

Is the current EU legal framework for orphan medicines fit for purpose?

Maria Isabel Manley, Partner and Head of the UK Life Sciences Practice, and Chris Boyle, Associate, at Sidley Austin discuss the impact of regulatory frameworks on medicines for rare diseases

Following the success of the US and Japanese orphan regulatory frameworks (respectively enacted in 1983 and 1993), the EU established its own regulatory framework in 2000 to stimulate R&D in medicinal products for the treatment of rare diseases: namely, diseases affecting no more than 5 in 10,000 people in the EU. Historically, such diseases were neglected, primarily due to the lack of incentives to make the development of new treatments commercially viable.

The adoption of Regulation 141/2000 (the Orphan Regulation) provided long-awaited incentives for the development of medicines for rare diseases, which, as of 2018, have led to the grant of over 164 orphan marketing authorisations.¹ The key incentive is a 10-year period of ‘market exclusivity’, which prevents competitors from applying for or being granted a new marketing authorisation (or extension) for a “similar medicinal product” for the “same therapeutic indication”.²

Market exclusivity is extendable up to 12 years as a reward for conducting paediatric studies in accordance with a paediatric investigation plan (Regulation 1901/2006, Paragraph 37). The period of market exclusivity can also be reduced to 6 years if the orphan designation criteria are no longer met after 5 years.

The successes of the Orphan Regulation so far are hugely important to the 30 million (or 1 in 17 individuals) affected by rare diseases in the EU.³ However, it is

questionable that nearly 20-year-old orphan legal framework can still be considered fit for its purpose and sufficiently robust to continue incentivising the development of new orphan medicines, especially at a time where orphan designation is becoming harder to maintain and technology assessments and pricing/reimbursement procedures are acting as a barrier to effective patient access. Alternatively, should we take the opportunity presented by the European Commission’s review of IP regulatory rights to boost and reinforce the current legislation to reflect the new challenges faced today by the pharmaceutical companies in this field?⁴

Key features of the Orphan Regulation

The regulatory procedure encompasses two main phases: the ‘orphan designation’, which triggers the possibility of incentives such as fee reductions and protocol assistance, and ‘marketing authorisation’, which, if granted and orphan designation is maintained, leads to market exclusivity being awarded.

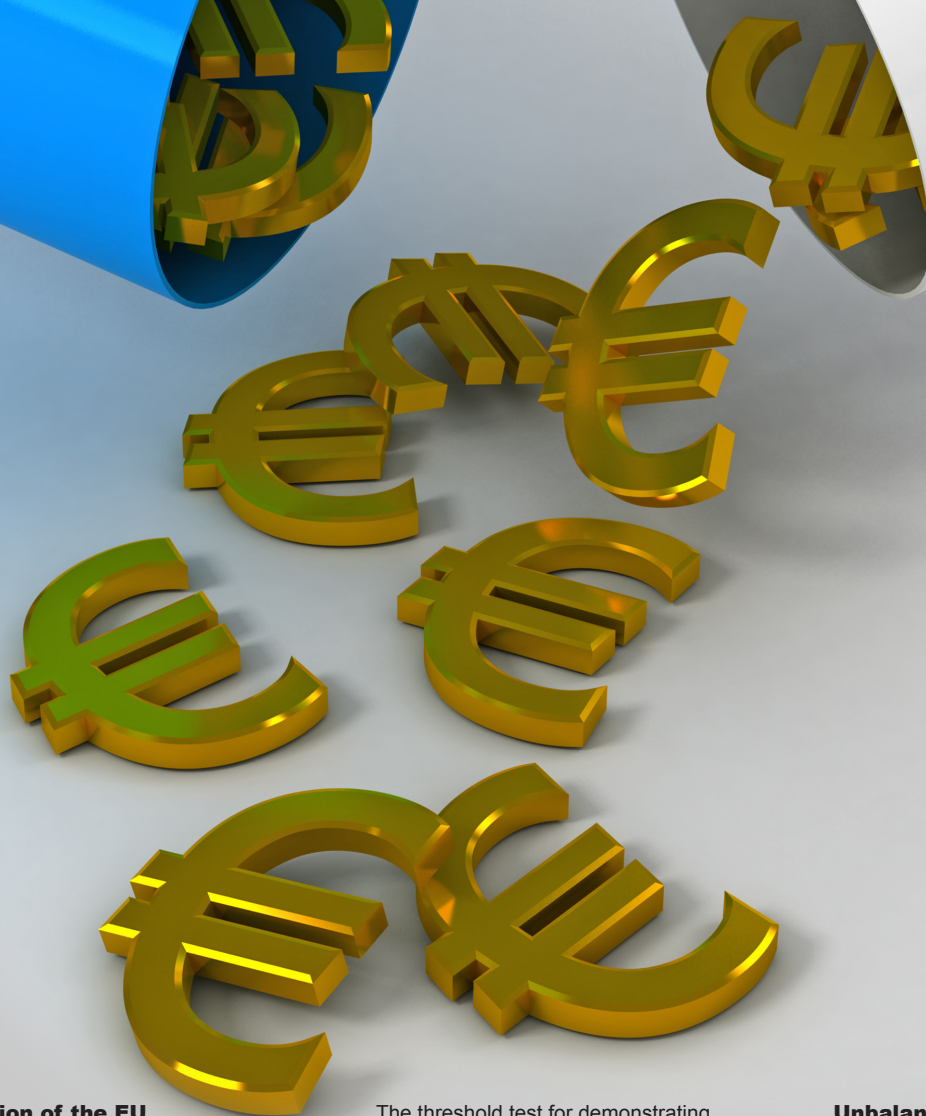
Orphan designation is reserved only for the treatment of life-threatening, debilitating, and/or serious and chronic conditions (more fully, the ‘prevention, diagnosis, or treatment’ of rare diseases). Applicants, known as sponsors, must also demonstrate they meet designation criteria based on the prevalence of the condition, economic factors, and the lack of existing satisfactory methods of treatment of the orphan condition or the significant benefit over such existing methods; these criteria must be met on both phase one and two.

In practice, demonstrating significant benefit is often a key obstacle to orphan designation (in approximately one third of cases), which is made more difficult by the fact that it can be a moving target.¹ Sponsors have to demonstrate significant benefit in comparison with any methods of treatment that emerge before their own marketing authorisation is granted – even a marketing authorisation granted after the sponsor’s application has been submitted can derail the maintenance of the sponsor’s orphan designation.⁵

Market exclusivity

Market exclusivity provides an opportunity for sponsors to recoup their investment costs without facing new competition. However, the protection afforded is not as strong as patent protection, and certain exceptions (known as ‘derogations’) also exist, such as in instances where it is demonstrated that the new product is safer, more effective, or otherwise “clinically superior” to the original product.⁶

Market exclusivity plays a unique and vital role to incentivise the development of orphan medicines and is to be distinguished from the other IP regulatory rights. Indeed, the European courts have confirmed this in the jurisprudence by expressly holding that market exclusivity “cannot be regarded as equivalent to the data protection periods... as the effects and scope of each of those mechanisms are different”.⁷ They have also held that market exclusivity must be granted “in all cases in which an orphan product has been given marketing authorisation”.⁸ Importantly, the general court has also supported market exclusivity by preventing circumvention of this right through off-label prescribing.⁹



Evolution of the EU orphan framework

The orphan framework has continued to be clarified and evolve in this way. For example, the definition of “similar active substance” (itself part of the definition of “similar medicinal product”) has been amended to facilitate its application to advanced therapeutic medical products and biologicals, and the jurisprudence has developed the test for significant benefit so that not only must the application of the criteria be strictly applied, but a sponsor must now demonstrate it on the basis of “concrete and substantiated evidence and information”.¹⁰⁻¹¹

In the UK, HTA authorities conduct a ‘cost-effectiveness’ assessment of medicinal products before recommending the product for use by the NHS. This process can be very lengthy and painful for the companies and the patients or patients associations involved.

The threshold test for demonstrating significant benefit has been steadily increasing in this way, while, surprisingly, European Commission guidance suggests that comparators (against which significant benefit must be demonstrated) should be expanded to include off-label or unlicensed compounded products.¹²⁻¹³ This has the troubling effect of removing an incentive to replace off-label and unlicensed medicines with authorised medicines that have demonstrated quality safety and efficacy for the indication in accordance with Directive 2001/83. Such recent developments are expected to make it more difficult for sponsors to demonstrate significant benefit and maintain orphan designation. Indeed, it is already common for sponsors to fail to maintain designation at the time of marketing authorisation, missing out on market exclusivity protection. The fact that there has been a substantial mismatch between the number of orphan designations granted at phase one (2,121) and the number of orphan market authorisations granted at phase two (164), a ratio of more than 10:1, illustrates these difficulties and potential missed opportunities for patients.¹

Unbalanced challenges for sponsors

Unfortunately, the challenges faced by sponsors do not cease upon obtaining marketing authorisation and market exclusivity. In practice, the next step of securing appropriate pricing, reimbursement, and a positive health technology assessment (HTA) has proven, in many cases, to be a further substantial barrier to effective market access. In some cases, this leads to significant delays or even prevents new orphan medicines from being placed on the market altogether.

The pricing of medicines is indeed a complex and thorny issue to resolve, not least because pricing remains a prerogative of member states and is, therefore, determined nationally. However, positive pricing and HTA decisions (or in the UK, highly specialised technology evaluations for very rare conditions) are particularly challenging to obtain in relation to orphan medicines because of the small patients populations, making it difficult (if not impossible) for sponsors to provide the

data requested by the pricing authorities in order to conduct their assessment.

In some respects, the current Orphan Regulation is failing because patients are ultimately unable to access medicines due to pricing and reimbursement issues. For example, the existing incentives under the Orphan Regulation were not sufficient to make the commercialisation of the EU's first gene therapy treatment, Glybera, sustainable. As a consequence, the marketing authorisation for Glybera was not renewed in 2017. As a further example, almost four years after Clinuvel obtained a marketing authorisation for its orphan medicine Scenesse™, Clinuvel are still waiting a final HTA. This means that patients do not have *de facto* access to the medicine under the NHS, and Clinuvel is prevented from enjoying the benefit of the market exclusivity afforded to it, which is being significantly eroded though the lengthy HTA process.

Looking forward

In its review, the Commission should analyse the challenges and uncertainties facing sponsors today, which are hampering the development of new orphan medicines despite the continued and significant unmet patient need. The review should recognise the low conversion rate of orphan designations compared to authorised orphan products and the fact that some promising products have either had to be withdrawn from the market or have not made it to market authorisation because they were not commercially viable under the existing framework. The review should also acknowledge that the increasing thresholds for sponsors to demonstrate significant benefit, including in comparison to compounded products, is already making orphan designation harder to obtain and maintain.

These challenges come at a time where market exclusivity is under threat of circumvention by some member states, which are facilitating the widespread

use of unlicensed or off-label compounded medicines for short-term cost savings, despite the fact that this risks undermining the very pillars of market authorisation (quality, safety, and efficacy). The careful balancing exercise of the interests of all stakeholders conducted by the Commission while drafting the Orphan Regulation did not take into consideration the extensive challenges faced by the pharma industry in developing and bringing orphan medicines to the market.

While the Orphan Regulation has been a success overall, it is already facing very real challenges that hinder its central aim of bringing new medicines for rare diseases to the market. Therefore, the Commission should take the opportunity in its review to ensure the orphan legal framework provides the necessary incentives to continue to stimulate the development of orphan medicines. In particular, it should take into account the significant delays faced by orphan medicines in effectively reaching the market due to the lengthy HTA process, which results in the significant erosion of market exclusivity – a key feature of the success of the Orphan Regulation.

Declaration

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Maria Isabel Manley leads Sidley's UK Life



Sciences Practice and is a distinguished thought leader and adviser on EU and UK regulatory law and acts as Chairperson of the Legal Affairs Community for the DIA. Marie advises clients before national and European courts and regulatory agencies in the UK and across Europe. She represents leading pharma and life science companies in litigation before the EU and English courts, as well as before the national and EU regulatory authorities. Maria earned an LLM from Columbia University School of Law, US, and Lausanne University, Switzerland, as well as a Postgraduate Diploma on EU Competition Law from Kings College London, UK.

Chris Boyle is a life science lawyer focusing on advising and litigating in the highly regulated fields of human and veterinary medicinal products and



medical devices. The clinical experience Chris gained as a veterinary surgeon is a particular asset to his practice. Chris is experienced in representing clients before both the UK and EU courts. In particular, he represents a pharma company in high-value follow-on damage proceedings in the UK concerning the intersection between competition, regulatory, and patent law. Chris has also successfully enforced orphan drug market exclusivity before the general court in Luxembourg.