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The Revision of the EU Regulations on medicines for children and rare diseases – Background and discussion

1. Rare diseases & Orphan Medicinal products

Orphan drugs are medicines used for the diagnosis, prevention and treatment of rare diseases. A disease is defined as rare when its prevalence does not exceed the threshold set by the European Union (EU) of **5 in 10,000 people**.[1] Despite their low prevalence, there are more than 6,000 different rare diseases and about 30 million people affected in Europe alone. In addition, 80% of rare diseases are of genetic origin, and are often chronic and life-threatening.[2]

Drugs aimed at treating rare diseases are defined as 'orphan' as **they would not be developed under normal market conditions** due to their limited commercial attractiveness. There are several reasons behind this, including the high complexity of such pathologies, on which **scientific and clinical knowledge is limited** given the **small patient population** they affect, and the related **challenging research and development (R&D) process**. The orphan status can be therefore granted to certain drugs to encourage investment in their R&D process.

2. The existing European framework for rare diseases

Specific legislations were put in place to encourage the research, development and placing on the market of designated orphan medicinal products in order to compensate for the risk of development failure and considering the small size of the target population**.** The EU, following the United States' (US), adopted Regulation (EC) 141/2000 (the so-called 'Orphan' Regulation) and subsequently Regulation (EC) No 847/2000.[3] This Regulation provides a set of incentives to orphan drugs developers including protocol assistance, ten years of market exclusivity and fee reductions for regulatory activities of SMEs (see box for more details).[4] The **European regulatory framework has undoubtedly encouraged investment in orphan drug R&D by pharmaceutical companies**, as shown by available data. From 2001 to 2019, 170 orphan drugs have received

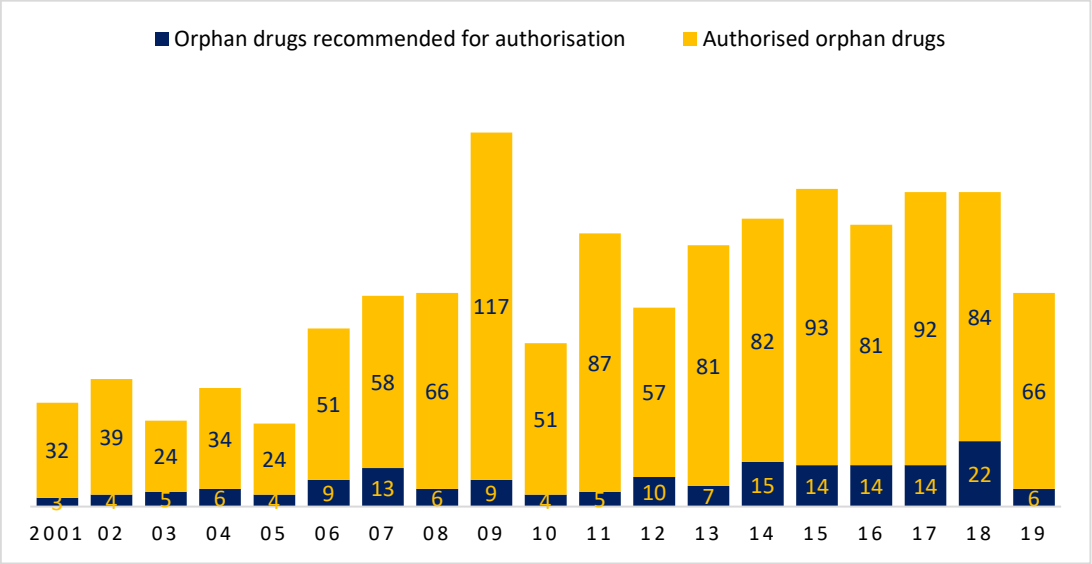
EU Incentives for OMPs in a nutshell

- ***A rare disease** is defined as a life-threatening or chronically and seriously debilitating condition affecting not more than **5 in 10,000 people in the EU.***
- *The OMP regulation grants **10 years of market exclusivity** to a medicinal product approved for a rare disease, extended by 2 years for medicines that have complied with an agreed paediatric investigation plan.*
- *Additional incentives are available for micro**, small and medium-sized enterprises such as fee reductions,** administrative and procedural assistance.*

[1]Orphan medicine [Internet]. European Medicines Agency. 2021 [cited 30 March 2021]. Available from: https://www.ema.europa.eu/en/glossary/orphan-medicine
[2]About Rare Diseases [Internet]. EURORDIS. 2021 [cited 30 March 2021]. Available from: https://www.eurordis.org/about-rare-diseases
[3]About orphan drugs [Internet]. Orphanet. 2021 [cited 30 March 2021]. Available from: https://www.orpha.net/consor/cgi-bin/Education_AboutOrphanDrugs.php?lng=EN&stapage=ST_EDUCATION_EDUCATION_ABOUTORPHANDRUGS_EUR
[4] Orphan incentives [Internet]. European Medicines Agency. 2021 [cited 16 June 2021]. Available from: https://www.ema.europa.eu/en/human-regulatory/research-development/orphan-designation/orphan-incentives

marketing authorisation (Figure 1).[5] Before the introduction of the Orphan Regulation, only 8 marketing authorisations had been granted. According to EMA data, between 2000 and 2018, orphan designations grew by 15% each year, reaching 2,233 at the end of 2019. Since the adoption of the Orphan Regulation, 23 Member States have established at least one national plan for rare diseases.[6]

Figure 1: Authorised orphan medicines 2001-2019.[11]



It can be thus said that the EU OMP Regulation was a turning point and significantly transformed the lives of 6.3 million rare diseases patients and their families in the EU, improving health outcomes and quality of life, and proving to be pivotal for the development of treatments for conditions that were previously untreatable.

3. The Revision of the EU OMP Regulation

In recent years, there have been several issues that led to increased controls on incentives. The **commercial success of some rare disease treatments** raised questions on whether these incentives should be reduced; **health budgets are under increasing pressure** and national health services see market exclusivity and incentives as one of the reasons for **high healthcare expenditure.** Finally, legislative frameworks need to be adapted to **cater for scientific progress** such as personalised medicine and the use of biomarkers. As such, the European Commission reviewed the legislation to assess if reform is necessary and what this could look like.

[5]Orphan medicines in the EU [Internet]. European Medicines Agency. [cited 31 March 2021]. Available from: https://www.ema.europa.eu/en/documents/leaflet/leaflet-orphan-medicines-eu_en.pdf
[6]National Plans [Internet]. EUROPLAN. [cited 31 March 2021]. Available from: http://www.europlanproject.eu/NationalPlans?idMap=1

The Commission's Staff Working Document (SWD) published in 2020 showed that **both the Orphan and Paediatric Regulations have stimulated the R&D of orphan and paediatric medicines**. According to scientific literature, the Orphan Regulation has led to clinical benefits, as many patients can now access treatments previously unavailable, and research is now more effectively translated into clinical knowledge. However, the Commission SWD highlighted that the current legal framework presents a number of shortcomings, including **insufficient flexibility in supporting scientific developments** and **R&D in the context of 'unmet needs',** noting that no authorised treatment is available for 95% of rare diseases (see box for more details).The SWD also called out **the excessive burden and inefficiency of some procedures,** including within the European Medicines Agency**.** [7]

Unpacking orphan unmet needs

- *There are 6-7,000 rare diseases*
- ***80% of population burden** of rare diseases is attributable to **149 diseases***
- ***98% of people** with rare diseases have **one of the 390 most prevalent rare diseases***
- *Around 85% of all rare diseases have a prevalence of less than 1 in 1,000,000*

The drawbacks identified also relate to **differences across Member States in terms of orphan drugs accessibility and availability.** The options assessed by the Commission's 'Inception Impact Assessment' (a stage preceding the Impact Assessment, where stakeholders are asked to provide initial feedback on the intended initiative, document available *here*) aim to address these regulatory issues. A consultation on the Inception Impact Assessment was launched in November 2020 and lasted for a period of 12 weeks. The Inception Impact Assessment has been followed by additional stakeholder consultations that will feed into a study commissioned by the European Commission with the aim to inform the possible options for legislative review. The Commission is expected to present a proposal for a Regulation in 2022. This will then be discussed by the European Parliament and Council via the Ordinary Legislative Procedure.

[7]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 – Executive summary of the evaluation [Internet]. European Commission. 2020 [cited 31 March 2021]. Available from: https://ec.europa.eu/health/sites/health/files/files/paediatrics/docs/orphan-regulation_eval_swd_2020-164_exec-sum_en.pdf