

EURORDIS response to the European Commission Inception Impact Assessment (IIA) on Paediatric Medicines and Orphan Medicinal Products

EURORDIS Rare Diseases Europe welcomes the opportunity to provide feedback to the European Commission Inception Impact Assessment (IIA) on Paediatric Medicines and Orphan Medicinal Products. **EURORDIS is of the opinion that moving forward, any future improvements to the Regulation on Orphan Medicinal Products and Paediatric Medicines are to reinforce the EU processes in a structured and seamless way for all rare disease therapies, from regulation to access.**

We understand that both the Evaluation of the two regulations and the Inception Impact Assessment recognise the important contribution of the Paediatric Medicines and Orphan Medicinal Product Regulation to public health; we wish to underline that the spirit of the Regulation(s) should be upheld, as to provide the same quality treatments to special populations as to the general one. After twenty years, it is important to take stock of the great advancements provided by the Regulations: for instance, 193 orphan products authorised and over 2300 orphan designations, with 75 medicines for children, are markers of a successful public policy.

However, the IIA points to the inefficiencies in four key areas (both for the Paediatric Medicines and Orphan Medicinal Product Regulations) indicating that continuing with the status quo will not bring forward the much needed developments to bring life transforming treatments to people living with a rare disease and children. Any revision of the existing Regulations to be meaningful need to **1) achieve greater competitiveness in a global environment and 2) enhance the attractiveness of the European ecosystem for scientific development.** In this context, we recommend that a rigorous assessment be included for new incentives proposed such as regulatory vouchers, as well as for suggested changes to the existing ones.

We welcome the opportunities provided by the recently published Pharmaceutical Strategy for Europe to address the issues above in a comprehensive manner. 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: creating a “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 delivered¹.

In this paper, we outline some of the suggestions and commentary that EURORDIS wished to submit to the attention of the European Commission. In particular, we recommend:

- early-stage multi-stakeholder identification of unmet needs and subsequent priorities and investments;
- a threshold of eligibility that includes incidence in addition to prevalence of 5/10000 individuals and avoids artificial breakdown of non-rare diseases;
- a graduated system of incentives, rewarding earliest dialogue and areas with no therapeutic options yet;
- a strengthened mandate for the Committee on Orphan Medicinal Products at the European Medicines Agency (EMA);
- a functional and efficient EU Health Technology Assessment (HTA) Framework and in the interim increased uptake of joint EMA/HTA assessment at the European level;

¹ EURORDIS (2018), Breaking the Access Deadlock to Leave No One Behind.

http://download2.eurordis.org.s3.amazonaws.com/positionpapers/eurordis_access_position_paper_final_4122017.pdf

- the introduction of a common European Table of Negotiations to allow for structured collaboration amongst Member States to allow for timely and equitable access to therapies across Europe, building on existing initiatives;
- a continuum of comparative evidence generation throughout the patient journey and product/technology lifecycle collected in disease registries, supported by a European fund.

Addressing insufficient development in areas of greatest unmet medical needs for patients

Unmet medical need does not mean the same thing for everybody - not only patients with disregarded / underserved diseases have unmet medical needs, patients with diseases in 'crowded areas' might also have unmet medical needs. Article 3 of Regulation 141/2000 refers to life-threatening or chronically debilitating nature of the condition as requirement for orphan designation of a medicine. Unmet needs are implicit in the 'significant benefit' criteria for designation: it is the responsibility of the sponsor to establish that there exists no satisfactory method of diagnosis, prevention or treatment of the condition in question, or if such method exists that the medicinal product will be of significant benefit to those affected by that condition. An explanation to give a shared definition of satisfactory method is expected. The relevant regulatory committee, i.e. the COMP, could convene ad hoc or permanent Scientific Advisory Groups (SAGs) to address issues at hand, with a multi-stakeholder composition (see below).

Even with no objective definition of unmet medical need, 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. It is preferable to ensure that early dialogue takes place at a very early stage, on a specific disease, in a multi-stakeholder format including patients' 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.

In relation to one of the key issues (prevalence), we suggest keeping the threshold of prevalence to 5/10 000 and add incidence criteria (for example rare cancers may be identified as those with an incidence of less than 6 per 100,000 persons per year.). There should be a definition of ultra-rare diseases agreed upon, based on either a combination of low prevalence/low incidence (below the 400 most prevalent RDs as identified by Orphanet²) or following existing definitions in use such as the Scottish Medicines Consortium (SMC)³. This approach would really help focusing on the rare disease community by removing diseases that are artificially rare because of the prevalence calculation, but often encountered by the healthcare systems.

Improve equitable availability and accessibility across Member States

Results on access to treatments from our latest Rare Barometer quantitative survey of 7,500 respondents across EU and World, presented at our European Conference on Rare Diseases and Orphan Drugs in May 2020⁴ revealed

² 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). <https://doi.org/10.1038/s41431-019-0508-0>

³ <https://www.scottishmedicines.org.uk/how-we-decide/ultra-orphan-medicines-for-extremely-rare-conditions/>

⁴ Rare Barometer survey on Rare disease patients' experience of treatments (2019); Results presented at the 2020 European Conference on Rare Diseases and Orphan Products; data available on request.

that 69% of respondents have already experienced a treatment, but only 5% have already experienced a centrally approved curative treatment. 31% have never experienced any treatment (because there is no treatment, or they could not take part in the clinical trial, or the treatment is not affordable). Great variation of the number of treatments the patient could access depends on the disease area. Many treatments experienced were not centrally approved (e.g. off label use therapies, compassionate use).

One of the main shortcomings of the IIA is to look at the regulatory framework in isolation from improvement in access structures and initiatives at European level, which EURORDIS have been calling for since several years, in order to speed up access and ensure equity across countries. We believe that there is interest from all parties involved to embed access pathways into the Regulation e.g. by providing it as an incentive to target underserved diseases (e.g. forming a voluntary table of negotiation based on the experience of the Mechanism of Coordinated Access – MoCA - and based on ongoing discussion between EMA/Payers).

In particular, the creation of a Member States Table of Negotiation would allow for structured collaboration between competent authorities to assess the value and negotiate fair and equitable prices at European scale in exchange of an immediate access to patients across Europe, a multi-year buying commitment and revenue predictability for manufacturers; also, a European coordinated plan could address the uncertainties at time of marketing authorisation to provide additional evidence to reassess the value at an agreed time point.

How to exploit new scientific and technological developments

In our view, it would be key to avoid sub-setting and artificial breakdown of non-rare conditions: classification standards have to be worked out and agreed upon ahead of regulatory/scientific assessment. The definition of rare diseases conditions is linked to the work done with Orphanet and the World Health Organisation.

We suggest devising a graduation system to provide different level of incentives depending upon a series of conditions. For example, targeting ultra-rare conditions or conditions with no therapeutic option yet, may constitute a basis for getting a reward, perhaps even by modulating the options provided in the IIA.

In the same line of thinking, incentives might be higher if the sponsor approaches the regulatory body at the earliest possible moment, to introduce a dialogue between all relevant stakeholder to discuss the points to consider for product development (e.g. registries, endpoints); and / or if the sponsor creates an orphan drug development plan to obtain all the necessary data for authorisation (in many ways, similar to a Paediatric Investigation Plan – PIP). In this case, in order to obtain the above mentioned incentives, scientific advice (SA) / protocol assistance (PA) would become mandatory.

Similar incentives should be considered for EMA / HTA early dialogue, linked to a seamless pathway to access at a European level as explained above, in particular, for low prevalence and highly complex to treat disorders. In this sense, an additional incentive could be linked to the creation of a “European Fund” to support the generation of additional real-world evidence data in the years following marketing authorisation for selected, innovative and transformative medicines with true cross-border value, in order to foster a continuum of evidence generation and data collection post-marketing authorisation (within a post-marketing authorization plan agreed between the company, the regulators and the payers). This continuum will help collecting much needed comparative data through disease registries, for example.

Further incentives should be linked to research funding, preferably through structured approaches involving the European Reference Networks (ERNs) and all other necessary actors (European Joint Programming for Rare Diseases – EJPRD, International Rare Diseases Research Consortium – IRDiRC).

Improve procedures deemed inefficient and burdensome

We believe strengthening the mission of the Committee on Orphan Medicinal Products (COMP) could lead to better and more efficient process - a scientific committee specialised in rare diseases all along the development cycle with the right diversity of competences, providing quality advice and assessments from very early dialogue

to de-risk investments and developments, orphan designation, scientific advice, protocol assistance, benefit / risk assessment, post marketing safety and efficacy and effectiveness including registries and real world evidence. COMP should be able to assess together with the Committee for Human Medicines (CHMP) at the marketing authorisation (MA) time, in order to maintain the COMP involved in all phases from early dialogues to post marketing authorisation plans.

It should have the ability to require developers to go to scientific advice/protocol assistance, so to enhance the quality of developments and the ethically optimal participation of patients in clinical trials; scientific advice should be embedded much more into the scope of the COMP to direct impact on the design of clinical trials and continuum of data generation and collection. COMP representatives should be also integrated into HTA advice and HTA assessment, and HTA and payers' representatives (who ideally had already experienced this type of dialogue in the Mechanism of Coordinated Access – MoCA) should be involved in COMP work, particularly in scientific advice / protocol assistance, so to streamline, create a common culture, speed up processes in a seamless approach.

We suggest also that the COMP should become fee based, which in turn will lead to an increase of the engagement, resources and competences provided by the National Competent Authorities. In particular, the COMP should have Committee representatives as well as alternates for each Members states; same with the patient representatives (3 members and 3 alternates) and consideration should be given to reinforce any additional expertise needed.

Such suggestions should nevertheless be carefully assessed for their impact in order to ensure clarity of assessment remains manageable, given the likely increase in scope. Collaboration with other committees on issues of joint interest (particularly PDCO and CAT) should be intensified, as technology is evolving rapidly e.g. on advanced therapeutic medicinal product (ATMPs), so a need for different types of expertise depending on the dossiers exists.

###

EURORDIS-Rare Diseases Europe

EURORDIS-Rare Diseases Europe is a unique, non-profit alliance of 944 rare disease patient organisations from 73 countries that work together to improve the lives of the 30 million people living with a rare disease in Europe.

By connecting patients, families and patient groups, as well as by bringing together all stakeholders and mobilising the rare disease community, EURORDIS strengthens the patient voice and shapes research, policies and patient services. Follow [@eurordis](#) or see the [EURORDIS Facebook page](#). For more information, visit eurordis.org.

Rare diseases

The European Union considers a disease as rare when it affects less than 1 in 2,000 citizens. Over 6,000 different rare diseases have been identified to date, affecting an estimated 30 million people in Europe and 300 million worldwide. Due to the low prevalence of each disease, medical expertise is rare, knowledge is scarce, care offering inadequate and research limited. Despite their great overall number, rare disease patients are the orphans of health systems, often denied diagnosis, treatment and the benefits of research.