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"Orphan and Paediatric Medicines - the Way Forward"

The European Commission launched an evaluation of the Orphan Medicinal Product (OMP) and Paediatric Regulations. EUCOPE seizes the opportunity to contribute to this process, outlining **ways to strengthen the EU environment for the development of OMPs and Paediatrics.** The elements necessary to achieve these are the incentives provided for by the two Regulations, the broader pharmaceutical regulatory and IP framework, Health Technology Assessment (HTA) and national market structures for access to medicines. These elements should be coherent and complementary; however, gaps still remain:

OUR VISION

Bridging the gaps in the EU environment for the development of rare disease and paediatric treatments with actionable proposals to **strengthen the cycle of biopharmaceutical innovation.**

GAPS IN THE RARE DISEASE AND PAEDIATRIC ENVIRONMENT

The **20th anniversary** of the **OMP Regulation is an opportunity to celebrate** the substantial achievements of the EU in fostering research to the benefit of rare disease patients, their families, and carers. There are, however, more than 6,000 rare diseases and **95% of these still do not have an authorised treatment option**. Patients are unevenly distributed: **400 of the 6,000 rare diseases account for 98% of rare disease patients**, while only 149 of the 6,000 rare diseases account for 77-81% of patients. **For the 5%** of diseases that do have a treatment, the patient journey is far from simple.[1]

While up to 70% of rare diseases affect children, many lack treatment. **Current paediatric incentives do not adequately stimulate the development of OMPs for paediatric use**. The hurdles to obtain the approval and, in some cases, the need to modify a paediatric investigation plan (PIP) lead to increased administrative burden and longer time to market, discouraging the use of paediatric specific paths and missing out on the PIP reward.

There are often biological mechanisms in rare and paediatric diseases that are not fully understood yet. Moreover, in disease areas with few patients globally, there are enormous issues related to **scattered and scarce data. These barriers, and often the heterogeneity of the disease**, negatively impact R&D and regulatory approvals. Evidential uncertainty and **differing requirements along the lifecycle of OMPs and paediatrics,** from development to launch**,** pose significant hurdles, especially to smaller innovative companies focused on treatments for rare and paediatric diseases.

The Commission evaluation of the OMP and Paediatric Regulations highlights that these therapies **are not equally accessible to patients** in all EU countries. Access to medicines is primarily a Member State competence. Member States' policies, plans and strategies for rare diseases vary greatly across the EU. Indeed, **only some countries have distinct processes for OMPs** in place[2] and **delay in patient access to OMPs (both for paediatric and adult use)** across Member States can vary from a few months to years.

OUR COMMITMENT

EUCOPE leads and partakes in targeted partnerships aimed at developing actionable proposals to strengthen the **EU innovation ecosystem.**

[1] EURORDIS Rare Barometer: 7500 respondents: 69% of rare disease patients had received treatment for their rare disease, only 5% had received a transformative treatment approved for the entire European Union

[2] For instance, in England, Scotland, and Germany

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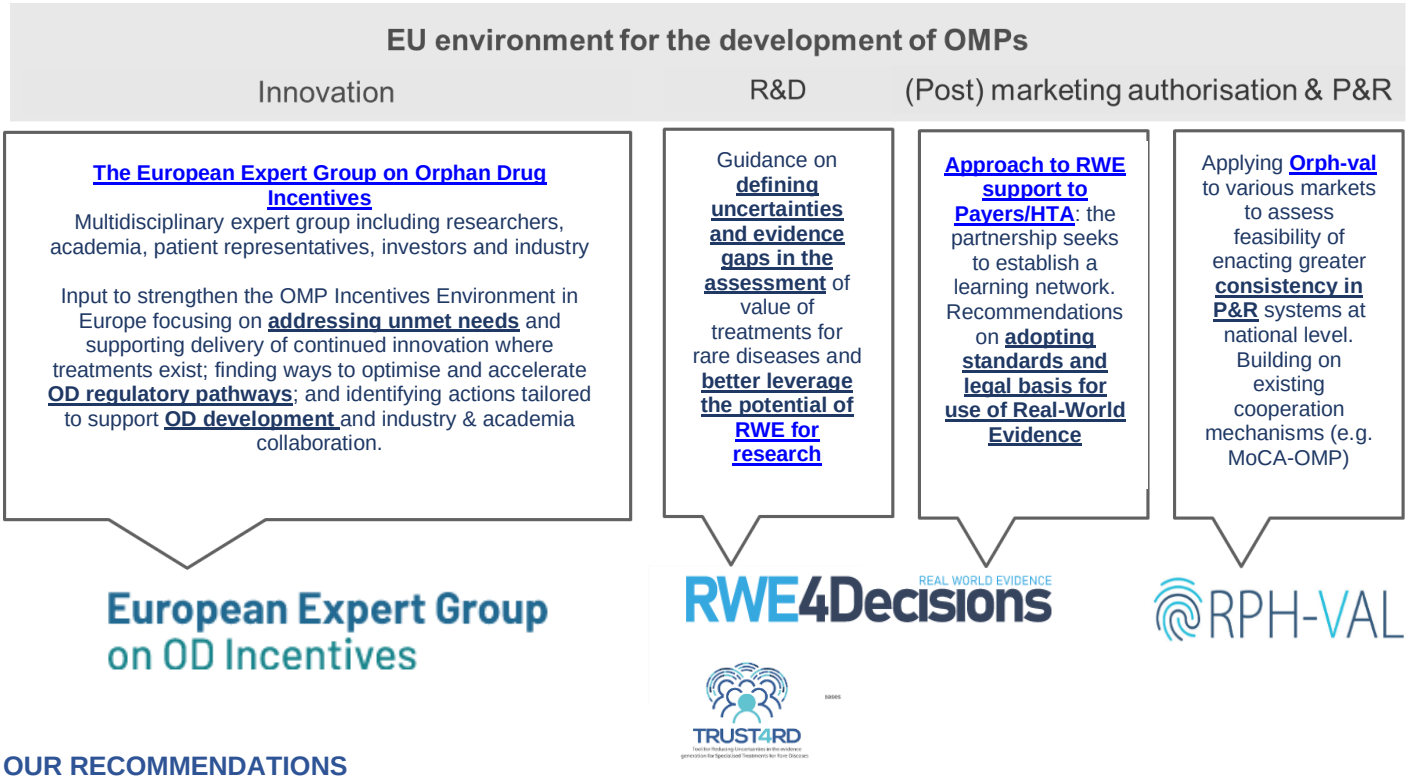
In the graphic below, we provide a representation of our commitments across the EU innovation ecosystem with a specific focus on the environment for the development of OMPs.



OUR RECOMMENDATIONS

The Regulations review will not directly provide solutions to improve access and affordability of paediatric and OMPs. A holistic approach is needed to strengthen the whole EU environment for the development of OMPs and Paediatrics. We call upon **European institutions, Member States, medical and research community, biopharmaceutical industry and patients** to work together and:

1. *Develop more incentives for biopharmaceutical companies active in rare diseases and paediatrics to overcome challenges in basic research and clinical development. A **big leap in funding of new research** is very much needed to address unmet medical needs and identify new solutions.*

2. *Optimise and streamline regulatory pathways **to reconcile innovation value and uncertainty**. This includes larger use and acknowledgement of the value of **Real-World Evidence (RWE), HTA that adequately takes into account the specificities of OMPs** and further alignment between regulators and payers' requirements.*

3. *Ensure consistent and widespread support across Member States to develop and implement **HTA Value Frameworks (VFs)**, which capture the broader benefits the OMPs bring to patients and their families, health systems, the economy, and society. This will require **a modern approach to value and the uptake of innovative payment models.***

4. ***Ensure coordination and synergy** between OMPs and Paediatrics Regulations and **pharmaceutical and industrial policies at national and EU level.***

This virtuous cycle allows for **re-investment in R&D of therapies for children and rare diseases patients.**

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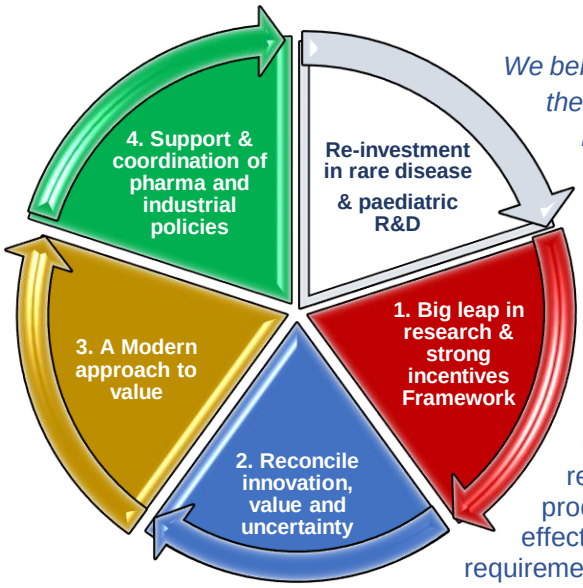
DEEP DIVE IN RECOMENDATION N 2: RECONCILE INNOVATION, VALUE AND UNCERTAINTY



*We believe there is room for **improvement in the current system** throughout the whole patient pathway. Building on the past 20 years of scientific and regulatory developments, we believe it is possible to optimise and accelerate **regulatory pathways for orphan and paediatric drugs**, including the application of novel biomarkers, acceptance of new trial design, leveraging of RWE generation, and establishing further regulatory flexibilities as demonstrated during the COVID-19 crisis**. In this section, we deep dive into our recommendation N 2.***

Streamline and integrate the provision of regulatory advice throughout the OMP and paediatric development pathway: EUCOPE strongly supports the EMA's intent to invest the necessary resources to streamline the current scientific advisory platforms, so that product-driven advice can address multiple development options effectively. For rare and paediatric diseases, one pivotal study should satisfy requirements from multiple EMA committees and hence coordination between the committees should be strengthened significantly for the industry be able to provide timely access to rare disease medicines for patients in need. Such model can benefit from previous dialogue in cross-stakeholders initiatives (e.g. R&D Stakeholder Platform discussions).

Provisions to solve operational and timelines challenges in relation or Paediatric drug development: In Paediatric drug development, there are additional challenges related to the fact that the studies often need to be discussed and planned at an early stage. If adults are not affected by the disease, the EMA Paediatric Committee (PDCO) needs to be consulted early on in the process, which is, next to Scientific Advice, an additional step that often takes considerable time. To further streamline the process, initial PDCO input should be incorporated together with the Scientific Advice. This would also ensure synergies and more sustainable use of Member States' resources allocated to EMA Committees.

Strengthen bridges from evaluation to access through collaboration with payers: EMA activities to collaborate with and bridge to HTAs and payers are very welcome. This would help to develop a dialogue platform and enable ultimately a single evidence generation plan, particularly in rare and paediatric diseases where there are still unmet medical needs. The end goal should be that clinically relevant innovative medicines can seamlessly be evaluated on clinical aspects linked to effectiveness that support reimbursement decisions, particularly rare diseases and products licensed under exceptional circumstances. This entails, for instance, increasing the acceptance of single-arm studies, new trial designs, and novel biomarkers in HTAs processes.

Conduct further work on the acceptability of the use of Real World Evidence (RWE) and Artificial Intelligence: natural history studies and single-arm studies in diseases where patient numbers are low can hugely benefit from post-licensing evidence generation through registries and other observational methods. It is important that the EMA provides adequate advice and supports regulatory science initiatives that increase the suitability of such evidence for regulatory decision-making. This is an area where international collaboration (e.g. with the FDA) can be of particular benefit, as well as cross-stakeholders' collaboration with partners such as HTA bodies and healthcare professionals.

Multistakeholder collaborations such as TRUST4RD[3] and RWE4Decisions produced guidance on defining uncertainties and addressing evidence gaps in the assessment of the value of specialised treatments for rare diseases. They provided guidance on the potential of RWE to help address these uncertainties, including the typology of evidence uncertainties, the importance of different uncertainties and the data sources available to address them before and after HTA submission. In making use of the guidance, authorisation and reimbursement discussions on such treatments can be embedded in an evidence-rich context, thereby ensuring value to all parties, particularly to patients.[4]

Evaluate and further increase capacity building on the PRIME scheme: We support the Commission's intention of enhancing regulatory support for rare and paediatric diseases products developed to address unmet medical needs. According to the inception impact assessment, these products would be eligible for priority assessment and increased scientific support from the EMA (like the existing PRIME scheme). With regards to the current functioning of PRIME, we note that the first marketing authorisations for products designated as eligible for PRIME were granted only in June 2018; hence it is essential to review the performance of the scheme after 3 and 5 years, to ensure that it delivers the expected impact on public health (i.e. faster priority medicines to market).

To ensure that all applicants would continue to see the benefit of using the scheme, a fast lane approach should be designed for PRIME products which would include: shorter timeline for eligibility and kick-off meeting, continuous access to the EMA contact person, rolling opportunity to receive advice on product development and the possibility to seek Rapporteurs views on scientific matters, as well as a similar 2-pager system used by the US FDA that allows for a pre-screening of applications, supporting efficiency.

Gene/cell therapies, genomics, digital biomarkers in combination with therapeutic options open new opportunities for many rare diseases, but also uncertainties, and might require quite distinct (and possibly wider reaching) regulatory approaches not encompassed by the current OMP Regulation, with the objective of gathering as much informative data as possible from clinical use[5].

Administrative simplification: Based on the 20 years of experience and reports in organisational barriers, better alignment between the Committee for Medicinal Products for Human Use (CHMP) and the Committee for Orphan Medicinal Products (COMP) can be achieved to expedite decision processes within the EMA. Administrative simplification could be achieved if the EMA granted the OD designation rather than the European Commission, saving on average one month in the granting process. Finally, further alignment between the EMA and the FDA on paediatric and OMP requirements would also be key to ensure smooth and faster regulatory processes.

COVID-19 Lessons learnt on cooperation and digitalisation: The COVID-19 pandemic acts as a magnifying glass for existing challenges related to the rare disease and paediatric community, in research, clinical trial continuation as well as availability of treatments and care. According to a recent EURORDIS survey, 9 out of 10 people living with rare diseases experienced interruption of care because of COVID-19. There are lessons to be learned from this crisis: from the potential of stronger cooperation to foster development and faster access to therapies, to the opportunities brought about by digital health and telemedicine solutions. The COVID-19 pandemic has spurred the scientific community and policymakers to reconsider the current state-of-play of research & innovation, and from this, we can move towards innovative and more efficient ways of enhancing and accelerating OMP developments for patients such as decentralised trials. COVID-19 also highlighted the **need for local expertise and local innovation** in order for Europe to remain an attractive location to develop new technologies.

[3] https://ojrd.biomedcentral.com/articles/10.1186/s13023-020-01370-3
[4] https://ojrd.biomedcentral.com/articles/10.1186/s13023-020-01370-3
[5] https://www.karger.com/Article/FullText/509272