Review of REGULATION (EC) No 141/2000 on Orphan Medicinal Products (OMP)

Position Paper of the European Social Insurance Platform (ESIP)

30 May 2019

ESIP aisbl
Maison Européenne de la Protection Sociale
Rue d'Arlon 50 • 1000 Bruxelles • +32 2 282 05 60 • +32 2 282 05 98
esip@esip.eu • www.esip.eu • @ESIP_EU • VAT: BE 0808.072.950

About the European Social Insurance Platform (ESIP)

The ***European Social Insurance Platform*** **(ESIP)** represents over **50 national statutory social insurance organisations** in **17 EU Member States and Switzerland**, active in the field of health insurance, pensions, occupational disease and accident insurance, disability and rehabilitation, family benefits and unemployment insurance. The aims of ESIP and its members are to preserve high profile social security for Europe, to reinforce solidarity-based social insurance systems and to maintain European social protection quality. ESIP builds strategic alliances for developing common positions to influence the European debate and is a consultation forum for the European institutions and other multinational bodies active in the field of social security.

Statement regarding positions submitted by ESIP: *ESIP members support this position in so far as the subject matter lies within their field of competence.*

ESIP, rue d'Arlon 50, B – 1000 Brussels
Tel: +32 2 282 05 62; Fax: +32 2 282 05 98
Web: www.esip.eu

Contact: christine.dawson(AT)esip.eu

Review of REGULATION (EC) No 141/2000 on Orphan Medicinal Products (OMP)

At the end of 2017, the European Commission launched a joint evaluation of the legislation on medicines for children and rare diseases (medicines for special populations). The intended purpose of the evaluation is to assess to which extent the EU legislation is efficient and effective and considers whether it is fit for purpose in the light of developments in the area of pharmaceuticals. In particular, it will assess the impact of the incentives introduced for research, development and marketing, for these specific medicines[1].

ESIP welcomes the initiative from the European Commission to **evaluate the legal framework concerning orphan medicinal products (OMPs)** and the interaction between the Regulation on OMPs and the Regulation on paediatric medicines.

Background

Regulation (EC) No 141/2000 (the orphan regulation) was adopted in 1999 and came into force in January 2000. The main objective of the orphan regulation is to **ensure that patients suffering from rare conditions have the same quality of treatment as any other patient** in the EU. The Regulation aims to incentivise companies to develop and market medicinal products for the diagnosis, prevention and treatment of rare conditions (including those for children), for which the **expected return would not cover the necessary upfront investment costs**.

From 2000 to the end of 2018, 2,121 orphan designations have been issued by the European Commission, resulting in 164 authorised medicinal products with about 60% of designated OMPs intended for paediatric use[2]. Thus, Regulation (EC) No 141/2000 has undoubtedly led to some level of success resulting in an increased availability of OMPs for the treatment of patients with rare diseases.

The OMP Regulation: a target for abuse

However, concerns regarding the correct application of the orphan regulation have been expressed repeatedly: the **Council Conclusions of June 2016** on strengthening the balance in the pharmaceutical systems in the European Union[3] highlighted that incentives and rewards of the regulatory framework on OMPs should not lead to inappropriate market behaviour. Member States also noted an increasing number of **market failures where patients' access to effective and affordable essential medicines was endangered by very high and unsustainable prices**. In addition, the European Parliament called on the Commission to evaluate existing incentive schemes to facilitate the development of effective, safe and affordable medicines for rare diseases compared to the best available alternative. [4]

Further criticism of the orphan regulation concerns so-called "orphanisation" of disease: the **increased targeting of specific subgroups of broader disease groups**, such as cancers, to

[1] https://ec.europa.eu/info/law/better-regulation/initiatives/ares-2017-6059807_en
[2] https://www.ema.europa.eu/en/documents/report/annual-report-use-special-contribution-orphan-medicinal-products-2018_en.pdf
[3] https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:52016XG0723(03)&from=EN
[4] http://www.europarl.europa.eu/doceo/document/A-8-2017-0040_EN.pdf

the point that they become rare. Therefore, OMPs are often developed **to maximise profit** rather than to tackle real unmet medical need. Due to further legislative changes such as conditional marketing authorisation or authorisation under exceptional circumstances, an increasing number of OMPs are authorised based on limited evidence only and therefore often with an unknown added benefit.

ESIP thus calls for a timely revision of the regulatory framework on OMPs in order to address these issues without discouraging the development of medicinal products needed for the treatment of rare diseases, especially in children.

ESIP proposes amending Regulation (EC) 141/2000 as follows:

- **Revising the current prevalence threshold**

  Since the implementation of the Regulation, the Community has expanded to 28 Member States changing the potential return on investment due to market exclusivity in Europe. In the absence of a universal definition of rare disease and with worldwide average prevalence thresholds ranging from 5 to 76 individuals in 100 000[5], the **current prevalence threshold** as defined in article 3(1)a of the Regulation (i.e. 5 individuals in 10 000) **should be re-assessed** to ensure that only areas with real unmet medical need profit from the incentives set out in the Regulation. A thorough **investigation of international definitions for OMPs and varying organisational thresholds** should guide this revision.

  In addition, when a revision of the current threshold is undertaken, **regional differences should be taken into account**: Some rare diseases will fulfil the criteria in the European Union but are more prevalent in other regions, and even within the European Union the prevalence might vary significantly between different Member States. Therefore, a general European focus alone does not always seem adequate.

  Furthermore, to avoid subsequent extensions of market exclusivity caused by splitting conditions into subgroups or by first obtaining an orphan designation for a product and then extending marketing authorisation to more common diseases, **the prevalence of all indications that a medicinal product is licensed for should be combined**. If the combined prevalence of all indications exceeds a certain limit, orphan status could be revoked, either immediately or after a specified delay.

- **Combining the current criteria for orphan designation**

  Article 3(1)a of Regulation (EC) 141/2000 states that a medicinal product shall be designated as an OMP either when a life-threatening or chronically debilitating condition does not affect more than 5 in 10,000 persons *or* when low financial return can be expected.

  According to recital 1 of Regulation (EC) 141/2000 one central reason for creating the incentives for orphan medicinal products was that "some conditions occur so infrequently that the cost of developing and bringing to the market a medicinal product to diagnose,

[5] Richter T. et al. Rare Disease Terminology and Definitions – A Systematic Global Review: Report of the ISPOR Rare Disease Special Interest Group. Value in Health 18:906-914.2015

prevent or treat the condition would not be recovered by the expected sales of the medicinal product". At this time, it could probably not have been foreseen that medicinal products receiving orphan designation might also be judged as potential blockbuster drugs[6].

Therefore, the **prevalence criterion should be tied to the criterion of an expectation of a low return of investment by combining the two criteria** under Article 3(1)a **with an "and"** instead of the current "or".

- **Including a refined definition of "significant benefit"**

To foster truly innovative OMPs, the standard definition of "significant benefit" should be revised. Against the background of conditional or exceptional approvals, ESIP emphasises that market exclusivity should be confined to OMPs unambiguously providing patient relevant benefits. Efficacy has to be established **based on direct comparative data showing a significant improvement in patient-relevant outcomes** to ensure that the goal of the Regulation, that is provision of high-quality care, is met.

The definition of the current stand-alone criterion **"major contribution to patient care" should be re-evaluated**. Ease of self-administration or improved adherence are not sharply delineated concepts and might vary within health care settings or the natural history of disease.

- **Regularly reviewing the case for market exclusivity**

According to article 8.2, the period of market exclusivity can be reduced at the end of the fifth year if a Member State has informed the agency that one or more criteria for orphan designation is no longer met. Notably, article 8.2 has apparently only been invoked once and even then, unsuccessfully[7]. However, **EMA should be required to regularly review whether the basis for market exclusivity is still valid** and not only at the end of the fifth year. In any case, such a review should take place if an applicant extends the therapeutic indication, especially if a new (non-orphan) indication is applied for. Thus, article 7(3) needs to be modified.

Since the implementation of the Regulation, further regulatory tools have been introduced that allow faster marketing authorisation based on limited evidence, while at the same time prices for OMPs have been steadily increasing. Therefore, legislation regarding market exclusivity should be adapted accordingly. It should be possible to reduce the period of market exclusivity and to remove a product from the community register of OMPs at any given point in time and not only after the first five years if the criteria in article 3 are no longer met.

[6] 2018 could be a record year for blockbuster drugs, April 9th 2018, http://www.pharmatimes.com (retrieved April 14th 2019)

[7] Copenhagen Economics. Study on the economic impact of supplementary protection certificates, pharmaceutical incentives and rewards in Europe. 2018

- **Including a standard definition of "sufficiently profitable"**

  It seems also reasonable to create a standard definition of "sufficiently profitable" to make this criterion actionable for shortening market exclusivity. As with the prevalence criterion (see above), **all indications regardless of their orphan status should be taken into account** when determining the profit generated. At the same time, **the profitability of a product alone should be sufficient to revoke orphan status** even if the other criteria of article 3 are still met. Incentives should not be artificially maintained for products that have proven to no longer need them. For an informed decision on profitability more transparency on the real development cost and risks would be necessary.

Further remarks and recommendations

- **Steering R&D towards public health needs**

  To ensure that the Regulation achieves its target of encouraging real innovation in areas with high unmet medical need, public and private investment in R&D should be steered towards clearly defined public health needs, including paediatric OMPs. To achieve this goal, an **improved coordination and priority-setting mechanism is needed on a European but also on a global scale**.

- **Ensuring public return on public investment**

  Basic research often takes place in the public sector, at universities and publicly funded research institutions. To ensure public return on investment, increased transparency is needed concerning the real costs of research, innovation and development in the field of rare diseases, the cost borne by the industry and those borne by the public. **Public investment in R&D must also be reflected in the price or via licensing agreements that profit the public sector** to avoid double payment by the public.

- **Improving access to OMPs**

  Market authorisation holders should be obliged to make OMPs available throughout Europe immediately after receiving marketing authorisation to avoid that innovative products are withheld from smaller countries with lower purchasing power[8].
  Furthermore, to improve access to treatment for rare disease, we call for **reasonable pricing**. Besides **transparency on prices and pricing strategies**, initiatives on **voluntary cross-border collaboration**, for example on information sharing, joint evaluations and pricing negotiations, can help to **increase the negotiating power** of Member States.

- **Supporting European initiatives in the field of OMPs**

  To ensure equal access to highly specialised healthcare for rare diseases and to improve knowledge, diagnosis and treatment of rare diseases within Europe, **European cooperation and support is essential**. In this context, ESIP welcomes the European initiatives such as the European Platform on Rare Disease Registration launched in February 2019 and the European Reference Network. We **call on the European Institutions to continue to fund and support such initiatives**.

[8] Vella Bonanno et al. Adaptive Pathways: Possible Next Steps for Payers in Preparation for Their Potential Implementation. Frontiers in Pharmacology 2017.