Seizing opportunities for continued innovation, investment, and excellence in orphan medicines in Europe

The Orphan Medicinal Products (OMP) Regulation has delivered significant societal benefits by incentivising increased investments into R&D for treatments for the rare disease patient population, and especially for the rarest diseases, overcoming limited market potential.[1] Ultimately, more orphan medicines have been made available on the market and patient access to innovative treatment has been accelerated with all orphan medicines being available to people across the EU on average 9 months earlier than before the adoption of the Regulation, a life-changing benefit for patients with previously limited therapeutic options.[2]

Europe can build on this success for patients, improving the environment for OMPs further, to ensure that novel treatments continue to be developed and made available for the roughly 80% of rare disease patients who are affected by 4.2% of the most prevalent rare diseases, and stimulate R&D for the remaining 95% of rare diseases currently without treatments.[3]

As the Commission prepares its revision of the Orphan Regulation, it is important to recognise and reinforce these successes by preserving and improving the incentives for all rare diseases where there are still unmet medical and patient needs. Europe should seek to grow on a success story for the benefit of patients and science.

Consolidating Incentives to Accelerate Innovation for Rare Diseases: Rewarding Frontrunners

EuropaBio believes that incentives should remain the main element to attract additional R&D investments in the development of orphan medicines. The revision should continue to guarantee the predictability of incentives and ensure that investors and sponsors are encouraged to channel R&D investments within Europe, both through innovative SMEs and mid/large companies, in turn fostering growth.[4]

To reward innovation frontrunners, innovative breakthroughs addressing underserved rare diseases could be awarded an additional 2 years of marketing exclusivity. Medicines that meet the existing criteria for orphan designation could continue to benefit from the 10-year marketing exclusivity period.

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[1] Technopolis/Ecorys (2019). Study to support the evaluation of the EU Orphan Regulation, pp. 206 and 301.
[2] Ibid, p. 100.
[3] Nguengang Wakap, S., Lambert, D.M., Olry, A. *et al.* (2019). Estimating cumulative point prevalence of rare diseases: analysis of the Orphanet database. *European Journal of Human Genet*ics, 28(2)**,** 165–173.
[4] EuropaBio position on novel incentives to stimulate the of development of Orphan Medicinal Products in Europe for rare disease patients with unmet medical needs (2021).

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Such an approach would reward research in rare diseases that has a higher risk of failure by attracting investments that can sustain such a long and complex development process, and continue to ensure that substantial medical advances for patients are maintained. It would also enable the launch and growth of SMEs that are at the heart of rare disease innovation by enabling them to leverage incentives to secure R&D funding.

In addition, the system of incentives could be combined with novel incentives, such as transferable market exclusivity vouchers and priority review vouchers. Additional incentives could also be introduced to target early development and improve the links between basic research and clinical developments. This strengthens the work of the biopharmaceutical industry who invests based on the science and medical knowledge throughout the pathway from basic, applied, and translational, in addition to companies' expertise in therapeutic areas or technologies developed over decades.

Why incentives contribute to the development of novel therapeutics for rare diseases:

In the EU, orphan medicines can benefit from a range of regulatory and economic incentives. These include protocol assistance, scientific advice, reduced fees, research grants, and 10-year marketing exclusivity. These incentives are essential, as the development of orphan medicines can take between 10 to 15 years, and still lead to market failures in areas of high-risk science and low patient numbers. In fact, from the 2,300 orphan designated medicines by the EMA, by the end of 2021, only 207 medicines with orphan status had received a marketing authorisation.[5]

According to a recent study, out of the 142 orphan medicines developed between 2000 and 2017, 74 products would not have been economically viable without the existing incentive framework.[6] The same study concludes that, despite the incentives, investments in orphan development continue to be precarious.[7]

By improving the viability of orphan development, through regulatory support and potential economic returns from the marketing exclusivity, the EU's system of incentives ensures that a growing number of rare diseases have adequate treatment.

A strong, stable, and predictable framework of incentives enables the EU to retain and attract biotechnological development that translates to a faster EU market launch for medicines and ensures the EU remains a centre of excellence for healthcare biotechnology that can power Europe's innovative industries and growth across all

[5] European Medicines Agency (2022). Orphan Medicinal Product Designation: Overview 2000-2021, available online here (last accessed 23/05/2022), p. 14
[6] Dolon (2020). Estimated Impact of the EU Orphan Regulation on incentives for innovation, available online here (last accessed 23/05/2022), p. 19
[7] Ibid, p. 22

company sizes, from the innovative SMEs that translate cutting edge research into the therapeutic pathway, through to the mid and large-sized companies that manufacture at scale and conduct clinical trials worldwide.[8]

Improving Regulatory Efficiency for the 21st Century: Faster Pathways for Earlier Access

EuropaBio believes regulatory improvements are necessary to promote the development of new treatments, building on the experience of the past 20 years and the lessons learnt from other regulatory authorities.

EuropaBio considers the following regulatory solutions to be key to securing the EU's regulatory efficiency:

- Improved predictability of the outcome of assessments;
- Simplification of the OMP Regulation;
- Improved accelerated pathways that can support innovation;
- Increased flexibility in the regulatory process.

The pandemic has demonstrated that the European Medicines Agency (EMA) and the European medicines regulatory network can adopt a flexible manner of working, including the application of iterative reviews - however, to expand this throughout the network requires adequate resourcing. Improving regulatory efficiency would ultimately help treatments reach patients faster.

In addition, efforts should be directed at improving the coordination between EMA scientific committees to avoid inconsistencies and delays but also to establish mechanisms to align requirements between regulatory and HTA processes.

[8] EuropaBio/WifOR Institute (2020). Measuring the Economic Footprint of the Biotechnology Industry in Europe, available online here (last accessed 23/05/2022).

Why improving regulatory pathways can speed up patient access to novel therapeutics:

Under the centralised authorisation procedure for medicinal products, a medicine can receive marketing authorisation in 210 active days and 67 days for the adoption of the Commission Decision.[9]

In reality, the average number of days for centralised procedures was 419 days in 2020. For SMEs, the average number of days was 471 in 2020. For medicines under accelerated assessment, which aims to approve medicines faster, the average length for authorisation was 216 days in 2020. For orphan medicines, the average assessment time may be longer to account for the finalisation of the review of orphan designations carried out by EMA's COMP.[10]

Improving regulatory pathways by maximising efficiency and reducing administrative barriers would radically speed up patient access.

The revision should also seek to strengthen the PRIME scheme to accelerate the development of orphan medicines through increased regulatory and scientific support. Additional regulatory and scientific support should be made available to SMEs as they often do not have the capacity to cross the regulatory maze toward marketing authorisation.

Addressing the Needs of Rare Disease Patients: Leaving No One Behind

For over 20 years, the OMP Regulation has supported the development of innovative medicines for rare diseases. For EU patients, this translates to a radically improved quality of life and an added 210,000-444,000 quality-adjusted life years.[11]

This success in spurring innovation stems, in part, from the scientifically sound criteria for orphan designation. The current criteria on prevalence, significant benefit, and economic viability provide the necessary stability and predictability to innovators but also guarantee that new orphan medicines put on the market meet patient needs to ensure no one is left behind by supporting innovation across the 5 in 10,000 prevalence class.[12]

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[9] European Medicines Agency (2019), From Laboratory to Patients: The Journey of a Medicine Assessment by EMA, available online here (last accessed 23/05/2022), pp. 17 and 22.
[10] European Medicines Agency (2021). Annual Report 2020, available online here (last accessed 23/05/2022), p. 68.
[11] European Commission (2020). Commission Staff Working Document, 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, p. 58.
[12] European Medicines Agency (2022). Orphan Medicinal Product Designation: Overview 2000-2021, available online here (last accessed 23/05/2022).

Reducing the prevalence threshold or introducing a cumulative prevalence criterion for medicines with a potential for more than one orphan designation will decrease the appetite to continue clinical research and reduce research on other possible rare disease indications impacting patients. For example, had the threshold been lower, conditions such as mucoviscidosis, Duchenne muscular dystrophy, and Amyotrophic lateral sclerosis would have not benefited from orphan designation. As most of the rare diseases with no treatments have a prevalence lower than 1 in 1 000 000, decreasing the threshold would not address these very rare diseases. On the contrary, it would deter investments in the development of medicines for rare diseases with larger prevalence. For SMEs active in the rare diseases space, this will have a detrimental impact on the possibility to build attractive pipelines that are dearly needed to build strong biotechnology champions in the EU.

The Commission rightly identified addressing unmet medical needs (UMN) as a priority when revising the orphan and paediatric framework.[13] EuropaBio believes that addressing UMN should not be done to the detriment of the entire rare disease population by adopting a narrow understanding of UMN driven by economic or political motives.

Building on this reflection, EuropaBio has identified three core elements for conceptualising UMN:

- Adequacy of authorised treatments and burden of authorised treatments;
- Disease severity or burden of disease;
- Population-based considerations.[14]

The above elements aim to encapsulate the perspectives and experiences of patients with UMN while providing a predictable and favourable environment that can support research and innovation for existing and future UMN, from basic research to clinical development.

EuropaBio considers that any conceptualisation of UMN should be flexible and future-proof, built on the existing conceptualisation of UMN in the EU legal framework, and agreed upon in a multi-stakeholder forum involving all relevant stakeholders.

[13] European Commission (2020). Inception Impact Assessment: Revision of the EU legislation on medicines for children and rare diseases, Ares(2020)7081640.
[14] EuropaBio, Reflection Paper on Core Criteria for Unmet Medical Need (2022)

Why a prescriptive definition of a rare disease would be detrimental to patients:

The size of the rare disease population is estimated to be between 18 and 30 million in the EU and between 263 and 446 million worldwide.[15] Yet, the rare disease population is not monolithic and population size varies widely across 6,000 rare diseases identified to date. A disease defined as rare in the EU (80% of which are of genetic origin and life-threatening) can affect as few as 1 patient and as many 245 000 people across the 5 in 10,000 prevalence threshold.[16]

Narrowing the legal definition of a rare disease will negatively impact the rare disease population, as fewer orphan medicines will be developed, and create disparities between patients by assigning artificial value to certain diseases over others.

Any prescriptive definition of a rare disease or the creation of a legally binding list of UMN, would not only fail to address patient needs but ultimately stifle innovation and leave patients behind.

Agile, Stable, and Sustained: Tomorrow's Innovation, Investment, and Excellence Is Built Today

The orphan ecosystem is a complex and interconnected system that demands predictability and certainty to foster, as exemplified by the success of the existing framework in accelerating the development of orphan medicines. Future policies should aim to foster that ecosystem to ensure it can address challenges of today and tomorrow, and contribute to Europe's growth and competitiveness.

The ability to provide life-changing treatment to European patients requires an agile regulatory environment, a stable incentives framework, and sustained investment to drive innovation in areas of unmet medical need. Europe has a strong research base whose growth and innovation potential should be supported. Greater attention should be directed towards basic research to improve the scientific understanding of orphan diseases to better guide clinical developments. Efforts should also be made to increase the complementarity between different actors of the biopharmaceutical value chain to reduce the time products take to reach patients.

The revision of the OMP Regulations is an opportunity to build on past successes and enable Europe to become a leading centre of excellence for orphan and paediatric innovation in the decades to come.

[15] Nguengang Wakap *et al.* (2019). Estimating cumulative point prevalence of rare diseases: analysis of the Orphanet database, p. 171.
[16] Eurodis (2022). About Rare Diseases, available online here (last accessed 23/05/2022).

About EuropaBio

EuropaBio, the European Association for Bioindustries, promotes an innovative and dynamic European biotechnology industry. EuropaBio and its members are committed to the socially responsible use of biotechnology to improve quality of life, to prevent, diagnose, treat and cure diseases, to improve the quality and quantity of food and feedstuffs and to move towards a biobased and zero-waste economy. EuropaBio represents 79 corporate and associate members and bio-regions, and 19 national biotechnology associations in turn representing over 2,300 biotech SMEs. Read more about our work at www.europabio.org.

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