,000 persons per year, which was reached through consensus by all stakeholders. Whilst the progress of medical research is now leading to a better understanding of the mechanism of the diseases, and genetic determinants of sub-types of diseases leading to more targeted therapies, this approach would help to focus the model by removing diseases that are artificially rare because of the prevalence calculation, but often encountered by the health system.

It should also allow for a definition of ultra-rare diseases, based either on a combination of low prevalence/low incidence (e.g. below the 400 most prevalent rare diseases as identified by Orphanet) or following existing definitions (such as the Scottish Medical Council definition).
Encourage structured early dialogue in a multi-stakeholder format to address unmet needs at the right time point: a process rather than criteria

We do not believe that unmet needs should be defined in the regulation, but there should be a multi-stakeholder mechanism to define them, supported by the EMA to give the authority of the regulatory agency. Unmet medical need does not mean the same thing for everybody. It is not only patients with disregarded and underserved diseases who have unmet medical needs, but also patients with diseases in so-called ‘crowded areas’.

Even with no objective definition of unmet medical needs, regulators, clinicians and patients have no problem identifying them. A legally binding definition could raise more problems than it would solve, leading potentially to long discussions to the detriment of the populations intended to be served.

Unmet needs are implicit in the ‘significant benefit’ criteria for designation, which acts as a proxy. De facto, all designated orphan products are developed to address unmet medical needs.

In order to qualitatively assess the unmet medical needs, it is, therefore, preferable to ensure that early dialogue takes place at a very early stage, on a specific disease, in a multi-stakeholder format including patients’ organisation representatives, clinicians from the European Reference Networks (ERNs) on rare diseases, regulators, HTA experts and payers, as it can help to refine existing assumptions on unmet needs and satisfactory method, under appropriate guidance. This first assessment at the time of designation is then refined as the development and the medical field evolves and is reassessed at the time of Market Authorisation. There should also be a strong link with the new Clinical Research Networks on rare diseases, emerging as part of the Rare Disease Partnership.

This early dialogue should include discussions on:

- The knowns and unknowns about the disease;
- The needs in terms of disease registries;
- A natural history study;
- Comparators to facilitate discussions for the regulators and HTA discussions;
- Clinical endpoints and surrogate endpoints, in particular biomarkers; and
- PROMs validated by the EMA.
We would strongly encourage the regulation to build on the experience of the FDA’s Patient-Focused Drug Development Guidance Group, which ensures developers include in their proposals information on how and where patients have been included. This ensures a patient-centric approach, based on early dialogue and expertise in the specific disease area. This makes it easier for all stakeholders to include patient experience in their assessments, alongside clinical trials.

Importantly, issuing methodological guidance to support patient-focused drug development is a statutory requirement under the 21st Century Cures Act of 2016 Section 3002 (c) and a commitment made under the Prescription Drug User Fee Act (PDUFA) VI (authorised under the FDA Reauthorization Act of 2017 (FDARA), Title I). We would encourage this statutory status in the OMP regulation.

**03. Introduce an “Orphan Drug Development Plan” to guide the development of new treatments with the continuous input of experts**

Other European regulations have plans included in their narrative, such as the Paediatric Investigation Plan in the Paediatric regulation and the Risk Management Plan in the Pharmacovigilance regulation. We propose to use this concept of a “Plan”, meaning a ‘contractual’ agreement between the developer and the regulators in order to guide the development all along the different steps that are under the EMA scope of activities and that would at the same time allow for building of knowledge and supporting interactions with the HTA bodies and payers.

This ODDP builds on the experience of the PRIME scheme which allows continuous interactions between the developer and the regulators through iterative scientific advice, the ILAP scheme in the UK and the work performed in IRDiRC with the Orphan Drug Development Guidebook.
The COMP, composed of representatives from each Member State, patient representatives and other experts, could be the arena and the guarantor for this process. Building upon the work done at IRDiRC, we can imagine a kick-off multi-stakeholder meeting assessing the unmet need in the related field (see section 2 above) combined with the filling of the START checklist by the developer. The process would be supported by the identification of the main rapporteur and an expert group to follow the product’s journey through the EMA and by a document that would help gather all the knowledge gained during the R&D phase (such as the Target Product Profile used by the FDA, the Target Development Profile in ILAP or the Target Patient Value Profile proposed by IRDiRC. We believe that this process and the supportive documentation could lead to a better clinical development pathway, encompass the discussions regarding Scientific Advice/Protocol Assistance, reduce the attrition rate in OMPs and inform the future steps at HTA and payers levels as well.

04. A modulation of incentives, rewarding earliest dialogue and favouring areas with no therapeutic options

A graduation system to provide different levels of incentives depending on factors to best address the unmet needs of people living with a rare disease should be introduced. For example, targeting very to ultra-rare conditions, or those with no therapeutic option yet, may constitute a basis for a reward. Products identified as particularly innovative could also receive a bonus incentive. There should also be incentives linked to research funding, utilising existing structures such as European Reference Networks (ERNs). The 3 archetypes developed in the context of the European Expert Group of Orphan Drug Incentives are presented, confidentially as not yet published, in the scheme below.
Equally, processes that encourage faster access to treatments should be rewarded, such as early dialogue between the sponsor and regulatory bodies. A "European Fund" that supports the generation of additional Real World Evidence in both the context of compassionate use and in the years following marketing authorisation would help collect much-needed comparative data, for example through registries, and therefore should also be encouraged.

We believe this approach to incentives offers a greater chance for success than vouchers, which are being discussed, for which we have not seen evidence to show their benefit. In particular, we are concerned that it could lead to companies making choices for the wrong reasons, based on the most profitable options and not addressing unmet needs.

05. Maintain Market Exclusivity as an incentive, to ensure global competitiveness

There is a common misconception that market exclusivity leads to a sponsor’s monopoly in a certain disease area. In fact, we have seen for example in the field of spinal muscular atrophy (SMA) in the past five years that three different therapies have been able to emerge, which are transformative for patients, which all fit under the regulation.

The length of market exclusivity should not be shortened, and at the very least should not be less than in the United States. Linear graduation could be introduced i.e. 8, 10, 12 years or 10 and 12 years ME for Archetypes 1 & 2 and less for Archetype 3 that were presented in the section 4. Launching a product first to the European market could also see an added year of market exclusivity in order to drive competitiveness.

06. Conditional significant benefit until the conversion into full Marketing Authorisation

In the case of Conditional Market Authorisation, the limited data packages make it, in the vast majority of cases, impossible to assess the Significant Benefit at the time of Market Authorisation. The consequence is that products may lose their orphan drug status, and therefore the benefits of market exclusivity. The product will still get a Marketing authorisation but it might hamper access to patients in the rare disease field.
07. Strengthen the responsibilities and functioning of the Committee for Orphan Medicinal Products (COMP), while reporting to CHMP

Through the revision of the regulation, there should be adequate resources allocated to the EMA and a strengthening of the COMP mandate. This would mean that the COMP should oversee orphan products all along the development cycle.

The composition of the COMP

The COMP should not be a standalone committee but should report to the CHMP, like all other committees. It should be composed of members and alternate members representing Member States, as well as patient representatives, also with members and alternates. The COMP should become fee-based, in order to increase the engagement and the allocation of resources and competencies provided by the National Authorities.

The role of the COMP

The role of COMP should be reinforced to allow its capacity to follow the orphan medicinal product during its whole lifecycle, from the early dialogue mentioned in section 2, through orphan drug designation, scientific advice/protocol assistance, and up to the marketing authorisation and post-marketing phase. This should be articulated through the ODPP (as explained in section 3). Collaboration should be also ensured with the other Committees and more specifically with the PDCO, the Paediatric Committee when the product is included in a Paediatric Investigation Plan.

Preparing the risk-benefit assessment ahead of the CHMP decision would be a way to delegate a significant part of the work to the COMP, especially in light of the growing number of orphan drug applications. This is aligned with the CAT, who already fulfils this duty for Advanced Therapies.

The COMP should also expand on the OMAR (Orphan Medicines Assessment Reports) and produce assessment reports with a legal basis, equivalent to the EPARs. They currently are published with them, but without the legal basis.
Encouragement of EMA-HTA Parallel Scientific Advice/Protocol Assistance

It is important to mention in the regulation that the COMP, particularly in the case of the assessment of the significant benefit, a concept very close to the relevant effectiveness used by the HTA bodies, should be articulated by encouraging EMA parallel scientific advice with HTA.

**08. Include PRIME within the revision of the OMP Regulation or within the wider Pharmaceutical Package as it applies beyond rare diseases**

Accelerated approval is absolutely essential to bring innovation to patients as early as possible, when a medicine is transformative, or potentially curative, in areas of unmet needs. Europe has gained significant experience and success with PRIME: rare diseases represent the half (56%) of the products designated under PRIME and two thirds (89%) of those approved through PRIME. The USA has had a similar experience through the breakthrough designation scheme. This should be explored within the revision of the OMP regulation, but also more widely in order to bring innovation as early as possible to all patients.

EURORDIS calls for these important points to be taken into consideration in the upcoming revision of the Orphan Medicinal Products and Paediatrics Regulations and remains open for any future dialogue.