European Union Review of Pharmaceutical Incentives: *Suggestions for Change*



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Medicines Law & Policy

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Pharmaceutical incentives and patients: A lost balance

Patents and other forms of exclusive rights, such as data exclusivity and market exclusivity, are meant to stimulate innovation by rewarding innovators with temporary monopolies over their innovations. These monopolies enable them to reap commercial rewards if they are successful and encourage yet more innovation. But when exclusive rights are granted over medical innovations, the consequences of monopoly pricing can be catastrophic if a high price means that access to the treatment is not provided to patients or is postponed until lower-priced versions of the product are available. In pharmaceuticals, the importance of striking the right balance between rewarding innovation and ensuring that medicines are available and affordable is particularly critical: Access to medicinal products can be a matter of life and death, of wellbeing and illness.

Unfortunately, this balance has been tipped hugely in favour of private firms and away from maximising the public benefit. Market exclusivities granted through the patent system and the medicines regulatory system are stacked atop each other, and never rolled back. They are adopted based on assumptions, rather than data that provides evidence for their need. The pharmaceutical industry now benefits from a web of protections in the European Union (EU) that together delay market competition for long periods of time and allow companies to set

"The system is broken.... Patent and intellectual property exclusivities are the only cornerstone of the current model. Companies can ask the price they like. This will no longer do. We need to develop alternative business models..."

Netherlands Ministers E. Schippers (Health) and L. Ploumen (Foreign Trade and Development Cooperation) in the Lancet¹

profit-maximising prices that are unaffordable for many. Companies obtain those rights without needing to demonstrate that their turnover is insufficient to recoup investments and make new ones. The rulemaking for exclusive rights in the EU seems to be driven by a blind belief that exclusivity is good and more exclusivity is better.

¹Lilianne Ploumen, 'Better life through medicine–let's leave no one behind' (The Lancet, 7 November 2016) <www.thelancet.com/journals/lancet/article/PIIS0140-6736(16)31905-5/fulltext>.

Review of Pharmaceutical Incentives: A chance to begin restoring the balance

The Council of the European Union decided in 2016 to find ways to "strengthen the balance in the pharmaceutical system in the EU and its Member States."² This process offers the EU and its members the possibility to introduce changes to pharmaceutical regulations to ensure innovation is sufficiently incentivised without sacrificing EU citizens' access to affordable medical treatments.

This series of briefing papers focuses on three areas of legislation that warrant particular readjustment, and offers recommendations to strike a better balance between private sector incentives and public health needs:

Supplementary Protection Certificates:

A supplementary protection certificate (SPC) provides up to 5 years of additional patent-like protection of a registered medicine upon expiration of the 20-year patent term. The SPC was designed to make up for years in which a patent could not be commercially exploited due to required regulatory procedures. The SPC system is meant to ensure the patent holder can enjoy a 15-year monopoly.

Data Exclusivity:

Data exclusivity means that clinical test data submitted by the original company cannot be used for the registration of a generic product or biosimilar product for a certain period of time. The EU has the world's longest data exclusivity period – namely, 8 years – complemented with up to 3 additional years of market exclusivity when the generic or biosimilar product may be registered but may not yet be marketed.

Orphan Medicinal Product Legislation:

Orphan medicinal product (orphan drug) incentives are meant to promote the development of medicines to treat rare diseases. Rare diseases affect small numbers of patients and therefore lack market pull to entice commercial drug developers to invest in R&D. The EU orphan medicinal product incentives include regulatory assistance, fee waivers from the European Medicines Agency, funding for research, and 10 years of market exclusivity which can be extended for 2 more years for the development of a paediatric indication. In recent years, however, concern that this system is being abused to make unjustifiable profits has arisen.³

² Council conclusions on strengthening the balance in the pharmaceutical systems in the EU and its Member States [2016] C269/31. https://www.consilium.europa.eu/en/press/press-releases/2016/06/17/epsco-conclusions-balance-pharmaceutical-system/.

³ See, for example: Marc-André Gagnon, 'New Drug Pricing: Does it Make Any Sense?' (2015) 24 Prescrire International 192; Sarah Jane Tribble and Sydney Lupkin, 'Drugmakers Manipulate Orphan Drug Rules To Create Prized Monopolies'

Principles for rebalancing pharmaceutical incentives in the EU

The briefing papers suggest policy recommendations to improve legislation on SPCs, data exclusivity and orphan medicinal products based on the following principles:

- There needs to be a clearer link between risk and reward. Pharmaceutical research and development is expensive, complex, and risky. But risks and cost vary depending on many factors, such as the type of disease, stage of development of the product, and size of the clinical trials. The pharmaceutical industry relies on inflated impressions of the cost of drug development to overstate the exclusive marketing time needed to recoup investment and become profitable.
- Historical reasons underpinning the EU's generous data and market exclusivity system are no longer valid. The array of market exclusivity rights developed over time, in part to re-enforce what were once weak patent rights and a diversity in protection regimes in the EU, were based on the assumption that market exclusivity is the best incentive to innovation and that "longer is always better." But a growing body of evidence puts the reliance on exclusive rights in question. Therefore, additional protections can be scaled back and tailored to fit a more rational approach.
- The idea of 'sufficient' profit should guide policy makers, with 'sufficiency' estimates driven by transparency of cost and pricing. Transparency on the actual cost of research and development, including clinical trials, as well as pricing information will be essential to determine rates for 'sufficient' profit that must be recouped so originator companies receive a fair award. The EU and its member states should be encouraged to take measures requiring transparency as a condition of obtaining supplementary protection.

⁽Kaiser Health News, 17 January 2017) <https://khn.org/news/drugmakers-manipulate-orphan-drug-rules-to-create-prized-monopolies/>; and Ellen 't Hoen, 'Inside Views: Time To Put a Stop to the Abuse of Orphan Drug Regulation – The Latest Scandal' (Intellectual Property Watch, 10 January 2019) <https://www.ip-watch.org/2019/01/10/time-put-stop-abuse-orphan-drug-regulation-latest-scandal/>.

- Flexibilities inherent in patent law should not be rendered ineffective by exclusive rights granted through the medicines regulatory system. In cases of public health need, the patent system has an in-built flexibility in the form of compulsory or government use licences. These can be used when a patent impedes access to a needed medicine and are an essential part of EU members' duty to protect the health of their citizens. Equivalent provisions need to be available in the regulation of data and market exclusivities.
- Trade and investment agreements should not be used to demand third countries implement more stringent intellectual property (IP) protection than they are required to have under the rules of the World Trade Organization. Flexibilities inherent in the IP system provide important safeguards for public health, and the EU should protect rather than harm those safeguards.



Figure 1: Relation between the different patent/SPC and regulatory protections for pharmaceutical products

Blue represents patent protection; Red represents regulatory protection. The purple colour for the SPCs indicates the combination of features of patent and regulatory systems. Dotted lines show the relationships between patent application and marketing authorisation dates and how they relate to certain protection mechanisms. The width of the boxes (and the positioning of the two boxes exemplifying the patents) represents the scope of protection provided by the respective instruments. Note that the above depiction is a simplification: the situation could become more complex when considering, for example, the possibility to apply for different SPCs invoking the same basic patent. Figure extracted from Technopolis Group report "Effects of supplementary protection mechanisms for pharmaceutical products," May 2018.

Policy recommendations for a better balanced pharmaceutical system in the EU and its member states

For supplementary protection certificates:

- 1. Make granting of SPCs conditional on applicants providing evidence that "the period of effective protection under the patent [is] insufficient to cover the investment put into the research." Upon application for an SPC, applicants would be required to provide patent offices with data on all past and future development costs, excluding public funding, and expected revenues.⁴ Such data could be made public to increase transparency and trust in the system. If an SPC is granted, patent owners would be required to submit return on investment data either on a yearly basis, or at the latest, six months before the entry into force of the SPC, so that the need of the SPC could be confirmed based on actual reported profits. If the period of effective patent protection was sufficient to cover the investments put into the research programme that launched the medicine, the SPC would be cancelled.
- 2. Alternatively, make the entry into force of an SPC subject to review six months before the expiration of the basic patent. Patent owners would be required to provide patent offices with full data of development costs of the related programme, excluding public funding, and of reported profits during the effective period of patent protection.⁴ Review of such data six months before the expiration of the patent would confirm whether the period of effective protection under the patent needs to be supplemented by the SPC or not.
- 3. Give third parties an opportunity to submit "observations" to the patent office to pre-empt the entry into force of an SPC based on evidence, from actual reported profits, that the period of effective protection under the patent was sufficient to cover the investment put into research.
- 4. Make procedures to revoke a granted SPC, modelled on opposition procedures against patents, available in all EU countries. Such procedures, which are currently lacking in many countries, could include an extra ground of sufficient return on investments to challenge the SPC.
- 5. Tie the entry into force of an SPC to a requirement on pricing. For example, a company could benefit from extra years of protection if it both demonstrated that extra protection is necessary to cover R&D investment and that the product is affordable during the protection period.

⁴ In the context of orphan medicinal product protection, a European Commission notice indicates that 'sufficient return' will be assessed "...on the basis of all past and future development costs and expected revenues": Commission notice on the application of Articles 3, 5 and 7 of Regulation (EC) No 141/2000 on orphan medicinal products [2016] C 424/03.

For data exclusivity:

- 1. Replace the data exclusivity regime with a data compensation regime. Replace the EU data exclusivity regime with a data protection regime that acknowledges the investment needed to generate the data, but does not allow the investor to exclude others from using the data: *a data compensation regime*. Under a *data compensation regime*, the registration of a generic medicine or biosimilar medicine is considered fair commercial use and thus not hampered by the data protection. The originator company that made the investment that was needed to generate the data receives adequate remuneration for the use of that data, but cannot prevent its necessary use for the medicines agency to perform its public health duties, for example using it to register generic versions.⁵
- 2. Introduce waivers to data and market exclusivity to facilitate effective use by governments of patents in the public interest, compulsory licensing or other measures needed for the advancement of public health and access to medicines for all within the European Union. This would bring coherence to EU law and assist member states that are seeking ways to ensure the availability of new medicines without undue burden on their health budgets. Legal coherence can be achieved by inserting the following provision into the EU legal framework governing medicinal products for human use:

'The protection periods set out in article 14 (11) of Regulation 726/2004 shall not apply in cases where it is necessary to allow access to and the use of pharmaceutical test data to register a generic of a reference medicinal product, which is or has been authorised under article 6 of Directive 2001/83/EC, for reasons of public interest including public health, in case of compulsory licensing of patents, including for public non-commercial use, and in situations of national emergency or extreme urgency.'

A payment of an adequate remuneration for the use of or reliance on test data to the holder of the marketing authorisation of the reference medicinal product may be required; for example, in the absence of patents and thus absence of remuneration normally payable in case of a compulsory licence or government use licence.

3. Remove the requirement to implement data exclusivity from trade negotiations with other nations and instead focus on agreements with other nations that address medical R&D needs and mechanisms for burden and benefit sharing of medical R&D.⁶

⁵ Such a provision would further advance the objective to reach greater transparency on R&D expenditure.

⁶ For a discussion of how such new R&D models could be shaped see: 'Delinkage' <www.delinkage.org>.

For orphan medicinal products:

- Fully operationalise Article 8 (2) of Regulation 141 / 2000 by defining the line between 'sufficient' and 'excessive' profitability and therefore between 'sufficient' and 'insufficient' Return on Investment (ROI). The ROI approach (stipulated in implementing Regulation 847 / 2000, Commission guideline 2008/C and Commission notice 2016/C) should aim for the minimum return necessary to achieve the goals of the Regulation in encouraging the development of orphan medicinal products (and the 'how much can the market bear' approach to pricing should be rejected). This will introduce some much-needed transparency into the European institutions on the subject of pharmaceutical firms' business models (and questions about their efficiency and continuing viability). Although there is concern about discouraging pharmaceutical firms' engagement with this field, 'sufficient' profitability should surely be, by definition, just that.
- 2. The prevalence threshold of not more than five per ten thousand people in Article 3 (1)(a), equivalent to a maximum current EU patient population of circa 250,000, should be re-examined in the light of experience gained since 2000. This threshold defines the line between those orphan disease markets which are assumed to be insufficiently profitable (permitting the 'prevalence' route for orphan designation to be used) and those which have to be shown to be insufficiently profitable (requiring the use of the 'ROI' route for orphan designation). The unprecedentedly high prices charged for orphan medicinal products by some pharmaceutical firms have meant, however, that orphan disease markets with < 10,000 patients can be made to produce 'blockbuster' profits. It is therefore clear that it does not make sense to set a prevalence threshold based on an assumption about profitability, without considering pricing behaviour. As it stands, the threshold has been overly generous in letting sponsors access the incentives provided under the Regulation without having to show any evidence to support a case of insufficient profitability: only 1 out of the 2,302 applications for orphan medicinal product designation between 2000 and 2015 made use of the ROI route and was required to do so.⁷

⁷ European Commission, 'Inventory of Union and Member State Incentives to Support Research Into, and the Development and Availability of, Orphan Medicinal Products – State of Play 2015" SWD(2015)13 final.

- 3. A mechanism similar to the 'withdrawal clause' from the early drafts of the Regulation should be re-introduced to the present Art. 8 (2). This could take various forms, for example:
 - (i) The prevalence route mentioned in Recommendation (2) could be removed altogether. All applications for orphan medicinal product designation would use the ROI route. Orphan exclusivity could therefore be removed in any cases where an orphan medicinal product proved sufficiently profitable.
 - (ii) Article 8 (2) could be amended in line with the text of the 'withdrawal clause' in the earlier drafts of Regulation 141 / 2000, such that orphan exclusivity could be removed irrespective of whether the prevalence or the ROI route had been used, in any cases where an orphan medicinal product proved sufficiently profitable or where the price charged for it was such that an unreasonable profit had been made, or where the price charged was unjustifiable.
 - (iii) Article 8 could be amended such that a shorter period of orphan exclusivity is initially provided, with an extension of that period available if evidence shows that the necessary ROI has not yet been achieved.

The re-introduction of such a mechanism should provide a meaningful brake on the behaviour of pharmaceutical firms operating in the orphan disease field, certainly in those cases where orphan exclusivity extends beyond the life of their other intellectual property rights and where there are other firms able and willing to compete. Although the information necessary for the assessment of ROI would have to be provided in all cases, the commensurately improved transparency of the orphan medicinal product regime should improve confidence that the incentives provided under Regulation 141 / 2000 were not being improperly exploited.

- 4. In particular cases where marketing authorisation (and orphan exclusivity) is granted for an orphan medicinal product which essentially 'formalises' the use of a product which has previously been used 'off label' or has been compounded by pharmacists, such that the majority of the information required by the sponsor was already in the public domain, provision should be made to ensure that:
 - (i) the prior users can continue to make the same use of the product that they have before; and
 - (ii) the commercial reward accorded to the sponsor is matched to the relatively small development risk and cost.

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Supplementary Protection Certificates (SPCs) in the EU: *Briefing Document*

SPCs: *Sui generis* rights at the interface of patent and regulatory systems

Supplementary protection certificates (SPCs) are certificates providing a supplementary market protection for pharmaceutical products in the European Union. Patents in the EU last 20 years from the filing date. SPCs can add up to five years of supplementary protection to certain patents covering pharmaceutical products at the expiration of the patent term, to make up for periods when the patent could not be exploited because the medicine had not yet been granted regulatory approval for commercial use.

Pharmaceutical product development requires the generation of pre-clinical and clinical studies to evaluate the safety and efficacy of a medicine before it can be approved for commercial use in humans or animals. Given drug development timelines are estimated to be an average of around 10 years,¹ patents generally are filed several years before the application for marketing authorisation is made. Patent holders cannot get returns on their investments until the product is authorised (or registered) with the relevant medicines regulatory agency. As a result, economic exploitation during the early years of patent protection is not possible because the medicine cannot be sold.

Therefore, mechanisms of patent term *restoration*, *extension*, and in Europe, SPCs were created to compensate for the lack of commercial exploitation possibilities during the years of medicines development and regulatory approval processes of a pharmaceutical product.

¹ Copenhagen Economics, 'Study on the Economic Impact of Supplementary Protection Certificates, Pharmaceutical Incentives and Rewards in Europe' (*European Commission*, May 2018), p.182.

<https://ec.europa.eu/docsroom/documents/29521>. Some have argued that given that SPC periods are on average 3.5 years long (as recognised by several studies of the Commission) and are designed to give 15 years total enjoyment of exclusivity, the effective patent protection, from the date of the marketing authorisation to the expiration of the patent, must be 11.5 years (i.e. 11.5 years + 3.5 years of SPC = 15 years) on average. Therefore, it can be concluded that the development time, before the product is approved, is on average 8.5 years, after deduction of 11.5 years from the 20-year patent protection.

SPCs Uniform Legal Framework

At the EU level, SPCs were triggered by the publication in 1988 of a "Memorandum on the necessity to restore the effective duration of patents for pharmaceutical products" by the European Federation of Pharmaceutical Industry Associations.² One of the objectives was to ensure a level of protection to medical research equal to that enjoyed in other sectors, but mostly to create a normative framework for European industries comparable to that of industries in the United States (US) and Japan, to support competitiveness in Europe. The US had introduced patent term restoration in 1984 via the *Drug Price Competition and Patent Term Restoration Act* (also known as

the Hatch-Waxman Amendments),³ and in Japan, a system for Patent Term Extension was introduced by the 1987 revision of Patent Act.⁴

This prompted France and Italy to adopt distinct SPC regulations. To avoid a proliferation of various national SPCs regulations in Europe, Council Regulation (EEC) No 1768/92 of 18 June 1992 concerning the creation of a supplementary protection certificate for medicinal products, was adopted to ensure a "uniform solution at Commu The effect of an SPC granted for a pharmaceutical product is exactly like the effect of the basic patent claiming the product: SPCs extend the duration of the exclusive right benefiting the patent holder, delaying generic competition and resulting price decreases.

adopted to ensure a "uniform solution at Community level."⁵

At the time, the Regulation applied only to nine countries. Today the agreement is in force in all EU member states and the European Economic Area (EEA) countries Norway and Iceland. A recent study reports over 20,000 SPCs have been granted since the adoption of the Regulation in 1993.⁶

The stated objective of the regulation is "to provide adequate effective protection" so that manufacturers of new pharmaceutical products "enjoy an overall maximum of 15 years of exclusivity from the time the medicinal product in question first obtains authorisation to be placed on the market in the Community." However, to take account of "public health"⁷ interests, "the certificate cannot be granted for a period exceeding five years" … like the US patent term restoration system

² European Commission, 'Explanatory Memorandum to the Proposal for a Council Regulation (EEC), of 11 April 1990, concerning the creation of a supplementary protection certificate for medicinal products' COM(90) 101 final – SYN255, available at http://aei.pitt.edu/12237/1/12237.pdf>.

³ Under the Drug Price Competition and Patent Term Restoration Act, a maximum of 5 years can be restored to the patent, but not exceeding 14 years from the product's approval date.

⁴ In Japan, the duration of a patent may be extended for a maximum of 5 years.

⁵ Now superseded by Regulation 469/2009 Concerning the Supplementary Protection Certificate for Medicinal Products [2009] OJ L152/1.

⁶ Copenhagen Economics (n 1).

⁷ Recital 10 Regulation 1768/92 Concerning the Creation of a Supplementary Protection Certificate For Medicinal Products [1992] OJ L182/1.

of maximum 5 years extension / 14 years of effective protection,⁸ plus one year to add value to the European market possibly?

To take an example, the basic patent of human immunodeficiency viruses (HIV) medicine dolutegravir,⁹ one of the recommended first line treatments for HIV, was filed on 28/04/2006. But the medicine was only authorised by the European Medicine Agency (EMA) 8 years later in January 2014. This means that the patent owner and manufacturing company ViiV Healthcare could benefit from more than 12 years of market exclusivity, based on the granted patent, between 2014 and the date of expiration of the patent on 28/04/2026. ViiV Healthcare requested and obtained SPCs in several European countries to prolong its exclusive rights on dolutegravir for 3 additional years until 21/01/2029, 15 years after the date of approval of the product, as allowed by the EU Regulation.¹⁰

To summarise, if the period between the patent filing date and the medicine authorisation date is less than five years, no SPC can be obtained because the patent holder will enjoy at least 15 years of effective patent protection. If this period is between five and ten years, an SPC up to 5 years may be granted to restore the effective patent protection term lost before the medicine was authorised for marketing. If the period between the patent filing date and the authorisation date is more than ten years, any SPC granted will have a maximum five-year term. A one-off paediatric extension of six months on top of the maximum five years SPC is also possible, provided the applicant has complied with what is called an agreed Paediatric Investigation Plan (PIP).

SPCs are not granted automatically. Article 3 of the Regulation establishes conditions under which a patent office can grant an SPC:

- (a) the medicine should be protected by a "basic patent in force" which can be a national or European patent
- (b) a marketing authorisation should have been granted for the medicine in question either by the national regulatory authority or by the European Medicines Agency
- (c) the authorised medicine should not have already been the subject of an SPC; and
- (d) the marketing authorisation should be the first to place the medicine on the market.

Even though SPCs are based on a European regulation, they must be applied to the patent office of each country where supplementary protection in sought. The patent owner may apply for an SPC within 6 months from the grant of the market authorisation, or from the grant of the "basic patent," whichever is later.

⁸ Drug Price Competition and Patent Term Restoration Act (Public Law 98-417).

⁹ European Patent Office Application Number 06758843.

¹⁰ According to Article 13 Regulation 469/2009 (n 5), the SPC term is calculated by taking the difference between the filing date of the patent and the marketing authorisation date of the medicinal product protected by the patent, minus 5.

Supplementary Protection Certificates (SPCs) in the EU: Briefing Document

Given that the SPC is linked to a patent and a marketing authorisation, if the patent or the marketing authorisation are invalidated, the SPC is cancelled.¹¹ A patent, in the absence of a marketing authorisation, does not provide a right to obtain an SPC. Additionally, the scope of the certificate may be more limited than the basic patent, as it is only intended to cover the product (intended as active pharmaceutical ingredient, as specified in the Explanatory Memorandum of the SPC Regulation)¹² as approved for use, whereas the scope of a pharmaceutical patent can be broader. The link with the existence of a market authorisation and the narrower scope of the SPC compared to a patent confirms the *sui generis* nature of the SPC.

Preparatory work leading to the adoption of the SPC regulation indicates that the original intention of Article 3 was to grant one SPC per any one medicinal product, only for substances that were authorised for the first time as active ingredients of a medicine.¹³ If the product had already been authorised in the past, and the applicant identified new uses or a new formulation of the product and obtained a more recent marketing authorisation, an SPC was meant to be excluded. This is coherent with the fact that research and development of new chemical entities is longer and riskier than it is for new indications or new uses of known molecules. In practice, however, the SPC regulation gave rise to a handful of jurisprudence from national courts and the Court of Justice of the European Union (CJEU) far away from the original principle of only one SPC for one new medicine. One of the most discussed rulings of the CJEU, in the Neurim case, has established the possibility to obtain an SPC for a second medical use indication based on a second medical use patent.^{14,15}

¹¹ Article 15 of the SPC Regulation (n 5) provides that "The certificate shall be invalid if: (a) it was granted contrary to the provisions of Article 3; (b) the basic patent has lapsed before its lawful term expires; (c) the basic patent is revoked or limited to the extent that the product for which the certificate was granted would no longer be protected by the claims of the basic patent or, after the basic patent has expired, grounds for revocation exist which would have justified such revocation or limitation."

¹² See the Commission Explanatory Memorandum (n 2) 8: "a product being understood to mean an active substance in the strict sense."

¹³ Ibid.

¹⁴ Case C-130/11 Neurim Pharmaceuticals (1991) Ltd v Comptroller-General of Patents [2012] EU:C:2012:489.

¹⁵ See in Figure 8 of the Technopolis Group report: "Possibilities to obtain SPCs on different types of patents for the same compound": Thyra de Jongh and others, 'Effects of Supplementary Protection Mechanisms for Pharmaceutical Products' Final Report (*Technopolis Group*, May 2018) 54 <http://www.technopolis-group.com/wp-content/uploads/2018/06/2718-Technopolis-report-on-supplementary-protection-mechanisms.pdf>.

Diverse interpretations of conditions for SPC grant by national patent offices

Unlike patents, which can be granted by the European Patent Office, SPCs are granted only by national patent offices, in accordance with Regulation (EEC) No 469/2009.¹⁶ As a result, despite this common European legal framework intended to prevent a heterogeneous development of national laws, national patent offices and courts have interpreted the Regulation in different ways, generating disparities of protection among EU countries. The hybrid nature of SPCs, which are granted based on the existence of both a basic patent and a marketing authorisation covering the product, contributed to a plethora of judicial decisions based on the SPC Regulation. The Max Planck Institute Study on the legal aspects of Supplementary Protection Certificates¹⁷ in the EU provides a thorough analysis of the SPC case law developed in the past 25 years.

The case of the medicine Truvada,¹⁸ a fixed-dose combination of tenofovir disoproxil fumarate (TDF) and emtricitabine (FTC) used for the treatment and prevention of HIV, illustrates well the differences of interpretation in the SPC Regulation among national patent offices.

The basic patent covering tenofovir expired in July 2017. However, an SPC had been granted to extend the protection of Truvada by several patent offices, including France, the United Kingdom (UK), Spain and Switzerland. By contrast, the Netherlands, Italy and Greece refused to grant the same SPC. The main reason for the rejection of the SPC was that the patent in question claimed tenofovir but not emtricitabine specifically, so these patent offices decided that the patent did not protect the product tenofovir/emtricitabine, as required by the Regulation, but only part of it. In France, the generic drug maker Mylan challenged the granted French SPC and the courts confirmed that the SPC was invalid.¹⁹ The same happened in Spain.²⁰ In the UK, where several generic companies challenged the granted SPC, the judge of the High Court asked clarification to the European Court of Justice on how to interpret the EU Regulation.

¹⁶ Although this could change when the unitary patent comes into effect: 'Unitary Patent' (*European Commission*) <https://ec.europa.eu/growth/industry/intellectual-property/patents/unitary-patent_en>.

¹⁷ Max Planck Institute for Innovation and Competition, 'Study on the Legal Aspects of Supplementary Protection Certificates in the EU' (*European Commission*, 2018) https://ec.europa.eu/docsroom/documents/29524>.

¹⁸ Pascale Boulet, 'Will the European Court of Justice Put a Stop to the Evergreening of Truvada Patents?' (*Medicines Law & Policy*, 8 May 2018) <https://medicineslawandpolicy.org/2018/05/will-the-european-court-of-justice-put-a-stop-to-the-evergreening-of-truvada-patents/>.

¹⁹ Tribunal de grande instance de Paris, 'Ordonnance de référé rendue le 5 septembre 2017' No. RG 17/57112.

²⁰ Núria Ribera, 'Preliminary injunctions revoked due to prima facie invalidity of Truvada SPC' (*International Law Office*, 8 January 2018) .

Supplementary Protection Certificates (SPCs) in the EU: Briefing Document

The CJEU ruling in July 2018 clarified the definition of 'basic patent', especially with regards to combination products, such as Truvada.²¹ Importantly, the Court recalled that "In the light of the need, referred ... in ... the preamble to Regulation No 469/2009, to take into account all the interests at stake, including those of public health, to accept that an SPC that could grant ... protection which goes beyond ... the invention it covers, would be contrary to the requirement to balance the interests of the pharmaceutical industry and those of public health as regards the encouragement of research within the European Union by the use of SPCs."²² In other words, the Court pointed to the risks of SPCs being used to 'evergreen' patent protection, in contradiction with the text and spirit of the Regulation to take "all the interests at stake," and in particular public health interests.

The question of the beneficiary of the SPC, not specified in the Regulation, also gave rise to caselaw when the owner of the basic patent differs from the holder of the marketing authorisation.²³ According to the SPC Regulation, the holder of a basic patent claiming an authorised medicine is entitled to an SPC without having to ask permission from the marketing authorisation holder. This situation does not raise issues in most cases; generally, the marketing authorisation holder is the patent owner, or a licensee. However, this is not always the case. The following question was only recently referred by a UK court to the CJEU for clarification: "Does the SPC Regulation preclude the grant of an SPC to the proprietor of a basic patent in respect of a product which is the subject of a marketing authorisation held by a third party without that party's consent?"²⁴

Effect of SPCs on prices and affordability of medicines

The effect of an SPC granted for a pharmaceutical product is exactly like the effect of the basic patent claiming the product. SPCs extend the duration of the exclusive right benefiting the patent holder. The grant of an SPC therefore further delays generic competition and resulting price decreases. The extended monopoly position is usually used by the patent/SPC holder to impose the highest possible price that the market can bear for the product. Conversely, the refusal or lack of SPC can result in significant improvements in a medicine's affordability. The disparities of SPC protection within EU countries illustrate the price difference for the same medicine in a country which granted an SPC as compared to a country that did not.

²¹ Pascale Boulet, 'CJEU Ruling on Truvada recalls "evergreening" goes against public health interests' (*Medicines Law & Policy*, 10 September 2018) https://medicineslawandpolicy.org/2018/09/cjeu-ruling-on-truvada-recalls-evergreening-goes-against-public-health-interests/.

²² Case C-121/17 Teva UK and Others v Gilead [2018] EU:C:2018:585.

²³ See Max Planck Institute for Innovation and Competition (n 17) Chapter 13 of MPI Study on the legal aspects of Supplementary Protection Certificates.

²⁴ Eli Lilly & Co v Genentech, Inc [2019] EWHC 388 (Pat)

<https://www.bailii.org/ew/cases/EWHC/Patents/2019/388.html>.

The Truvada example described above is useful to understand the consequences of SPCs on pricing and affordability of medicines. Truvada is a critical medicine for HIV treatment and prevention. The use of Truvada as pre-exposure prophylaxis or PrEP can reduce HIV transmission by over 90%. Affordable pricing of the product is

While the benefits of expanded patent protection for commercial companies are clear, the key question is what are the costs/benefits of patent term extensions such as SPCs from a public interest perspective.

therefore important for public health. Since July 2017, Truvada has been progressively available in generic forms in European countries without SPCs (e.g. the Netherlands and Greece) but not in others with SPCs in force (e.g. Switzerland).

A report from the Technopolis Group for the government of the Netherlands titled the *Effects of supplementary protection mechanisms for pharmaceutical products*, published in April 2018,²⁵ evaluated the cumulative costs of the supplementary protections to the Dutch healthcare system for three drugs. For Lipitor (atorvastatin, used to prevent cardiovascular disease) and Losec (omeprazole, used to treat gastrointestinal illnesses), the total costs of the supplementary protections that delayed competition are estimated to have been over €600m for each medicine. For Cozaar (losartan, which treats high blood pressure), the estimate is lower, at around €118 to €130m, mostly as a result of a significantly lower number of users. The authors conclude that "for high-grossing drugs, the supplementary protections can represent a substantial amount of additional revenue for companies, which is borne as a cost by the healthcare system."²⁶

Country	SPC status	Price TDF/FTC box (30 tablets) in €
The Netherlands	never granted	30.6527
France	revoked	170 ²⁸
Switzerland	in force	800 ²⁹

Table	1. SPC	status	and	correspo	ndina	nrices	of	TDF/FTC	in	Furon	ρ
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²⁵ Technopolis Group (n 15).

²⁶ Technopolis Group (n 15) 151.

²⁷ Zorginstitutt Nederland, 'Medicijnkosten.nl' <https://www.medicijnkosten.nl/>.

²⁸ EurekaSanté, 'Truvada' <https://eurekasante.vidal.fr/recherche/index/q:truvada/>.

²⁹ Stephen Mossaz, 'La Prep, cette pilule "anti-VIH" efficace, mais peu utilisée en Suisse' (*RTS info*, 1 décembre 2017) < https://www.rts.ch/info/sciences-tech/medecine/9133952-la-prep-cette-pilule-anti-vih-efficace-mais-peu-utilisee-ensuisse.html>.

SPCs not required by the TRIPS Agreement

Article 33 of the World Trade Organisation Agreement on Trade Related Aspects of Intellectual Property Rights (TRIPS) provides that "The term of protection available shall not end before the expiration of a period of twenty years counted from the filing date" of the patent application, therefore patents should have a minimum 20-year patent term from the filling date.

In addition, TRIPS Article 1 states that "Members may, but shall not be obliged to, implement in their law more extensive protection than is required by this Agreement."

Read together, both articles clearly indicate that WTO member states have an obligation to make available patents for a minimum of 20 years from the filing date, but are not obliged to extend protection beyond that duration. Therefore, SPCs are clearly not mandated by the WTO.

While the benefits of expanded patent protection for commercial companies are clear, the key question is what are the costs/benefits of patent term extensions such as SPCs from a public interest perspective.

Have SPCs generated the expected outcome?

Council Regulation (EEC) No 1768/92 (as now superseded by Regulation 469/2009) was based on two premises, as quoted:

- "Medicinal products, especially those that are the result of long, costly research will not continue to be developed in the Community and in Europe unless they are covered by favourable rules that provide for sufficient protection to encourage such research;"³⁰
- 2. "The period that elapses between the filing of an application for a patent for a new medicinal product and the authorisation to place the medicinal product on the market makes the period of effective protection under the patent insufficient to cover the investment put into the research."³¹

Twenty-five years after the adoption of the SPC Regulation, it is necessary to assess whether it generated the expected outcome; that is, if the period of effective protection under patents *needs* to be supplemented "to cover the investment put into the research" and whether such supplementary protection has incentivised research and development (R&D) in Europe.

³⁰ Recital 3 Regulation 1768/92 Concerning the Creation of a Supplementary Protection Certificate For Medicinal Products [1992] OJ L182/1.

³¹ Recital 4 Regulation 1768/92 Concerning the Creation of a Supplementary Protection Certificate For Medicinal Products [1992] OJ L182/1.

The report of the Technopolis Group concludes that "The SPC Regulation offers innovator companies an adequate compensation for their effective loss of patent term." However, as an incentivising measure, the report says, "the effect is much less clear. First, the SPC Regulation has failed to incentivise pharmaceutical R&D in Europe sufficiently to narrow the gap with the US. Furthermore, the relation between investment incentives and a

Given that investments put into research on medicines are not available in a clear and transparent format, it is difficult to conclude if the period of effective protection needs to be supplemented "to cover the investment put into the research" or if there is clear evidence that such supplementary protection has encouraged research.

'reward' that is not received until many years, or even decades, after the decision to invest in development of a product is made – particularly when the outcomes of that investment decision are highly uncertain – remains unclear."³²

In May 2018, Copenhagen Economics published its *Study on the economic impact of supplementary protection certificates, pharmaceutical incentives and rewards in Europe*, commissioned by the European Commission.³³ The report found that 45% of medicinal products approved in 1996-2016 have obtained an SPC in at least one of the European countries, and that SPCs delay an average price drop of approximately 50% following the entry of generics. The Copenhagen Economics report also concluded the longer protection stimulates R&D; other studies do not support this conclusion, however, including the Technopolis Group study noted in the previous paragraph.

Given that investments put into research on medicines are not available in a clear and transparent format, it is difficult to conclude whether the period of effective protection *needs* to be supplemented "to cover the investment put into the research" and whether there is clear evidence that such supplementary protection has *encouraged* research. However, annual revenues of pharmaceutical companies provide an indication that, with very high prices, a pharmaceutical firm might still make the necessary return on investment in the remaining (five +) years of the patent term, without the need for supplementary protection.

Further, as noted by the Technopolis Group, "whilst the SPC regulation clearly embodies an intent to promote pharmaceutical innovation in Europe, it does not contain any provisions to favour innovation originating from Europe over that from elsewhere. Rather, all pharmaceutical innovation is treated equally, regardless of the country where the applicant is based or where the R&D has been performed. Consequently, the greatest economic returns from the SPC regulation appear

 $^{^{\}rm 32}$ Technopolis Group (n 15) 9.

³³ Copenhagen Economics (n 1).

destined to flow towards where the greatest research and innovation intensity is, which makes it even more difficult to draw evidence-based conclusions."³⁴

Indeed, a study published by the European Commission on the Economic Analysis of Supplementary Protection Certificates in Europe shows that the majority of the SPCs in Europe derive from the US: "[t]here is no clear geographic bias in the use of SPCs by the location of patent holders. Almost 44% of SPC applicants are US-based, while the EU has close to 30%, followed by Japan and Switzerland at roughly 7% and 6%, respectively. These figures track those of the geography of R&D activity overall."³⁵

Similarly, a study on SPCs conducted by the Max Planck Institute for the European Commission concludes that "the expectation expressed by the historical lawmakers about the impact on (re)location of research centres [to Europe] was somewhat unrealistic from the beginning."³⁶

The SPC Regulation, among its aims, also included the possible reduction of prices of medicines due to the extended exclusivity period, as stated in the Explanatory Memorandum of the regulation: "the present proposal, moreover, favours a possible fall in prices of the medicinal products covered by this proposal in light of the extension of the period for recuperation of investments."³⁷

However, the Technopolis Group report confirms that "[f]rom an economic perspective, the [...] case studies give no indications for any difference in pricing between the time that a drug is under 'ordinary' patent protection and when it is under protection by an SPC. Price changes typically do not occur before generics enter the market."³⁸ As a consequence, the Technopolis Group concludes that "[t]he implicit objective of encouraging lower prices for still-protected products, by offering pharmaceutical innovators increased time to recoup their investments, appears not to have been realised at all."³⁹

³⁴ Technopolis Group (n 15) 86.

³⁵ Margaret Kyle, 'Economic Analysis of Supplementary Protection Certificates in Europe' (2017) 4

< https://ec.europa.eu/docsroom/documents/25621/attachments/1/translations/en/renditions/native>.

³⁶ Max Planck Institute for Innovation and Competition (n 17) 22.

³⁷ Commission Explanatory Memorandum (n 2) 22.

³⁸ Technopolis Group (n 15) 157.

³⁹ ibid 163.

SPC waiver reform: A missed opportunity to address excessive pricing

SPCs are often discussed in the context of a manufacturing waiver for export or stockpiling purposes. The waiver will enable EU-based (generic and biosimilar) companies to manufacture medicines protected by SPCs exclusively for export to non-EU markets, or to stockpile medicines until the expiration of the SPC for launch in the EU markets. Currently, EUbased manufacturers of generics and/or biosimilars can manufacture samples for submitting a regulatory dossier under the Bolar patent exception,⁴⁰ but export outside the EU to countries where SPC protection has expired or

Given skyrocketing prices of some patented new medicines introduced onto the market and the consequences of those prices on public health expenses in all EU countries, it might be opportune for EU policy makers, to consider measures to better balance dual objectives to "cover investments put into research" and "to take public health interests into account," as outlined in the SPC Regulation.

does not exist is not possible in the absence of a voluntary licence or a compulsory licence for export.⁴¹ The main objective of this waiver is to remove the competitive disadvantages of EU-based manufacturers of generics and biosimilars in non-EU markets where protection does not exist or has expired.

While this measure will certainly have a positive effect on the growth of the EU generic industry, it fails to address the question of whether an SPC is justified for any newly approved medicine protected by a basic patent. The amendment of the SPC Regulation to enable the grant of SPCs based on the Unitary patent may offer such an opportunity.

⁴⁰ The Bolar exemption is governed by European Directive 2001/83/EC on the Community Code relating to medicinal products for human use, as amended by European Directive 2004/27/EC, particularly Article 10 thereof. Article 10 (6) excludes from infringement of patent rights or supplementary protection certificates (SPCs): "Conducting the necessary studies and trials with a view to the application of paragraphs 1, 2, 3 and 4." Paragraphs 1-4, i.e. Articles 10 (1)-(4) of the Directive, concern the provision of data during the marketing approval process.

⁴¹ 'Special Uses of Compulsory Licences for Export of Medicines, or "Article 31 bis" (*Medicines Law & Policy*) <https://medicineslawandpolicy.org/tools/special-compulsory-licences-for-export-of-medicines/>.

Conclusions and recommendations

SPCs are not dependent on the revenue or profit a pharmaceutical company obtains from a given product. The calculation of the SPC extension is exclusively awarded based on the time elapsed between the patent filing date and the market authorisation date to ensure that medicinal products have 15 years of exclusive market protection. But is that justifiable in the case of blockbuster products such as Humira, an arthritis treatment that generated sales of more than USD 16bn in 2016 alone⁴²?

Recent analysis and reports indicate that the Regulation has been used opportunistically as a tool to maximise exclusivity rents whenever the effective market protection is less than 15 years exclusivity, without clear evidence that such exclusivity is systematically necessary "to cover the investment put into the research."

Given skyrocketing prices of some patented new medicines introduced onto the market and the consequences of those prices on public health expenses in all EU countries, it might be opportune for EU policy makers to consider measures to better balance *dual* objectives to "cover investments put into research" and "to take public health interests into account," as outlined in the SPC Regulation. The initial objectives of the Commission were to create a "system effective and appropriate for the Industry's requirements without neglecting other substantial aspects of national and Community health policy."⁴³

Medicines Law & Policy therefore makes the following recommendations:

1. Make granting of SPCs conditional on applicants providing evidence that "the period of effective protection under the patent [is] insufficient to cover the investment put into the research." Upon application for an SPC, applicants would be required to provide patent offices with data on all past and future development costs, excluding public funding, and expected revenues.⁴⁴ Such data could be made public to increase transparency and trust in the system. If an SPC is granted, patent owners would be required to submit return on investment data either on a yearly basis, or at the latest, six months before the entry into force of the SPC, so that the need of the SPC could be confirmed based on actual reported profits. If the period of effective patent protection was sufficient to cover the investments put into the research programme that launched the medicine, the SPC would be cancelled.

⁴² Alex Philippidis, 'The Top 15 Best-Selling Drugs of 2016' (*Genetic Engineering & Biotechnology News*, 6 March 2017) <http://www.genengnews.com/the-lists/the-top-15-best-selling-drugs-of-2016/77900868>.

⁴³ Commission Explanatory Memorandum (n 2).

⁴⁴ In the context of orphan medicinal product protection, a European Commission notice indicates that 'sufficient return' will be assessed "...on the basis of all past and future development costs and expected revenues": Commission Notice on the Application of Articles 3, 5 and 7 of Regulation (EC) No 141/2000 on Orphan Medicinal Products [2016] C424/03.

- 2. Alternatively, make the entry into force of an SPC subject to review six months before the expiration of the basic patent. Patent owners would be required to provide patent offices with full data of development costs of the related programme, excluding public funding, and of reported profits during the effective period of patent protection.¹ Review of such data six months before the expiration of the patent would confirm whether the period of effective protection under the patent needs to be supplemented by the SPC or not.
- 3. Give third parties an opportunity to submit "observations" to the patent office to pre-empt the entry into force of an SPC based on evidence, from actual reported profits, that the period of effective protection under the patent was sufficient to cover the investment put into research.
- 4. Make procedures to revoke a granted SPC, modelled on opposition procedures against patents, available in all EU countries. Such procedures, which are currently lacking in many countries, could include an extra ground of sufficient return on investments to challenge the SPC.
- 5. Tie the entry into force of an SPC to a requirement on pricing. For example, a company could benefit from extra years of protection if it both demonstrated that extra protection is necessary to cover R&D investment and that the product is affordable during the protection period.

Medicines Law & Policy

Data Exclusivity in the EU: Briefing Document

Medicines regulation and test data

A pharmaceutical company that wants to sell a new medicine needs a marketing approval for that product from a medicines regulatory authority. Regulatory agencies require drug companies to submit test data that shows efficacy, safety and quality of the medicine they want to put on the market. Assuring efficacy, safety and quality of medicines, be it innovative products or generic medicines, is an important public service meant to protect consumers and patients.

The European Medicines Agency (EMA) is responsible for the assessment of the applications made through the centralised procedure for marketing authorisation of new medicines in the European Union (EU).¹ The EU pharmaceutical regulation also has a decentralised and national procedure for

A data exclusivity regime creates strong monopolies that are automatically granted, quietly enforced by the medicines regulatory system and without exceptions or limitations.

obtaining marketing approval in EU member states. However, the centralised procedure through the EMA is compulsory for medicines for the treatment of HIV, cancer, diabetes, neurodegenerative diseases, auto-immune and other immune diseases, viral diseases, biotechnology products, advanced therapy medicines (e.g. gene therapy), and orphan medicinal products. The EMA has thus become the predominant route for obtaining marketing approval of new medicines in the EU.

A generic company applying for marketing authorisation for a generic product has to demonstrate that its product is bioequivalent to the originator product but is not required to generate its own clinical efficacy and safety data. For that, the generic company can make reference to the clinical test data that was submitted by the original applicant and which is on file with the regulatory agency. Also, applicants for biosimilar medicines (generic biologic medicines) can refer to data in the originator file. They are required to demonstrate through comprehensive **comparability studies**

¹ For information about regulatory requirements in the EU, see here: European Medicines Agency, 'Marketing Authorisation' <https://www.ema.europa.eu/en/human-regulatory/marketing-authorisation> and European Medicines Agency and the European Commission, 'Biosimilars in the EU: Information Guide for Healthcare Professionals' (2017) <https://www.ema.europa.eu/en/documents/leaflet/biosimilars-eu-information-guide-healthcare-professionals_en.pdf>.

(clinical and non-clinical) with the 'reference' biological medicine that the biosimilar medicine is highly similar to the reference biologic medicine and that there are **no clinically meaningful differences** in terms of safety, quality and efficacy. A biosimilar product can rely on the safety and efficacy experience gained with the reference medicine. This avoids unnecessary repetition of clinical trials already carried out with the reference medicine, which is costly and would be considered unethical.

Protection of test data

Most countries protect 'test data' against unfair commercial use. There are different ways in which undisclosed test data can be protected, including: protecting it against dishonest commercial practices, but allowing its use to register a generic product,² permitting generic reliance on the test data but with compensation to the entity that originally generated the data³ (one can call this a 'data compensation' regime); or denying generic reliance on the data by making its use exclusive to the originator (a 'data exclusivity' regime).

Increasingly, the protection of test data has taken the form of 'data exclusivity' whereby a generic company for a certain period of time cannot rely on or refer to another company's clinical test data when registering a generic product. Data exclusivity provisions can result in delayed generic entry into the market.

The idea behind data exclusivity is that the production of such data – by running, for example, clinical trials – requires significant investments. Protecting it against use by generic companies is thus seen as a means to encourage medical research and development (R&D). Data exclusivity was first introduced in the US in 1984 with the *"Drug Price Competition and Patent Term Restoration Act of 1984,"* also known as the Hatch-Waxman Amendments. The act provided several types of additional exclusivities to innovators as trade-offs for provisions to make market entry of generics easier and quicker.⁴

The global agreement on the protection of intellectual property, the World Trade Organization (WTO)'s Agreement on Trade-Related Aspects of Intellectual Property Rights (TRIPS), contains an obligation of WTO members to protect certain kinds of test data against unfair commercial use, but only where that data is related to new chemical entities, previously undisclosed, required as a condition of marketing approval, and required considerable effort to generate.

² Carlos Correa, 'Protection of Data Submitted for the Registration of Pharmaceuticals: Implementing the Standards of the Trips Agreement' (2002) South Centre http://apps.who.int/medicinedocs/en/d/Jh3009ae/.

³ For example, in the US, Knowledge Ecology International has proposed a cost sharing model. See for details: Judit Rius Sanjuan, James Love, and Robert Weissman, 'Protection of Pharmaceutical Test Data: A Policy Proposal' (2006) KEI Research Paper 2006:1.

⁴ Erika Lietzan, 'The Myths of Data Exclusivity' (2016) 20 Lewis & Clark L Rev 91.

TRIPS, section 7, article 39.3 reads as follows:

Members, when requiring, as a condition of approving the marketing of pharmaceutical or of agricultural chemical products which utilize new chemical entities, the submission of undisclosed test or other data, the origination of which involves a considerable effort, shall protect such data against unfair commercial use. In addition, Members shall protect such data against disclosure, except where necessary to protect the public, or unless steps are taken to ensure that the data are protected against unfair commercial use.

The TRIPS provision for the protection of undisclosed test data therefore does not require protection under a data exclusivity regime, neither does it preclude the use of the data for the approval of a competing product, which, as some have argued, does not fall within the definition of 'unfair commercial use'.^{5,6,7} In this context it is relevant to note that TRIPS negotiators explicitly rejected language that would have required granting exclusive rights to test data and that would have prohibited the use of the data by the government to fulfil its public health functions.⁸ This position was repeated by developing country members of the WTO in 2001 at the Doha Ministerial where they stated article 39.3 "does not require granting 'exclusive rights' to the owner of the data" and that it "does permit a national competent authority to rely on data in its possession to assess a second and further applications, relating to the same drug, since this would not imply any 'unfair commercial use'."⁹

Indeed, the vast majority of WTO members do not provide data exclusivity. A survey of the MedsPaL¹⁰ database shows that only around 16 middle-income countries provide data exclusivity, and that these data exclusivity regimes find their origin in trade agreements with the EU or the US that were reached outside of the WTO.

In the EU, however, the obligation to grant data exclusivity to the originator company goes well beyond the TRIPS requirement¹¹ for the protection of undisclosed test data against unfair commercial use. For a certain period of time a generic company cannot rely on or refer to pre-

⁵ Jerome H Reichman 'The International Legal Status of Undisclosed Clinical Trials Data: From Private to Public Goods?' (2009) 13 Marquette Intellectual Property L Rev 17.

⁶ Karin Timmermans, 'Monopolizing Clinical Trial Data: Implications and Trends' (2007) 4 PLoS Med e2.

⁷ Commission on Intellectual Property Rights, Innovation and Public Health, Public Health, Innovation and Intellectual Property Rights (World Health Organization 2006).

⁸ Correa (n 2).

⁹ 'TRIPS Council Discussion on Access to Medicines: Developing Country Group's Paper' (*World Trade Organization*, 20 June 2001) IP/C/W/296, paras 39–40 <https://www.wto.org/english/tratop_e/trips_e/paper_develop_w296_e.htm>.

¹⁰ 'MedsPaL: The Medicines Patents and Licences Database' https://www.medspal.org.

¹¹ During the Uruguay Round negotiations, the option of making data exclusivity an explicit obligation under the TRIPS Agreement was discussed, but negotiators instead adopted the general wording of the current Article 39.3. See: WTO, WIPO, and the WHO, *Promoting Access to Medical Technologies and Innovation* (2012) 64 https://www.wipo.int/policy/en/global_health/trilateral_cooperation.html.

clinical and clinical test data of the original manufacturer that demonstrate safety and efficacy of the compound for which it wants to obtain a marketing authorisation.

Data exclusivity rules do not prohibit the generic company from generating its own clinical efficacy data to circumvent data exclusivity, but this is costly and, in most cases, would raise serious ethical issues. Such tests may involve carrying out clinical studies with an already proven effective compound. The reality is that generic companies do not carry out such trials.

Therefore, a data exclusivity regime creates strong monopolies that are automatically granted, quietly enforced by the medicines regulatory system and without exceptions or limitations.

Data exclusivity in the EU: A tale of regulatory capture

EU's adoption of its generous data exclusivity regime is a tale of regulatory capture.¹² Data exclusivity was first introduced in the EU in 1987 after intense lobbying by the pharmaceutical industry that cited the need to protect European

The EU has the most generous data exclusivity regime globally. The adoption of this generous regime is a tale of regulatory capture.

R&D. Directive 87/21/EEC initially provided for six years of data exclusivity for most medicines from the first marketing approval and ten years for biotech products. Member states could extend data exclusivity to 10 years if they considered this was "in the interest of public health."

This led to diversity in data exclusivity regimes in different European countries. Importantly, the system allowed member states not to apply the six-year period beyond the date of expiry of a patent protecting the original product.

When data exclusivity was introduced in the EU, pharmaceutical patenting was also diverse in the different member states. For example, Greece, Spain and Portugal did not provide pharmaceutical product patents. In 1992, the EU introduced the Supplementary Protection Certificate (SPC), providing up to 5 years of additional patent protection for medicines. But the SPC only had effect in countries that had medicines patents and not yet in countries that had no medicines patent protection or had only recently introduced it. In this context, data exclusivity was seen as a partial remedy for what the industry saw as weak patent protection.¹³

The global harmonisation of patent rules through the General Agreement on Tariffs and Trade (GATT) negotiations that led to the 1994 establishment of the WTO and the adoption of the WTO TRIPS Agreement, as well as further European integration, strengthened medicines patenting in

¹² Sandra Adamini and others, 'Policy Making on Data Exclusivity in the European Union: From Industrial Interests to Legal Realities' (2009) 34 Journal of Health Politics, Policy and Law 979.

¹³ Cynthia Ho, 'Beyond Patents: Protecting Drugs Through Regulatory Laws' in Access to Medicine in the Global Economy: International Agreements on Patents and Related Rights (OUP 2011).

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European countries. One would expect that the introduction of strong patent regimes throughout the EU would slow down the drive for additional market exclusivities for medicines. It did not.

In 2004 the EU data exclusivity rules were further harmonised upwards and extended from the minimum of six years to eight years of data exclusivity, plus two years market exclusivity during which generic companies can prepare and apply for their marketing approval but not market the product. An additional one year of market exclusivity can be obtained by the originator company for a new indication with significant added clinical benefit. The new EU exclusivity regime became known as the 8+2+1 rule. It is the most generous exclusivity regime globally and extends to small molecules and biologic products.¹⁴ By contrast, the US grants five years of exclusivity for small molecule new chemical entities, three years for a new indication of a previously approved medicine and four years for biologics (complemented by a parallel 12-year market exclusivity). Japan grants six years of data exclusivity.

	WTO TRIPS	United States	European Union
Data protected	Undisclosed data that involved considerable effort to generate and of which the submission is required for marketing approval	Not specified	Not specified
Scope of protection	Against unfair commercial use and against disclosure	Grant of exclusive rights. No use/disclosure/reliance permitted	Grant of exclusive rights. No use/disclosure/reliance permitted
Type of drug	Limited to new chemical entities (NCEs)	NCEs and new indications/new uses	New medicinal product and new indications/new uses
Protection period	Not specified	5 years for NCEs + 3 years market exclusivity for new indications In parallel, 12 years for biologics	8 years data exclusivity + 2 years market exclusivity + 1 year market exclusivity for new indications

Table 1: A comparison of data exclusivity regimes

Adapted from Consumer Project on Technology, 12 April 2006.

¹⁴ Directive 2004/27/EC on the Community code relating to medicinal products for human use [2004] OJ L136/34. ¹⁵ Judit Rius Sanjuan, 'U.S and E.U Protection of Pharmaceutical Test Data' (CP Tech Discussion Paper – No. 1, 12 April 2006) < http://www.cptech.org/publications/CPTechDPNo1TestData.pdf>.

Practical consequences of data exclusivity in the EU

During the period of data exclusivity in the EU, no generic competitor product can be considered for registration.

The originator company maintains a market monopoly until the generic company can bring a generic product to market in the EU, which it can only do when it obtains a marketing authorisation from the EMA. The application for an authorisation cannot be considered by the EMA until eight years of data exclusivity has passed. And the generic company cannot bring the product to market until at least two additional years of market exclusivity have passed, providing the originator company with 10 years of market exclusivity. This market exclusivity is regardless of the patent status of the product and is regulated in the European pharmaceutical legislation. Companies can thus obtain a strong market monopoly position with a product that is not patented using the data exclusivity provisions of the pharmaceutical regulation.

Does data exclusivity stimulate innovation?

The stated objective of data exclusivity is to encourage innovation by protecting clinical test data from use by others than the originator company. The evidence that such additional exclusivity is indeed required is not at all clear. After all, data exclusivity generally co-exists with other forms of exclusivity such as patents or SPCs. The Dutch Technopolis Group report¹⁶ concluded that "this study cannot provide any evidence on whether, or to what extent, the impacts of these exclusivities and protections align with the intended objectives." Earlier, in 2009, the US Federal Trade Commission (FTC) concluded that a lengthy exclusivity period (12 to 14 years) is unnecessary to promote innovation by biologic drug manufacturers. The FTC considered existing incentives (patents and market-based pricing) to be sufficient to support biologic innovation.¹⁷

Data exclusivity: rock solid monopoly

In the case of patents, governments can rely on flexibilities in patent law to make use of the patent without the consent of the patent holder. Such an intervention by the government can be based on the need to act in the public interest.

Even in case of an urgent need or an emergency situation, the EU law fails to provide a safety valve to release the stronghold of data exclusivity

¹⁶ Thyra de Jongh and others, 'Effects of Supplementary Protection Mechanisms for Pharmaceutical Products' Final Report (*Technopolis Group*, May 2018) http://www.technopolis-group.com/wp-content/uploads/2018/06/2718-Technopolis-report-on-supplementary-protection-mechanisms.pdf>.

¹⁷ U.S. Federal Trade Commission, 'Emerging Health Care Issues: Follow-on Biologic Drug Competition' (*FTC*, June 2009) https://www.ftc.gov/sites/default/files/documents/reports/emerging-health-care-issues-follow-biologic-drug-competition-federal-trade-commission-report/p083901biologicsreport.pdf

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For example, when a patent forms a barrier to accessing a lower priced generic medicine and the originator product is priced too high, well above the country's willingness to pay. These flexibilities have been acknowledged in the 2001 WTO Doha Declaration on TRIPS and Public Health as important tools to promote and protect access to medicines for all.

A number of European governments including Belgium, Ireland, France, the Netherlands, Norway, Scotland, Spain, Sweden, Switzerland and the UK have been asked and/or are considering to issue compulsory licences for important medicines including treatments for hepatitis C and cancer that are not available at affordable prices for their health care systems. In principle, these countries have the required provisions for compulsory licensing or government use of patents in their patent legislation. But when it concerns medicines for which marketing approval has been obtained through the centralised procedure at the EMA, it may not be possible to give effect to the compulsory licence.

The reason for this is that EU data exclusivity bars any generic or biosimilar from being registered for a period of 10 years after the originator is registered, and data exclusivity holds even when a patent has expired or when a compulsory licence has been issued. When products fall within the category for which EMA registration is compulsory, the national procedure for registration is not an option.

In the EU, safeguards to lift the effect of data and/or market exclusivity when this forms a barrier to accessing a needed medicine do not exist. Even in case of an urgent need or an emergency situation the EU law fails to provide a safety valve to release the stronghold of data exclusivity. This became apparent in 2006 when the European Generic Medicines Association was seeking clarification on whether data exclusivity would apply in case of an emergency compulsory licence for the flu medicine Tamiflu (oseltamivir) within the European Union.

In response, the European Commission acknowledged that the "Community pharmaceutical acquis does not currently contain any provision allowing a waiver of the rules on data exclusivity and marketing protection periods."¹⁸ The European Commission, however, has yet to take initiative to propose an explicit waiver in the EU pharmaceutical legislation to allow effective use of compulsory licensing for production and supply within the EU.

¹⁸ European Commission, 'Letter from the European Commission to Mr Greg Perry, EGA-European Generic Medicines Association on the subject of Tamiflu application and data exclusivity in an emergency compulsory license situation' (Brussels, 2006).

Box 1: Case study, access to sofosbuvir in Romania

Access to hepatitis C medicines in Romania

In 2016, the government of Romania contemplated issuing a compulsory licence for the hepatitis C medicine sofosbuvir, which in Europe was only available from the originator company at a price of around \in 50,000 for a 12-week treatment.¹⁹ By contrast, generic sofosbuvir-ledipasvir has been available in Egypt, where there are no patents on the compound, for US\$ 400 for a full treatment.²⁰

However, the registration of a generic version of sofosbuvir in the EU is not possible before the expiry of the data exclusivity in 2022. Further, the EU market exclusivity for sofosbuvir expires at the earliest in 2024. As a result, Romania, like any other EU member state, cannot give effect to a compulsory licence. The case of Romania reveals the obstacles to the effective use of compulsory licensing created by EU data and market exclusivity.

Lack of legal coherence

Twelve years later, the EU pharmaceutical legislation still does not provide for exceptions to data and market exclusivity. Even in cases of national emergency or other situations of urgency, there are no explicit waivers in EU law to address the need to authorise the marketing of a generic product before the aforementioned exclusivity periods expire.

Even though issuing a compulsory licence to overcome patents blocking the use of a generic medicine is a matter of national law, regulatory requirements for EU-wide marketing authorisation, including data exclusivity, are a matter of European Union pharmaceutical legislation. These concurrent legal systems lack coherence, both with regards to the effective use of compulsory licensing by EU member states and with respect to public interest exceptions to data exclusivity more broadly.

The need to provide data exclusivity waivers to ensure effective availability of generic medicines is often acknowledged in voluntary licences. For example, all Medicines Patent Pool (MPP) licences include a data exclusivity waiver to facilitate regulatory approval of generic medicines manufactured by MPP's licensees.²¹

¹⁹ Paun C. Skyhigh, 'Drug Prices Made Romania Mull Patent Break' (*Politico*, 16 March 2016)

<http://www.politico.eu/pro/high-drug-prices-romania-changes-patents-hepatitis/>.

²⁰ Isabelle Andrieux-Meyer and others, 'Disparity in Market Prices for Hepatitis C Virus Direct-Acting Drugs' (2015) 3 The Lancet Correspondence E676.

²¹ See for example: 'Licence Agreement Between VIIV Healthcare Company and the Medicines Patent Pool Foundation' (*Medicines Patent Pool*, 2014) https://medicinespatentpool.org/uploads/2017/07/ViiV-MPP-Head-Licence-DTG-Paediatrics-Amendment-21032019-Web-page.pdf >.

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Waivers to data exclusivity and market exclusivity rules do exist when medicines manufactured using a compulsory licence and destined for markets outside the EU, via the *EU Regulation on compulsory licensing of patents for the manufacture of pharmaceutical products for export to countries with public health problems outside the EU.*^{22,23} Article 18 of the *EU Regulation* addresses the situation in which the applicant for a compulsory licence for manufacture and export of a medicine outside the EU may use the scientific opinion procedure of the European Medicines Agency (EMA), or any similar national procedures, to assess quality, safety, and efficacy of medicines intended exclusively for markets outside the EU. It provides waivers to exclusivity rules necessary to obtain such opinions from the EMA or national authorities.²⁴

Some WTO member countries, such as Chile, Colombia, and Malaysia provide for explicit data exclusivity waivers in medicines regulations or in relation to the use of compulsory licences in patent laws, for the purpose of facilitating generic medicines registration and sales where necessary to protect public health. While US law does not provide for an explicit exception to data exclusivity, the 2007 New Trade Policy of the US authorised an express public health exception to data and market exclusivity in the event of a compulsory licence or other public health need.²⁵

Professor Valérie Junod from the University of Geneva has argued in support of the application for a compulsory licence for the breast cancer drug pertuzumab (Perjeta) in Switzerland that the issuance of a compulsory licence for public interest reasons creates the obligation for the patent holder to provide a waiver to data exclusivity. Such a waiver would enable the use of test data for the registration of the generic product. She maintains that if a company holding a dominant position in the market denies access to the data held by the Swiss regulatory authority, it is likely to be viewed as abusive under Swiss competition law since a court has already decided that the public interest requires an additional product on the market.²⁶ However, enforcing this position will likely

²² Regulation 816/2006 on Compulsory Licensing of Patents Relating to the Manufacture of Pharmaceutical Products for Export to Countries with Public Health Problems [2006] OJ L157/1.

²³ This regulation implements the WTO 'August 30 2003 decision', which provided a waiver to the TRIPS Article 31(f) requirement that production under a compulsory licence be predominantly for the domestic market. This restriction seriously hampered the use of compulsory licensing by countries that were dependent on the importation of medicines. The 30 August 2003 waiver became a permanent amendment of the TRIPS Agreement in 2017 (see: WTO, 'WTO Members Welcome Entry Into Force of Amendment to Ease Access to Medicines' (30 January 2017) https://www.wto.org/english/news_e/news17_e/heal_30jan17_e.htm>.

²⁴ Article 18(2) (n 22) reads: 'If a request for any of the above procedures concerns a product which is a generic of a reference medicinal product which is or has been authorised under Article 6 of Directive 2001/83/EC, the protection periods set out in Article 14(11) of Regulation (EC) No 726/2004 and in Articles 10(1) and 10(5) of Directive 2001/83/EC shall not apply'.

²⁵ U.S. House Ways and Means Committee, 'A New Trade Policy for America' (*Bilaterals*, 2007) http://www.bilaterals.org/IMG/pdf/07_05_10_New_Trade_Policy_Outline.pdf>.

²⁶ Valérie Junod, Legal Analysis: The Interface Between Patent Protection and Data Exclusivity – The Issue of Compulsory Ilcensing in the Public Interest under Swiss Law' (*Public Eye*, 29 January 2019)

<https://www.publiceye.ch/fileadmin/doc/Medikamente/ValerieJunod_Legal-Analysis-CL_20190129.pdf>

lead to protracted legal procedures and delays in the availability of the medicine for which the compulsory licence was requested.

One could argue that, because waivers to data exclusivity and market exclusivity exist for compulsory licensing for the manufacture of pharmaceutical products *for export*, it would logically follow that such waivers can also be applied in other compulsory licensing situations. It would nevertheless be desirable to take away any legal uncertainty. Therefore, it would be preferable to introduce explicit data and market exclusivity waivers in the EU pharmaceutical regulation to enable national governments to use non-voluntary licensing effectively to intervene in high drug pricing when necessary.²⁷

This is particularly important now that European countries have indicated that they lack the negotiating power to obtain good results in price negotiations with pharmaceutical companies concerning patented products.²⁸ Table 2 shows the wide discrepancies between list price and target prices (based on cost of production) of selected important products demonstrating the potential gains health ministers can make when they can lift the monopoly effect of patents.

Strategic role of data/market exclusivity

Because of the 20-year patent term plus up to 5 years additional protection via SPC (see previous paper in this briefing series, on SPCs), the data exclusivity period for the product has usually expired before other exclusivities expire, which leads to the question whether the data exclusivity system might be obsolete. Industry is keen to maintain it but their main driver seems to be strategic: create as many layers of exclusive rights as possible to discourage competitors to enter the market. As a result, it may leave weak patents unchallenged because why would a generic company undertake a patent opposition when it knows in case of success it will still not be able to register the product until after the data exclusivity and market exclusivity periods have expired. Further, market exclusivity for example granted through the orphan medicinal product regulation creates similar problems (see also the following paper in this briefing document series, on orphan medicinal product regulation).

²⁷ Ellen FM 't Hoen, Pascale Boulet, and Brook K Baker, 'Data Exclusivity Exceptions and Compulsory Licensing to Promote Generic Medicines in the European Union: A Proposal for Greater Coherence in European Pharmaceutical Legislation (2017) 10 JOPPP.

²⁸ Emma Rumney, 'Drug Manufacturers Have Too Much Power in Price Negotiations, Says OECD' (*Public Finance International*, 16 January 2017) http://www.publicfinanceinternational.org/news/2017/01/drug-manufacturers-have-too-much-power-price-negotiations-says-oecd.

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The EU promotes data exclusivity with its trading partners, for example through demanding the introduction or strengthening of data exclusivity in trade agreements with other nations. See Box 2 on Ukraine-EU Trade Agreements, below. The EU is also demanding the introduction of data exclusivity in trade negotiations with the Latin American trading bloc Mercosur (Argentina, Brazil, Paraguay and Uruguay). Currently none of the countries provide data exclusivity.

Cancer medicines		
Medicine	Lowest-highest list prices in EU	Target price
Bortezomib ²⁹ Multiple myeloma	\$982 (Spain) - \$1,123 (UK) per month**	\$255 per month**
Dasatinib ²⁹ Chronic myeloid Ieukaemia	\$2,146 (UK) - \$3,624 (Latvia) per month**	\$12 per month**
Everolimus ²⁹ Breast cancer	\$3,155 (UK) - \$3,958 (Latvia) per month**	\$1,086 per month**
Gefitinib ²⁹ Lung cancer	\$1,786 (France) - \$2,568 (Latvia) per month**	\$13 per month**
Imatinib ³⁰ Chronic myeloid Ieukaemia	\$2,261 (Latvia) - \$32,906 (Spain) per year	\$172 per year
Erlotinib ³⁰ Lung, pancreatic and other cancers	\$26,416 (France) - \$36,678 (Latvia) per year	\$240 per year
Lapatinib ³⁰ Breast cancer	\$33,549 (Spain) - \$49,887 (Latvia) per year	\$4,020 per year
Sorafenib ³⁰ Kidney and liver cancer	\$45,162 (France) - \$67,877 (Latvia) per year	\$1,450 per year

Table 2: List prices versus target prices (based on production cost) of select medicines

²⁹Andrew Hill et al, 'Estimated generic prices of cancer medicines deemed cost-ineffective in England: a cost estimation analysis' (*BMJ Open*, 2017) <https://bmjopen.bmj.com/content/7/1/e011965>

³⁰ Andrew Hill et al, 'Target prices for mass production of tyrosine kinase inhibitors for global cancer treatment' (*BMJ Open*, 2015) https://bmjopen.bmj.com/content/6/1/e009586

Human Immunodeficiency Virus (HIV) and Hepatitis C Virus (HCV) medicines				
Medicine (Indication)	List price/pill in the UK	Target price/pill	Current price/ treatment in the UK	Target price/treatment
Daclatasvir ³¹ (HCV)	\$379.44	\$0.08	\$31,872.96 *	\$6.72*
Darunavir ³¹ (HIV)	\$12.90	\$1.45	\$387 a month*	\$43.50 a month*
Efavirenz + emtricitabine + tenofovir ³¹ (HIV)	\$23.09	\$0.15	\$692.70 a month*	\$4.50 a month*
Ledipasvir + sofosbuvir ³¹ (HCV)	\$603.26	\$1.02	\$50,673.84*	\$85.68*
Sofosbuvir ³¹ (HCV)	\$541.40	\$0.57	\$45,477.60*	\$47.88*
Tenofovir disoproxil fumarate (TDF) ³¹ (HIV)	\$8.85	\$0.07	\$265.50 a month*	\$2.10 a month*

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*HCV dosage assumes 1 pill/day for a 12-week regimen; HIV dosage assumes 1 pill/day over 1 month (30 days) **Converted from British pounds to USD using May 2019 conversion rates

Concerns about such demands were also made with regards to trade negotiation with India, which prompted the European Commission (EC) Trade Commissioner to commit to 'not pursue the issue of supplementary protection any longer', and to 'not require India to introduce any kind of data exclusivity provisions.'32 The Commissioner also stated that the negotiation with India should be conducted in the spirit of the Doha Declaration on the TRIPS Agreement and Public Health, and that protecting access to medicines should be taken fully into account in future trade negotiations.³³

Today the EU's objective with regards to intellectual property in trade talks remains to obtain similar levels of intellectual property protection in countries outside the EU as are maintained inside the EU.³⁴ For example, the EU–Vietnam trade and investment agreement binds Vietnam to introduce data exclusivity of at least 5 years.³⁵

³¹ Andrew Hill, Melissa Barber, and Dzintars Gotham, 'Estimated costs of production and potential prices for the WHO Essential Medicines List' (BMJ Global Health, 2018) https://gh.bmj.com/content/3/1/e000571>. Figures come from supplementary appendix.

³² European Commission, 'Q&A on Access to Medicines for EU-India Free Trade Agreement Negotiations' (April 2013).

³³ 'EC Trade Commissioner's response to MSF Letter on India-EU FTA' (MSF Access Campaign, 24 May 2010) <https://msfaccess.org/ec-trade-commissioners-response-msf-letter-india-eu-fta>.

³⁴ European Commission 'Intellectual Property' (9 July 2018) http://ec.europa.eu/trade/policy/accessing- markets/intellectual-property/>.

³⁵ 'Chapter 12: Intellectual Property' (September 2018).

<http://trade.ec.europa.eu/doclib/docs/2018/september/tradoc_157370.pdf>.

Box 2: The impact of data exclusivity provisions in trade agreements, Ukraine case study

Ukraine-EU Trade Agreement's effect on access to hepatitis C medicine

The Doha Declaration did not guide the trade talks between the EU and Ukraine. As a result of the EU-Ukraine Deep and Comprehensive Free Trade Agreement (DCFTA), Ukraine introduced fiveyear data exclusivity period for medicines. This introduction had an immediate effect on the treatment of hepatitis C in the country. Sofosbuvir, an essential medicine for the treatment of hepatitis C, was not patented in Ukraine. The Egyptian company Pharco was the first to apply for marketing authorisation for a generic version of sofosbuvir on 28 November 2014 (via its distributor Europharma International LLC). Later, the originator company, Gilead, applied for marketing authorisation on 9 June 2015 but was the first to obtain marketing authorisation on 9 October 2015. On 18 November 2015, Pharco also received marketing authorisation. In June 2016, Gilead filed a court case against Pharco's distributor in Ukraine and against the regulatory agency on the grounds that it was entitled to data exclusivity until 2020. Gilead also threatened with an investor state dispute. In response to this threat, the Ukraine government revoked Pharco's generic registration and established Gilead's monopoly position in the market.

Data exclusivity and the cost of R&D

One argument for the protection of test data is the need to protect the monetary investment that the company has to make to generate the data. It is true that developing a new medicine, particularly a new chemical entity, is costly and that a significant part of this cost is made up of the expenses for clinical studies. But the principle ignores the contribution by others. Most significant pharmaceutical innovations lean on earlier publicly funded research and it also ignores investment made by patients that take part in the trials.^{36,37} data exclusivity is granted regardless of the level of investment in generating the test data required to obtain a marketing authorisation for a medicine. Greater transparency with regards to the development cost would help to determine reasonable remuneration for the research efforts made. Cost of R&D can differ tremendously per product, and type of development, yet the incentive systems are based on a one size fits all (see Table 3, below).

³⁶ UCL Institute for Innovation and Public Purpose, 'The People's Prescription: Re-Imagining Health Innovation to Deliver Public Value' (2018) IPP Policy Report 2018-10 <https://www.ucl.ac.uk/bartlett/public-

purpose/publications/2018/oct/peoples-prescription>.

³⁷ Ekaterina Galkina Cleary and others, 'Contribution of NIH Funding to New Drug Approvals 2010-2016' (2018) 115 PNAS 2329.

Medicine (Manufacturer)	Indication	Total R&D costs, in US\$ millions*
Eculizumab (Alexion Pharmaceuticals) ³⁸	Oncology (orphan status)	\$817.6
Pralatrexate (Allos Therapeutics) ³⁸	Oncology (orphan status)	\$178.2
Ruxolitinib (Incyte Corporation) ³⁸	Oncology (orphan status)	\$1097.8
Enzalutamide (Medivation) ³⁸	Oncology (no orphan status)	\$473.3
Cabozantinib (Exelixis) ³⁸	Oncology (orphan status)	\$1,950.8
Ibrutinib (Pharmacyclics) ³⁸	Oncology	\$328.1
Fexinidazole (DNDi) ³⁹	Sleeping sickness	\$62.1
SCYX-7158 (DNDi) ³⁹	Sleeping sickness	\$66.9
Sodiumstibogluconate & paramomycin combination (DNDi) ³⁹	Visceral leishmaniasis	\$13.0
Nifurtimox-eflornithine combination therapy (NECT) (DNDi) ³⁹	Sleeping sickness	\$7.6

Table 3 Costs of R&D by type of product, for selected medicines

*These prices do not include the cost of failed formulations, which often goes into aggregated figures. The Drugs for Neglected Diseases Initiative (DNDi) estimates that if cost of failed candidates is included, it could bring a new chemical entity to market for between US\$ 110-170 million.

³⁸ Vinay Prasad and Sham Mailankody, 'Research and Development Spending to Bring a Single Cancer Drug to Market and Revenues After Approval' (JAMA Internal Medicine, 2017)

< https://jamanetwork.com/journals/jamainternalmedicine/fullarticle/2653012>.

³⁹ Amy Maxmen, 'Big Pharma's Cost-Cutting Challenger' (*Nature: News Feature,* 2016)

https://www.nature.com/polopoly_fs/1.20469!/menu/main/topColumns/topLeftColumn/pdf/536388a.pdf>

Conclusions and recommendations

In light of the growing drug price crisis including for non-patented medicines, a revision of the EU rules on data exclusivity is warranted. Such revision should account for the fact that the generous EU data and market exclusivity regime has its roots in an historical situation of diverse medicines patenting and data protection practices by member states. A situation that no longer exists. The EU has no obligations under international law to maintain its data exclusivity regime: the WTO TRIPS Agreement allows for a generic reliance model whereby the generic company can rely on the test data of the originator in exchange for compensation. One should also acknowledge that other high-income nations provide far less data exclusivity than the EU. Further, data exclusivity threatens to stifle the effectiveness of public policy tools such as government use of patents which contravenes the "Doha norm" that the TRIPS Agreement does not and should not prevent governments from taking measures to protect public health.

Medicines Law & Policy therefore makes the following recommendations:

1. Replace the data exclusivity regime with a data compensation regime. Replace the EU data exclusivity regime with a data protection regime that acknowledges the investment that goes into the generation of the data but does not allow the investor to exclude others from using the data: a *data compensation regime*. TRIPS leaves much flexibility for WTO members to design data protection regimes and such a *data compensation regime* would be compliant with the requirements for the protection of undisclosed data in the TRIPS Agreement. ⁴⁰ Under a *data compensation regime*, the registration of a generic medicine or biosimilar medicine is considered fair commercial use and thus not hampered by the data protection. The originator company that made the investment that was needed to generate the data will receive adequate remuneration for the use of the data but cannot prevent its necessary use for the medicines agency to perform its public health duties, for example using it to register generic versions.⁴¹

⁴⁰ Protection consistent with TRIPS means: to protect undisclosed test data the submission of which is required to register a new chemical entity, and the generation of which involved considerable efforts against unfair commercial use. Disclosure may only take place if necessary to protect public health or unless steps are taken to ensure that the data are protected against unfair commercial use. (TRIPS 39.3).

⁴¹ Such a provision would further advance the objective to reach greater transparency on R&D expenditure.

2. Introduce waivers to data and market exclusivity to facilitate effective use by governments of patents in the public interest, compulsory licensing or other measures needed for the advancement of public health and access to medicines for all within the European Union. This would bring coherence to EU law and assist member states that are seeking ways to ensure the availability of new medicines without undue burden on their health budgets. Legal coherence can be achieved by inserting the following provision into the EU legal framework governing medicinal products for human use:

'The protection periods set out in article 14 (11) of Regulation 726/2004 shall not apply in cases where it is necessary to allow access to and the use of pharmaceutical test data to register a generic of a reference medicinal product, which is or has been authorised under article 6 of Directive 2001/83/EC, for reasons of public interest including public health, in case of compulsory licensing of patents, including for public non-commercial use, and in situations of national emergency or extreme urgency.'

A payment of an adequate remuneration for the use of or reliance on test data to the holder of the marketing authorisation of the reference medicinal product may be required; for example, in the absence of patents and thus absence of remuneration normally payable in case of a compulsory licence or government use licence.

3. Remove the requirement to implement data exclusivity from trade negotiations with other nations and instead focus on agreements with other nations that address medical R&D needs and mechanisms for burden and benefit sharing of medical R&D.⁴²

⁴² For a discussion of how such new R&D models could be shaped, see: 'Delinkage' <www.delinkage.org>.

Medicines Law & Policy

Orphan Medicinal Products in the EU: *Briefing Document*

Introduction

A review of EU pharmaceutical intellectual property right (IPR) incentives is currently taking place.¹ This paper provides an overview of the incentives provided under Regulation 141 / 2000 to encourage the development of orphan medicinal products. Whilst conscious of the positive impact of the increased number of orphan medicinal products that have been made available since 2000, unprecedentedly high prices and consequent problems with patient access are a major cause for concern. This paper therefore includes recommendations in order to try to restore a more appropriate balance between the interests of private pharmaceutical firms and the public.

In particular, this paper notes that a public-health focussed 'withdrawal clause' was originally included in the draft Regulation, intended to protect quite specifically against pharmaceutical firms charging excessively high prices or making excessive profits. However, a subtle amendment at a late stage in the legislative process neutralised its effect almost completely. This paper therefore calls for the re-instatement of such a 'withdrawal clause' and for a long overdue discussion about what 'sufficient' profitability should mean in the context of orphan medicinal products.

History and philosophy of orphan medicinal product legislation

Up to 8,000 distinct rare diseases are already known and more are identified every year. Although they are rare in the sense that they are defined to have a prevalence of fewer than 5 patients per 10,000 of population, it is estimated that at least 30 million citizens of the European Union (> 6 % of a current population of circa 500 million) are affected by one or other of them. Some 80% of these diseases are genetic in nature, many involving defects in a single gene ('monogenic' or 'Mendelian' diseases). They can impose severe limitations on the quality and length of sufferers' lives. Study of

¹ Council conclusions on strengthening the balance in the pharmaceutical systems in the EU and its Member States [2016] C269/31. The European Council have invited the European Commission "46…to ascertain correct application of the current rules [on orphan medicinal products] and fair distribution of incentives and rewards and if necessary consider revision of the regulatory framework on orphan medicinal products without discouraging the development of medicinal products needed for the treatment of rare diseases."

these diseases is not only essential if the situation of these patients is to be improved but it is also extremely helpful in understanding disease mechanisms in a more general sense.²

These rare diseases were regarded as 'orphans' in the sense that their very small individual patient populations meant that it was not attractive for pharmaceutical firms to engage in the development of medicinal products for them. Although the public sector plays a pivotal role in providing the basic research underpinning the development of new medicinal products, governments have largely turned over the responsibility of that development to private sector pharmaceutical firms. This has the necessary but rather shocking consequence of treating diseases as 'markets'. It is entirely predictable that some disease markets will be regarded as desirably profitable, and some will not. Patients living with these rare or orphan diseases long had very little hope that the situation would improve.

The situation did change, though, in the 1970's, at least in the United States. Senator Waxman and the patients groups which together formed the National Organisation for Rare Diseases (NORD) pushed for the enactment of legislation that would encourage pharmaceutical firms to develop and market new medicines for these orphan diseases.³ It was hoped that a package of 'push' incentives (reducing the cost and uncertainty of the development of orphan medicinal products) and 'pull' incentives (increasing the likelihood of profitability once the orphan medicinal product is marketed) might nudge individual orphan disease markets over the line into profitability and encourage at least small or medium sized pharmaceutical firms (including the newly emerging biotechnology firms) to engage. The Orphan Drug Act (1983) accordingly provided a package of incentives including scientific and administrative support from the Federal Drug Administration (FDA), a 50% tax credit for research and development expenses (reduced to 25% in 2017) and a seven-year period of exclusivity for marketed orphan medicinal products. The Orphan Drug Act galvanised activity in orphan disease research and development and before long other countries enacted equivalent legislation, including Japan in 1993. For reasons both of improving the quality and length of life of EU citizens ('patients suffering from rare conditions should be entitled to the same quality of treatment as other patients') and, it has to be said, making sure that the EU was not left out in fostering new biotechnological firms, a European Union (EU) orphan medicinal products regime was established in 2000.

² See, for example, Leena Peltonen and others, 'Lessons from Studying Monogenic Disease for Common Disease' (2006) 15 Human Molecular Genetics R67.

³ The legislative history of the Orphan Drug Act is detailed in Henry A Waxman, and Joshua Green, *The Waxman Report: How Congress Really Works*, (Twelve 2009) (Senator Waxman's autobiography); and, for example, Koichi Mikami, 'Orphans in the Market: The History of Orphan Drug Policy' (2017) Social History of Medicine DOI: 10.1093/shm/hkx098.

The European Union orphan medicinal products regime⁴

Framework and incentives

The framework of the European Union (EU) orphan medicinal products regime is provided in Regulation 141 / 2000. Article 1 states that its purpose is to "...lay down a Community procedure for the designation of medicinal products as orphan medicinal products and to provide incentives for the research, development and placing on the market of designated orphan medicinal products." This procedure is operated as a centralised

The EU Regulation introduces 'push' incentives (reducing the cost and uncertainty of the development of orphan medicinal products) and 'pull' incentives (increasing the likelihood of profitability once the orphan medicinal product is marketed) intended encourage pharmaceutical firms to engage in orphan disease research.

procedure under the European Medicines Agency (EMA), rather than *via* member states.⁵ The Regulation explicitly introduces a number of 'push' and 'pull' incentives for orphan medicinal product 'sponsors' (typically pharmaceutical firms) as well as providing a framework for further incentives to be provided at a member states level.⁶ (see Table 1, below).

Designation as an orphan medicinal product

A sponsor can choose between two routes to apply for orphan designation for their medicinal product, either the:

Prevalence route

(Article 3 (1) (a)) "... that [the product] is intended for the diagnosis, prevention or treatment of a life-threatening or chronically debilitating condition affecting not more than five in 10 thousand persons in the Community when the application is made..."

Based on a current EU population of circa 500 million, a threshold prevalence of 5 / 10,000 equates to a maximum patient population of circa 250,000 for any particular orphan disease.

or the:

⁴ N.B. For an up to date summary of developments and URL links to the EC documents referenced below see European Commission, 'Orphan Medicinal Products – Major Developments' (*Europa*) https://ec.europa.eu/health/human-use/orphan-medicines/developments_en>.

⁵ The centralised EMA procedure has been mandatory since 20th November 2005 under Regulation 726/2004 Laying Down Community Procedures for the Authorisation and Supervision of Medicinal Products for Human and Veterinary Use and Establishing a European Medicines Agency [2004] OJ L136/1.

⁶ European Commission, 'Inventory of Union and Member State Incentives to Support Research Into, and the Development and Availability of, Orphan Medicinal Products – State of Play 2015" SWD(2015)13 final.

Туре	Provision	Incentive
Protocol assistance ('push')	Article 6 (1)	"The sponsor of an orphan medicinal product may request advice from the Agency on the conduct of the various tests and trials necessary to demonstrate the quality, safety and efficacy of the medicinal product"
		Between 2000 and 2015, some 951 protocol assistance procedures were completed.
Fee waiver ('push')	Article 7 (2)	"A special contribution from the Community shall be allocated every year to the Agency. The contribution shall be used to waive, in part or in total, all the fees payable under Community rules adopted pursuant to Regulation (EEC) No. 2309 / 93." Between 2000 and 2015, the sum waived amounted to \in 78.4 million, including protocol assistance and pre- and post- marketing authorisation activities.
Market exclusivity ('pull')	Article 8 (1)	"Where a marketing authorisation in respect of an orphan medicinal product is grantedthe Community and Member States shall not, for a period of 10 years, accept another application for a marketing authorisation, or grant a marketing authorisation, or accept an application to extend an existing marketing authorisation, for the same therapeutic indication, in respect of a similar medicinal product." See section on orphan market exclusivity, below.
Other incentives ('push')	Article 9 (1)	"Medicinal products designated as orphan medicinal products under the provisions of this Regulation shall be eligible for incentives made available by the Community and by the Member States to support research into, and the development and availability of, orphan medicinal products and in particular aid for research for small- and medium- sized undertakings provided for in framework programmes for research and technological development." At a community level, since 2007 more than €1.4 billion has been committed to more than 200 rare disease projects through the Seventh Framework Programme and Horizon 2020. See, for example, "Inventory of Union and Member State incentives to support research into, and the development and availability of, orphan medicinal products – state of play 2015" ⁷ and "Rare diseases: How Europe is meeting the challenges." ⁸ More recently, a new European Joint Programme on Rare Diseases (<u>www.ejprarediseases.org</u>) has been launched.

Table 1: 'Push' and 'pull' incentives provided under the Orphan Medicinal Products Regulation

⁷ ibid.

⁸ European Commission, 'Rare Diseases How Europe is Meeting the Challenges' (*Europa*, 2013)

 $<\!https://ec.europa.eu/research/health/pdf/rare-diseases-how-europe-meeting-challenges_en.pdf\!>.$

Return on investment (ROI) route

(Article 3 (1) (a)) "... that [the product] is intended for the diagnosis, prevention or treatment of a life-threatening, seriously debilitating or serious and chronic condition in the Community and that without incentives it is unlikely that the marketing of the medicinal product in the Community would generate sufficient return to justify the necessary investment."⁹

To begin to assess 'sufficient return', an implementing Regulation (847 / 2000) specified a list of all the information necessary to make the assessment (including data on past and expected future development, production and marketing costs, details of grants and tax incentives received and an estimate and justification for expected future revenues)¹⁰ and a Commission notice (2016/C) indicated that the assessment would be made "...on the basis of all past and future development costs and expected revenues."¹¹

It is interesting to note that this distinction between 'Prevalence' and 'ROI' routes seemingly stems from difficulties experienced in the United States with the early operation of the Orphan Drug Act. Eligibility for orphan drug designation under the Orphan Drug Act originally required that a pharmaceutical firm explain the 'facts and circumstances' that would make development of that drug unprofitable.¹² In the absence of any American requirement to provide data on expected development costs and revenues, however, the FDA found it difficult to reach a conclusion on likely profitability.¹³ A prevalence threshold, below which orphan diseases are simply assumed to be unprofitable, was suggested as a much simplified approach.¹⁴ Accordingly, the inference from the threshold set in Article 3 (1)(a) must be that EU orphan disease markets with a patient population of $\leq 5 / 10,000$ will be assumed to be insufficiently profitable, whereas evidence has to be presented to show that a given market above this threshold will likely be.

¹³ ibid.

⁹ N.B. Comments from the Head of Directorates-General (DG) III (of Pharmaceuticals and Cosmetics), at the 'Workshop on Rare Diseases and Orphan Drugs' (Brussels, 5 May 1998)

<https://ec.europa.eu/health/sites/health/files/files/orphanmp/doc/proc5598_en.pdf> jointly convened by the European Foundation for the Advancement of Medicine and the European Commission indicate that this route was included in the Regulation at the request of colleagues from DG XII (Science, Research and Development).

¹⁰ Regulation 847/2000 laying down the provisions for implementation of the criteria for designation of a medicinal product as an orphan medicinal product and definitions of the concepts 'similar medicinal product' and 'clinical superiority' [2000] OJ L103/5. See also the proscribed form and content of an application for orphan designation: European Commission, 'Guideline on the Format and Content of Applications for Designation as Orphan Medicinal Products and on the Transfer of Designations from one Sponsor to Another' ENTR/6283/00 Rev 5 https://ec.europa.eu/health/sites/health/files/files/orphanmp/doc/2019_cons_guideline_appdes_en.pdf>.

¹¹ Commission Notice on the Application of Articles 3, 5 and 7 of Regulation (EC) No. 141 / 2000 on orphan medicinal products [2016] OJ C424/03.

¹² See Mikami (n 3) or Matthew Herder, 'What is the Purpose of the Orphan Drug Act?' (2017) 14 PLOS Medicine DOI: 10.1371/journal.pmed.1002191.

¹⁴ ibid.

Whether making use of the 'Prevalence' or the 'ROI' route, it must also be demonstrated that:

(Article 3 (1) (b)) "...there exists no satisfactory method of diagnosis, prevention or treatment of the condition in question that has been authorised in the Community or, if such method exists, that the medicinal product will be of significant benefit¹⁵ to those affected by the condition."

The grant of the orphan designation requires a positive opinion from the EMA Committee for Orphan Medicinal Products which checks to see whether the Article 3 (1) designation criteria are met. On the basis of this opinion, the European Commission decides whether or not the designation is to be granted. Out of a total of 2302 applications for orphan designation submitted between 2000 and 2015, sponsors reportedly chose the prevalence route in 2301 cases (99.96%), and the ROI route in just 1 case (0.04%).¹⁶

Protocol assistance

In addition to the possibility of requesting the usual range of scientific advice from the EMA, one of the valuable 'push' incentives provided under the Regulation is that a sponsor may request supplementary 'protocol assistance' with a view to raising the likelihood that the data presented in the dossier for an orphan medicinal product seeking marketing authorisation will prove satisfactory.¹⁷

Application for marketing authorisation

The sponsor may apply to the EMA for marketing authorisation for its orphan medicinal product. Another valuable 'push' incentive provided under the Regulation is that fee waivers are applied for an orphan medicinal product. The grant of marketing authorisation requires a positive opinion from both the EMA Committee for Medicinal Products for Human Use (checking to see whether the usual marketing authorisation criteria are met, as well as whether or not the medicinal product is 'similar' to another for which marketing authorisation has already been granted) and the EMA Committee for Orphan Medicinal Products (checking to see whether, with the benefit of the additional data gathered since the initial application for orphan designation, the Article 3 (1) designation criteria are still met¹⁸). On the basis of these opinions, the European Commission decides whether or not marketing authorisation is to be granted. If it is, the orphan medicinal product benefits for up to ten years afterwards from a particularly valuable 'pull' incentive: orphan market exclusivity.

¹⁵ The scope of 'significant benefit' ('a clinically relevant advantage or a major contribution to patient care') is discussed in the Commission Notice (n 11).

¹⁶ Commission (n 6).

¹⁷ See, for example, EMA Guidance for applicants seeking scientific advice and protocol assistance, EMA/4260/2001, 30 June 2017.

¹⁸ See Commission Notice (n 11).

Orphan market exclusivity

Nature, scope and term of the orphan exclusivity

The pharmaceutical industry already benefits from a portfolio of IPRs in the European Union that can be used to acquire and maintain market exclusivity for their medicinal products: patents (term: 20 years), Supplementary Protection Certificates (SPCs) (maximum term: 5 years) and data protection (term of data exclusivity plus

An exclusivity incentive regime is supposed to be designed to last as long as is necessary to achieve its aims, but no longer. Competition is supposed to be re-enabled as quickly as possible thereafter.

market exclusivity: 10 - 11 years). The Regulation nevertheless introduces a new IPR-like 'orphan exclusivity' based on the American Orphan Drug Act model (without any requirement to do so in the WTO/TRIPS Agreement and without any detailed justification of why it is necessary: Recital (8) simply states that "data protection...is not a sufficient incentive..."). Art 8 (1) provides that:

"Where a marketing authorisation in respect of an orphan medicinal product is granted...the Community and Member States shall not, for a period of 10 years, accept another application for a marketing authorisation, or grant a marketing authorisation, or accept an application to extend an existing marketing authorisation, for the same therapeutic indication, in respect of a similar medicinal product."

Orphan exclusivity therefore protects an orphan medicinal product from competition from 'similar' medicinal products for the same therapeutic indication for a period of ten years.¹⁹ 'Similar' has later been defined with reference to "an identical active substance, or an active substance with the same principal molecular structural features (but not necessarily all of the same molecular structural features) and which acts via the same mechanism."²⁰

Since one of the aims of the American orphan exclusivity was to be able to give the holder a strong patent-like right at a time, in the 1980s, when it was uncertain whether or not biotechnology inventions could be patented, eligibility for this EU orphan exclusivity is not subject to any

¹⁹ This may be increased to twelve years if a Paediatric Investigation Plan (PIP) has been completed. See Regulation 1901/2006 on Medicinal Products for Paediatric Use [2006] OJ L378/1 (Article 37). An SPC extension of six months is available as an alternative (Article 36). The Glivec (imatinib) case discussed in Box 1 highlights behaviour opting in and out of incentive regimes to maximise benefit. Having completed a PIP, Novartis opted out of the orphan incentives by withdrawing the orphan medicinal product status of Glivec (imatinib) in 2012 so that they could still opt into the SPC extension instead. See, for example: Copenhagen Economics, 'Study on the Economic Impact of Supplementary Protection Certificates, Pharmaceutical Incentives and Rewards in Europe' (*Europa*, May 2018) <https://ec.europa.eu/docsroom/documents/29521>.

²⁰ See Regulation (EC) No. 847/2000 (n 10) and Commission Guideline on aspects of the application of Article 8(1) and (3) of Regulation (EC) No 141/2000 [2008] OJ C242/12.

patentability-like tests either. Accordingly, orphan exclusivity can be obtained in Europe, for example, for medicinal products which have long been known and used. For this and other reasons, orphan exclusivity is a valuable addition to pharmaceutical firms' IPR portfolio (see Table 2, below).

By way of exceptions to orphan exclusivity, three circumstances are identified in which another application for marketing authorisation will nevertheless be accepted: (Article 8 (3) (a)) if the holder of the market authorisation consents to another applicant being authorised; (Article 8 (3) (b)) if the holder of the market authorisation cannot supply sufficient quantities of the orphan medicinal product; or (Article 8 (3) (c)) if, although another medicinal product for the same therapeutic indication is 'similar' to the medicinal product with the marketing authorisation, it can nevertheless be demonstrated to be "safer, more effective or otherwise clinically superior."²¹

Existing IPRs	Advantages of orphan exclusivity for pharmaceutical firms vis-à-vis pre-existing IPRs
Patent	Obtaining a patent for an invention is often a time consuming, expensive and uncertain process, requiring a demonstration that patentability tests are met, including being 'new' and 'inventive', <i>whereas</i> orphan exclusivity applies as an automatic consequence of receiving marketing approval.
	Given that there are no such patentability-like tests, so long as the other qualifying orphan medicinal product tests are met under the Regulation, it is possible to obtain orphan exclusivity even for medicinal products which have long been known and used.
	Once a patent has been granted, it is subject to annual renewal fees and can still be challenged by competitors who disagree about the invention having met the patentability tests <i>whereas</i> orphan exclusivity itself requires no such annual renewal fees and is not independently subject to challenge by competitors.
	A patent holder is responsible for its enforcement in often time consuming, expensive, uncertain and possibly politically contentious litigation <i>whereas</i> orphan exclusivity is enforced by the regulatory authorities.
	A patent is subject to compulsory licence (or government use) provisions <i>whereas</i> there are no such provisions for orphan exclusivity (although see, for example, Article 8 (3) (b) and (c)).
Data protection	Data protection does not prevent a competitor pharmaceutical firm's medicinal product from being granted marketing authorisation if they have independently generated their own (for example, clinical trial) data <i>whereas</i> orphan exclusivity does.

Table 2: Advantages of orphan exclusivity for pharmaceutical firms vis-à-vis pre-existing IPRs

²¹ These derogations are discussed in the 2008 Commission Guideline (*ibid*).

Box 1: The case of Glivec (imatinib) orphan exclusivity

Evergreening the orphan way?

Glivec (imatinib) (Novartis) received marketing authorisation in November 2001 as an orphan medicinal product for chronic myeloid leukaemia (CML) related indications²² (although another four distinct oncological indications would be added in the next five years). Subsequently, Novartis applied for orphan designation (2006) and marketing authorisation (2007) for Tasigna (nilotinib), likewise for CML related indications.²³ To satisfy the orphan designation test in Article 3 (1)(b), they successfully argued that Tasigna (nilotinib) provided 'significant benefit' to patients compared to the existing Glivec (imatinib) product. Further, to overcome the finding of the EMA that Tasigna (nilotinib) and Glivec (imatinib) were 'similar' for the purposes of Article 8 (1), and that marketing authorisation would therefore otherwise be blocked, since they were the sponsor of both products Novartis were able to provide the necessary consent under Article 8 (3)(a). Following the expiry of the Glivec (imatinib) orphan exclusivity in November 2011, Teva Pharmaceuticals had been preparing to launch a generic version of imatinib for both CML and other indications.²⁴ However, the EMA refused marketing authorisation for their generic imatinib following their finding that it was 'similar' for the purposes of Article 8 (1) to the later Tasigna (nilotinib) to the extent that it covered the same therapeutic indications. In this case, Article 8 (3)(a) consent was evidently not going to be forthcoming from Novartis. Teva challenged the EMA decision and it eventually ended up before the Court of Justice of the European Union (CJEU). On 3 March 2016, dismissing the appeal from a decision of the General Court (Case T-140/12), the CJEU found in Teva v. EMA (Case C-138/15P) that the EMA had been correct in their interpretation of Article 8 (1) – that each orphan medicinal product receiving marketing authorisation was due an independent ten years of orphan exclusivity – and it dismissed Teva's arguments that this effectively extended the term of orphan exclusivity protection afforded to Glivec (imatinib) to sixteen years. Article 8 (3)(a) thus arguably places the first-comer pharmaceutical firm to a particular orphan disease therapeutic indication in a very privileged position and raises the possibility of improper 'evergreening' behaviour.²⁵ It is perhaps worth noting that even in 2013, over 100 leading CML experts wrote a joint letter denouncing the immoral pricing of Glivec (imatinib); it was foreseen that at the then prices, Novartis would recoup the development cost in just two years.²⁶ Subsequently, both Glivec (imatinib) and Tasigna (nilotinib) have proved to be multi-billion euro per annum blockbusters for Novartis.²⁷

²² per Case C-138/15P Teva v EMA [2016] EU:C:2016:136: "...the treatment of adult patients with CML in chronic phase after failure of interferon-alpha therapy, or in accelerated phase or blast crisis..." (para 9).

²³ *Ibid*: "..the treatment of adult patients with CML in chronic phase and accelerated phase, with resistance or intolerance to prior treatment involving Glivec..." (para 11).

²⁴ Case T-140/12 *Teva* v *EMA* [2015] EU:T:2015:41: "…first, the treatment of adult patients with newly diagnosed CML in chronic phase for whom bone marrow transplantation cannot be considered as a first line of treatment and adult patients with CML in chronic phase after failure of interferon-alpha therapy or in accelerated phase and, second, the treatment of the non-CML cancer indications for which the original orphan medicinal product had also been authorised" (para 19).

An obvious question is why a ten-year term was chosen in Europe when the equivalent orphan exclusivity lasts only seven years in the United States? In comments at a 'Workshop on Rare Diseases and Orphan Drugs' in 1998, the Head of Directorates-General (DG) III (Pharmaceuticals and Cosmetics) made plain that this question was viewed in terms of competition with the United States and that ten years was 'doing better' than the United States (and that, indeed, 'fifteen years would be better than ten, that is correct, and twenty would be better than fifteen').²⁸ Clearly, a simple argument that 'the longer the term the better' would fail to take into account the balance to be struck between the respective private (pharmaceutical firms) and public (patients and national health systems) interests: an exclusivity incentive regime is supposed to be designed to last as long as is necessary to achieve its aims *but no longer* and competition is supposed to be re-enabled as quickly as possible thereafter. It is particularly interesting, therefore, that the Head of DG III (Pharmaceuticals and Cosmetics) did recognise the need for a mechanism in the Regulation to be able to strike, at least in part, this balance. As discussed in the following section, a so-called 'withdrawal clause' was intended to be able to restrain pharmaceutical firms from making 'excessive' profits.

Withdrawal clause (withdrawn...)

In further comments, the Head of DG III (Pharmaceuticals and Cosmetics) indicated that:

"In response to a request from colleagues in DG XXIV [Consumer Policy and Consumer Health Protection], there would be a possibility of withdrawing the exclusivity after six years, but under very strict conditions. This would have to be requested by a Member State. The reasons for withdrawing the exclusivity would be that the prevalence criteria are no longer met, or that an excessive price is being charged or excessive profit is being made on the drug by the sponsor. This is a precaution to cope with the counter-argument that some blockbusters might go through. Again, experience in the United States shows that yes, there are a couple of them, but very few. At conferences and in literature in the U.S. the same product, EPO, and the new hormones, perhaps, are continually mentioned, but these

²⁵ See also Case T-80/16 *Shire* v *EMA* [2018] EU:T:2018:165 for a further development of these issues in circumstances where a pharmaceutical firm seeks an orphan designation and marketing authorisation for a medicinal product which has the same active ingredient as another of its already marketed orphan medicinal products.

²⁶ Hagop Kantarjian and others, 'The Price of Drugs for Chronic Myeloid Leukemia (CML) is a Reflection of the Unsustainable Prices of Cancer Drugs' (2013) 121 Blood Journal 4439.

²⁷ Andreas Hadjivasiliou, 'EvaluatePharma Orphan Drug Report 2017' (*Evaluate Group*, 4th edn, 2017)

<http://info.evaluategroup.com/rs/607-YGS-364/images/EPOD17.pdf>.

²⁸ 'Workshop on Rare Diseases and Orphan Drugs' (n 9).

are just 2 or 3 drugs out of around 800 designations. It does not seem to be a real problem. If there is a problem, the withdrawal clause will allow us to cope with it."²⁹

It could not be more clear that, contrary to the expectations via-à-vis the American Orphan Drug Act, a few orphan medicinal products had already proved to be 'blockbusters' (see section on how market incentives have worked in practice, below) and this was regarded as a problem by the European Commission. It is true that the particular effect of the removal of the last four years of orphan exclusivity will depend on, for example, whether the orphan exclusivity supplements other IPRs which may continue to protect the market regardless (in some cases the orphan exclusivity will be the only such right and in other cases it may extend beyond the lifetime of the other IPRs³⁰) and whether there are competitor firms interested and able to compete in that market. Nevertheless, by way of the safeguard envisaged, Article 8 (2) of the European Commission's draft Proposal for the Regulation (1998)³¹ provided that:

"This [ten-year market exclusivity] period may however be reduced to six years if, at the end of the fifth year, a Member State can establish that the criteria laid down in Article 3 are no longer met in respect of the medicinal product concerned or that the price charged for the medicinal product concerned is such that it allows the earning of an unreasonable profit."

In other words, there would be two independent grounds on which to withdraw the market exclusivity: *either* that the Article 3 criteria on which the marketing authorisation was obtained were no longer met *or* that the high price charged for the medicinal product meant that an 'unreasonable' profit was being earned (the explanatory text put it slightly differently: "...or that the holder of the marketing authorisation demands a price for the product which cannot be justified"). The form of Article 8 (2) was unchanged in the Amended proposal (1999).³²

By the time the European Council reached agreement on a common position, however, the form of Article 8 (2) had been amended to that which is now reflected in the Regulation:

"This [ten-year market exclusivity] period may however be reduced to six years if, at the end of the fifth year, it is established, in respect of the medicinal product concerned, that the criteria laid down in Article 3 are no longer met, inter alia, where it is shown on the basis of available evidence that the product is sufficiently profitable not to justify the maintenance of market exclusivity."

²⁹ ibid.

³⁰ Based on their chosen assumptions, the authors of the recent Copenhagen Economics study (n 19) indicate that: "Market exclusivity for orphan medicinal products has on average provided 1.6 extra years of protection to the orphan medicinal products where market exclusivity was the last protection scheme to expire."

³¹ European Commission, 'Proposal for a European Parliament and Council Regulation (EC) on Orphan Medicinal Products' COM (1998) 450 final.

³² Amended Proposal for a European Parliament and Council Regulation on Orphan Medicinal Products [2000] OJ C177/1.

The difference is subtle but its impact is significant. By replacing the 'or' with 'inter alia' ('among other things'), the independent high price / unreasonable profit ground vanishes and the 'sufficiently profitable' test is subsumed for use only under the Article 3 ROI test. Regrettably, this interpretation is fully reflected in the European Commission Guideline on the application of Article 8 (2).³³ For medicinal products that were initially granted orphan designation via the prevalence

route (c. 99.9% of the time), the Article 8 (2) review is undertaken on the basis of checking whether the prevalence tests are still met. The Article 8 (2) review is only undertaken on the basis of checking whether the medicinal product has proved to be 'sufficiently profitable' if it was initially granted orphan designation on the basis of the ROI test (c. 0.1% of the time) or, by way of a second 'bite at the cherry', if the prevalence test has been failed at this stage.

Although discussion in the literature sometimes gives the impression that the remnant Article 8

From the perspective of pharmaceutical firms interested in developing and marketing orphan medicinal products... not only is there is no real danger of having the last four years of the orphan exclusivity withdrawn on the grounds of having already made an unreasonably large profit, there is no real danger of having to define what an unreasonably large profit actually is, either.

(2) has the same effect as the well-intended withdrawal clause,³⁴ this amendment has arguably neutralised it almost completely. This has the double benefit, from the perspective of pharmaceutical firms interested in developing and marketing orphan medicinal products, that not only is there no real danger of having the last four years of the orphan exclusivity withdrawn on the grounds on having already made an unreasonably large profit, there is no real danger of having to define what an unreasonably large profit actually is either. It would be interesting to find out how and why this amendment came to be made, not least since, as will become clear below, the very thing that the withdrawal clause was supposed to prevent (the making of 'blockbuster' profits) has come to pass.

It is true that the European Commission did ask a consultancy firm to devise a methodology for evaluating the profitability of an orphan medicinal product at the point of having been on the

³³ Guideline on Aspects of the Application of Article 8 (2) of Regulation (EC) No. 141 / 2000 of the European Parliament and of the Council: Review of the Period of Market Exclusivity of Orphan Medicinal Products [2008] OJ C242/8. This issue was also referred to, in passing, in paragraphs 70 and 80 of the CJEU judgment in *Teva v EMA* (n 22). Strangely the two references appear at odds precisely on this point: "70…which may be reduced, under Article 8(2) of Regulation No 141/2000, only in situations in which it is established that the medicinal product in question no longer meets the requirements laid down in Article 3(1) of the regulation"; and "80…with the exception of the situations set out in Article 8(2) of the regulation, in which the period of exclusivity may be reduced, inter alia if the criteria laid down in Article 3(1) of the regulation are not met."

³⁴ See, for example, Jonathan CP Roos, Hanna I Hyry, and Timothy M Cox, 'Orphan Drug Pricing May Warrant a Competition Law Investigation' (2010) 341 BMJ DOI:10.1136/bmj.c6471; or Panos Kanavos and Elena Nicod, 'What is Wrong with Orphan Drug Policies? Suggestions for Ways Forward' (2012) 15 Value in Health 1182.

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market for five years, such that this remnant Article 8 (2) decision could be taken at the six year point.³⁵ However, re-iterating the requirements of the Article 3 ROI test, a subsequent Commission guideline $(2008 / C)^{36}$ states merely that the Article 8 (2) 'sufficient profitability' test should be understood as follows:

"5.1.1.2...If, after subtraction of the financial benefits gained as a result of the incentives under the Regulation, the return on investment is insufficient, market exclusivity will not be reduced."

Defining 'sufficiently profitable' in terms of 'an insufficient return on investment', without defining 'insufficient', does not seem to reflect much of a will to operationalise the provision.

The possibility and indeed the desirability of being able to use the remnant Article 8 (2) has been raised in several places very recently, for example, by Professor Bruno Sepodes,³⁷ ex-Chair of the EMA Committee for Orphan Medicinal Products, and in the Technopolis Report on IPR incentives.³⁸ However, it seems that the present day debate has so far neglected to take into account the scope of the original 'withdrawal clause', how and why it was effectively neutralised, and the fact that a similar mechanism needs to be re-introduced if Article 8 (2) is to properly play the role that was intended.

³⁵ Curiously, their report (Ariadne de Varax, Marc Letellier, and Géraldine Börtlein 'Considerations on the Application of Article 8.2 of EC Regulation No. 141/2000 Concerning Orphan Drugs' (*Europa*, 2004)

<https://ec.europa.eu/health/sites/health/files/files/orphanmp/doc/pricestudy/final_final_report_part_2_web_en.pdf>)
begins by outlining strong opposition to the idea that the use of Article 8 (2) should ever be contemplated. Based on "...a
large number of comments from the parties concerned by article 8.2.," the authors state that, for example: "Even if it
were justified, withdrawing market exclusivity would risk substantially reducing the attractiveness of the regulation for the
pharmaceutical industry, not least by simply eliminating the psychological value of this incentive." This is a strangely
recursive argument: if the use of Article 8 (2) is justified, it means that the orphan medicinal product is, by definition,
'sufficiently profitable'. What do the authors believe that 'sufficiently' means?

 $^{^{\}rm 36}$ Guideline on aspects of the application of Article 8 (2) (n 33).

³⁷ "Given the increasing number of medicines with orphan designation that are coming to the market and acknowledging that access to these products is often challenging, Bruno Sepodes also highlighted the need to fully exploit the legal possibilities in the Regulation to reduce protection periods for orphan medicines that do not meet the criteria over time. This also entails the need to generate relevant data for these products after authorisation." Reported comments in 'Press Release – EMA Management Board: Highlights of October 2017 Meeting' (*Europa*, 6 October 2017) https://www.ema.europa.eu/en/news/ema-management-board-highlights-october-2017-meeting>.

³⁸ "8.3.1...Explore whether Member States are sufficiently aware of the derogation options offered under Article 8(2) of the Orphan Drug Regulation that allow the period of market exclusivity to be reduced under particular conditions. In practice, however, the invocation of this article by individual MSs will likely be complicated due to lack of knowledge at national ministries about exact disease prevalence, and due to national variations in drug prices, resulting from underlying differences in procurement and reimbursement systems. Yet, the provision offers one of the few possibilities for concerted action against excessive profiteering on orphan drugs at the EU level." Thyra de Jongh and others, 'Effects of Supplementary Protection Mechanisms for Pharmaceutical Products' Final Report (*Technopolis Group*, May 2018) 54 <http://www.technopolis-group.com/wp-content/uploads/2018/06/2718-Technopolis-report-on-supplementaryprotection-mechanisms.pdf>.

How have the EU (and other) orphan medicinal product incentives worked in practice?

A complete analysis of how and to what extent pharmaceutical firms have changed their orphan disease research and development behaviour in response the incentives under the Regulation would be a complex and time-consuming task, not least since pharmaceutical firms operate internationally and so changes in their behaviour in Europe may well reflect elements of incentives provided elsewhere too, for example in the United States and Japan.³⁹

Orphan incentives have indeed made orphan medicine development into "an economically viable strategy for biopharma R&D. However, the unprecedentedly high orphan medicinal product prices often have little or no relation to development costs and are evidently more a reflection of what the pharmaceutical firm thinks the market will bear.

Nevertheless, the broad outlines of the response

are very clear. There were 8 orphan medicinal products on the market in 2000.⁴⁰ Since then, the number of EMA applications for medicinal product orphan designation has risen to a total of 3210 between the entry into force of the Regulation in 2000 and 2018, of which 2121 were or have been approved.⁴¹ Of these 2121 orphan designations, 524 (25%) related to new conditions and circa 1888 (89%) related to conditions with a prevalence of 3 or fewer patients per 10,000 of population.⁴² Commensurate with this data, there is also evidence pointing to a substantial increase in orphan disease clinical trial activity in Europe since 2006.⁴³ During this period, marketing authorisation has been granted for a total of 164 orphan medicinal products.⁴⁴ It is interesting that of the 236 applications submitted in 2018, the sponsors were small or medium sized enterprises in only 30% of cases.⁴⁵

³⁹ For recent attempts with a more particular scope see, for example Technopolis Group (*ibid*).; and Copenhagen Economics (n 19) and the assumptions therein.

 ⁴⁰ Pugatsch Consilium, 'Benchmarking Success: Evaluating the Orphan Regulation and its Impact on Patients and Rare Disease R&D in the European Union' (2019) http://www.pugatch-consilium.com/reports/Benchmarking_success.pdf.
 ⁴¹ EMA, 'Orphan medicines figures 2000-2018' (*Europa* 2018) http://www.pugatch-consilium.com/reports/Benchmarking_success.pdf.

⁴² ibid.

⁴³ Pugatsch Consilium (n 40).

⁴⁴ EMA (n 41).

⁴⁵ EMA (n 41).

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It is reported that the orphan incentives have indeed made orphan medicine development into "an economically viable strategy for biopharma R&D."⁴⁶ Part of this is a generally lowered cost of bringing an orphan medicinal product to market.⁴⁷ For example, although there are certainly both positive and negative factors associated with undertaking clinical trials for orphan diseases in the very small patient populations, the evidence points to an overall reduction in cost and risk compared to trials for non-orphan diseases: based on experience in the United States, Jayasundara et al. (2019), for example, have found that the out-of-pocket clinical costs per approved orphan medicinal product were US\$ 166 million (capitalised cost: US\$ 291 million) compared to US\$ 291 million (capitalised cost: US\$ 412 million) per approved non-orphan medicinal product; looking at new molecular entities in particular, the orphan cost was half that of the non-orphan cost.⁴⁸

Perhaps the key driver for the hugely increased involvement of pharmaceutical firms in orphan disease markets is, however, that they have found that they can often manage the small patient / consumer population problem by charging unprecedentedly high prices for orphan medicines. This seems unlikely to have been foreseen by those making the above-mentioned decisions on prevalence thresholds, below which orphan disease markets are assumed to be insufficiently profitable. Meekings et al. (2012) note that: "Orphan drugs can secure incredibly high pricing"; for example, "Soliris [eculizumab] (Alexion Pharmaceuticals) costs US\$ 409,500 per year for the treatment of paroxysymal nocturnal hemoglobinuria (PNH), which enabled it to capture US\$ 541 million in sales in 2010, an incredible feat bearing in mind there are only an estimated 4000 – 6000 patients in the USA with PNH." In 2015 Soliris (eculizumab) was approved for use in the management of atypical haemolytic uraemic syndrome (aHUS) in the National Health Service (NHS) in the UK at a price of £340,200 per patient per year (and an estimated total cost to the NHS of

⁴⁶ See, for example: Kiran N Meekings, Cory SM Williams, and John E Arrowsmith, 'Orphan Drug Development: An Economically Viable Strategy for Biopharma R&D' (2012) 17 Drug Discovery Today 660; Ian Philips, 'Big Pharma's New Model in Orphan Drugs and Rare Diseases' (2013) 1 Expert Opinion on Orphan Drugs

doi:10.1517/21678707.2013.752128; or Dyfrig A Hughes and Jannine Poletti-Hughes, 'Profitability and Market Value of Orphan Drug Companies: A Retrospective, Propensity-Matched Case-Control Study' (2016) 11 PLoS ONE DOI:10.1371/journal.pone.0164681. It is interesting that the improved predictive validity of "...models for specific cancer subtypes and other rare diseases with strong and simple genetic risk factors..." has also been cited (Jack W Scannell and Jim Bosley, 'When Quality Beats Quantity: Decision Theory, Drug Discovery and the Reproducibility Crisis' (2016) 11 PLoS ONE DOI:10.1371/journal.pone.0147215).

⁴⁷ Although there are significant difficulties with the notion of having single representative figures for the costs of orphan and non-orphan medicine development, one recent study (Gupta Strategists, 'The Cost of Opportunity: A Study on Pharmaceutical R&D Costs' (2019) <https://gupta-strategists.nl/storage/files/The-cost-of-opportunity-Gupta-Strategists.pdf > suggests that the cost of bringing an orphan medicine to market could be only 20% that for a nonorphan medicine.

⁴⁸ Kavisha Jayasundara and others, 'Estimating the Clinical Cost of Drug Development for Orphan Versus Non-Orphan Drugs' (2019) 14 Orphanet Journal of Rare Diseases DOI:10.1186/s13023-018-0990-4.

£57.8 million per year).⁴⁹ Although these particular costs are exceptionally high, there are many other orphan medicinal product costs that are comparable (> \leq 50,000 - 100,000 per patient per year)⁵⁰ and it cannot be emphasised enough that the pharmaceutical industry seems to have developed a strong general sense that 'orphan medicinal product' should be taken as virtually synonymous with 'high prices'.⁵¹

Pharmaceutical firms often try to justify these high prices by pointing to a combination of (overinflated) estimates of how much it costs to develop a typical new medicine⁵² and the fact that there are fewer patients than normal to charge. However, the unprecedentedly high orphan medicinal product prices often have little or no relation to development costs and are evidently more a reflection of what the pharmaceutical firm thinks the market will bear, meaning that price negotiations can unfortunately rather resemble ransom demands: 'How much do you value your citizens' lives?'.⁵³ Box 2 illustrates the high prices that resulted from two very different orphan medicinal product development paths.

In addition to obvious concerns about straightforwardly high prices, concerns have also been expressed internationally that pharmaceutical firms have been manipulating or 'gaming' orphan regimes in order to boost their overall profitability and performance.⁵⁴

⁵³ See, for example, Gagnon (*ibid*).

⁴⁹ Pharmaceutical Journal, "Eculizumab – with £340,200 price tag – gets go ahead from NHS" (28 January 2015) <https://www.pharmaceutical-journal.com/news-and-analysis/news-in-brief/eculizumab-with-340200-price-tag-gets-goahead-from-nice/20067720.article?firstPass=false>.

⁵⁰ Representative present-day figures presented in a leading industry survey (Hadjivasiliou (n 27)) indicate that the average orphan medicinal product cost per patient per year in the United States in 2016 was US\$ 140,443 versus US\$ 27,756 for a non-orphan medicinal product. The median orphan medicinal product cost per patient per year in the United States in 2016 was US\$ 83,883. However, an 'orphan medicine' is defined such that its first approved indication is an orphan one and that at least 25% of product sales is to be generated from orphan indications.

⁵¹ For example, "Drug pricing, higher prices were taken as an indicator of orphan status" (*ibid*).

⁵² See, for example, Donald W Light and Rebecca Warburton, 'Demythologizing the High Costs of Pharmaceutical Research' (2011) BioSocieties 34; and Marc-André Gagnon, 'New Drug Pricing: Does it Make Any Sense?' (2015) 24 Prescrire International 192. By contrast, a recent study (Pugatsch Consilium (n 40)) funded by Shire (one of the largest pharmaceutical firms in the orphan disease field), asserts that "[d]eveloping a new biopharmaceutical treatment is a highly challenging undertaking due to the very long and very risky process whose costs are estimated at over USD2 billion and chances of returning this investment are miniscule. These challenges are enhanced significantly when developing a treatment for a rare disease." If this were true, it would be hard to believe, would it not, that any orphan medicinal products would ever be developed?

⁵⁴ See, for example, André Côté and Barnard Keating, 'What is Wrong with Orphan Drug Policies?' (2012) 15 Value in Health 1185; Gagnon (n 52); Michael Daniel and others, 'The Orphan Drug Act: Restoring the Mission to Rare Diseases' (2016) 39 American Journal of Clinical Oncology 210; or Herder, M.,*ibid*. For a more equivocal European view see, for example, Kanavos and Nicod (n 34).

Box 2: Firdapse and Glybera – cases of orphan medical product development

Very different paths to orphan medicinal product development?

Firdapse (amifampridine phosphate)

From the 1990's onward, 3, 4, - diaminopyridine (amifampridine base), had been made up by pharmacists in the UK and used on an unlicensed individual patient basis in the treatment of Lambert Eaton myasthenic syndrome (LEMS),⁵⁵ an autoimmune disease which attacks the nervous system. LEMS has an estimated prevalence of 5 patients per 2 million. Building on work originally undertaken at Assistance Publique – Hôpitaux de Paris, BioMarin received an orphan (LEMS) designation for their Firdapse (amifampridine phosphate) in 2002 and a marketing authorisation in 2009. Taking into account the public domain information regarding the use of amifampridine base, BioMarin had to conduct only very limited additional tests and trials in order to reach this stage.⁵⁶ BioMarin indicates that their medicinal product is superior to the individual use of amifampridine base in that the dosage is more consistent and they are responsible for supporting and monitoring its use. However, against the estimated £800 - £1,000 cost per patient per year (depending on dose) of using amifampridine base, BioMarin priced their equivalent Firdapse (amifampridine phosphate) in the UK at £40,000 - £70,000.57 Following the licensing of Firdapse (amifampridine phosphate), the UK Medicines and Healthcare Products Regulatory Agency (MHRA) advised pharmacists in the UK that they were no longer permitted to prepare (10 mg) doses for individual use, prompting the Chair of the UK Commissioning Public Health Network to observe that: "It disgusts me, it really does....The price set for the drug is indecent... As a direct effect of the drug's price, some patients will not get the care they would have done - either because the primary care trust won't fund it, or because it will and other patients' care has to be cut to find the money." Catalyst Pharmaceuticals, who are responsible for marketing Firdapse (amifampridine phosphate) in the United States, have recently justified raising their price to US\$ 375,000 per patient per year by indicating that it is line with the price of other orphan medicinal products for similarly defined indications and would allow them to be 'properly compensated' for the costs they have incurred.

⁵⁵ See, for example, Marc Dooms and Maria Carvalho, 'Compounded Medication for Patients with Rare Diseases' Orphanet Journal of Rare Diseases' (2018) 13 DOI:10.1186/s13023-017-0741-y.

⁵⁶ See EMA, 'Firdapse (previously Zenas)' (*Europa*) <https://www.ema.europa.eu/en/medicines/human/EPAR/firdapsepreviously-zenas>; and Nigel Hawkes and Deborah Cohen, 'What Makes an Orphan Drug?' (2010) 341 BMJ DOI:10.1136/bmj.c6459.

⁵⁷ In NHS England, "Clinical Commissioning Policy: Amifampridine Phosphate for the Treatment of Lambert Eaton Myasthenic Syndrome" (2016) <https://www.england.nhs.uk/wp-content/uploads/2018/07/Amifampridine-phosphate-forthe-treatment-of-Lambert-Easton-myasthenic-syndrome.pdf> lower estimates of £730 and £29,448 per patient per year respectively are given.

Glybera (alipogene tiparvovec)

As mentioned in the introduction, many orphan diseases are genetic in nature. Rather than just managing the symptoms of an orphan disease, techniques to insert DNA into a patient's cells to correct the genetic defect and allow for normal protein expression ('gene therapy'), open the possibility that orphan diseases could be cured. From the pharmaceutical business model perspective, where diseases are treated as markets, the prospect of a cure may be viewed with a great deal of caution.⁵⁸ Nevertheless, from a patient's perspective it would be optimal. A number of companies are now progressing gene therapy-based treatments. Lipoprotein lipase deficiency (LPLD) is a genetic disorder which causes a metabolic failure to be able to break down certain protein-lipid complexes (chylomicrons), which can result in severe pancreatitis. It has an estimated prevalence of 1 or 2 patients per million. If normal LPL genes were able to be delivered into a patient's cells and their normal expression enabled, then normal metabolic function should be restored. Gene therapy is still a very new field and does appear to be truly commercially risky. Building on a viral vector delivery system acquired from Amsterdam Molecular Therapeutics (AMT), UniQure obtained the first European marketing authorisation for a gene therapy based medicinal product in 2012: their orphan (LPLD) designated Glybera (alipogene tiparvovec). A combination of difficulties, including a one-off treatment price set at €1 million per patient, an insufficiently large patient population to be able to market to, and the fact that the regulation of a medicinal product intended to be a cure places particular attention on Phase IV studies, caused UniQure to withdraw their marketing authorisation for Glybera (alipogene tiparvovec) in 2017. UniQure are now reported to be developing other gene therapy medicinal products based on the same viral vector delivery system.

Two examples are considered in Box 3: that of chenodeoxycholic acid (CDCA) in Europe where – as with the first example studied in Box 2 – a pharmaceutical firm has managed to obtain and exploit orphan market exclusivity on the basis of comparatively little investment to their financial advantage but to the clear disadvantage of patients; and that of Opdiva (nivolumab), in Japan, where a pharmaceutical firm managed to negotiate a very high price in relation to an orphan indication for their medicinal product and then tried to leverage that price across to non-orphan indications with much larger patient populations.

⁵⁸ A notorious Goldman Sachs report recently asked the question: 'Is curing patients a sustainable business model?'; see discussion at, for example: Tae Kim, 'Goldman Sachs Asks in Biotech Research Report: Is Curing Patients a Sustainable Business Model' (*CNBC*, 11 April 2018) https://www.cnbc.com/2018/04/11/goldman-asks-is-curing-patients-a-sustainable-business-model.html>.

Box 3: Case studies of using orphan medicinal product regimes to extend exclusivity

Gaming orphan regimes

Securing rewards out of all proportion to development risks?

Cerebrotendinous xanthomatosis (CTX) is a rare genetic disease which leads to an inability to produce sufficient quantities of the primary bile acid chenodeoxycholic acid (CDCA). In the Netherlands, CDCA was marketed from 1976 to 2008 for the treatment of gallstones, at a price of €0,28 per capsule. However, since at least 1999 it was also prescribed, off-label, for the treatment of CTX. Leadiant Biosciences, a pharmaceutical firm, managed to acquire the marketing rights to Chenofalk, the medicinal product containing CDCA for the gallstones indication, and then (a) withdraw that product from the market for the gallstones indication whilst (b) on the basis of limited new data to supplement what was already in the public domain, acquire marketing authorisation in 2017 for CDCA (Leadiant) as an orphan medicinal product for CTX.⁵⁹ Having therefore managed to acquire a sole supplier position in the market for CDCA as a medicinal product to treat CTX, they made use of this position by setting a price of €140 per capsule, representing a 500 fold rise over the previously available CDCA medicinal product, and raising the patient treatment price from c. €300 to €150,000 per year.⁶⁰ The Pharmaceutical Accountability Foundation described Leadient's "socially unacceptable" behaviour as an abuse of its dominant market position and accordingly submitted a competition law based complaint to the Netherlands' Authority for Consumers and Markets (ACM).⁶¹ In a recent policy paper, the ACM has noted that in a case such as this, where the orphan medicinal product is essentially just 'formalising' a long standing off-label treatment, it may be more simple to reach a determination that pricing is excessive compared to a truly innovative case.62

60 ibid.

61 ibid.

⁵⁹ See, for example, Ellen 't Hoen, 'New Dutch Foundation to Address High Medicines Pricing Announces Plan to File Complaint with Competition Authority' (*Medicines Law & Policy*, 25 August 2018)

<https://medicineslawandpolicy.org/2018/08/new-dutch-foundation-to-address-high-medicines-pricing-announces-planto-file-complaint-with-competition-authority/>; and competition law complaint regarding CDCA, available at: Pharmaceutical Accountability Foundation, 'Press Release' <https://www.farmaterverantwoording.nl/information-inenglish/>.

⁶² See Matthew Newman, 'Leadiant Given Pause for Thought by Dutch View of 'Orphan Drug' Price Hikes' (*MLex Market Insight*, 14 November 2018) https://mlexmarketinsight.com/insights-center/editors-picks/antitrust/europe/leadiant-given-pause-for-thought-by-dutch-view-of-orphan-drug-price-hikes.

Leveraging orphan prices across to larger patient populations?

Opdivo (nivolumab) (BMS / Ono Pharmaceutical) was first marketed in Japan in 2014 with a relatively narrow (unresectable malignant melanoma) orphan indication and small patient population. A high price of \$320,000 per patient per year was agreed with the Japanese health authorities. Subsequently, however, Ono applied for and received authorisation for two new non-orphan indications (non-small cell lung cancer and renal cell carcinoma) with much larger patient populations. The magnitude of the budgetary commitment that would entail at the agreed price caused accusations to be made that Ono was engaging in 'cynical life-cycle management'.⁶³ The scandal eventually caused the intervention of the Prime Minister and an initial price cut of 50% followed by another of 23%. Japan has now introduced a new 'ultra-expensive drug repricing rule'.⁶⁴

One way of reducing the likelihood of improper 'gaming' behaviour is to keep a close eye on the disease definition arguments made by sponsors in order to obtain orphan designation in the first place. Concerns have been expressed internationally over so-called 'salami slicing', where pharmaceutical firms could improperly sub-divide a disease into a series of smaller sub-diseases, advantageously making use of the orphan incentives for one of those sub-diseases and, once marketing authorisation has been obtained for their orphan medicinal product, expand the range of its indications back out to cover the whole disease. This has perhaps been a particular concern in oncology,⁶⁵ but it is clearly one which could grow in importance given the advent of 'personalised' medicine. The EMA has therefore been active in trying to require medically plausible justifications for specified orphan disease parameters.⁶⁶ Another way would surely be to continue to monitor the range of indications obtained for orphan medicinal products, whether other orphan indications or non-orphan indications, such that price negotiations with pharmaceutical firms take into account (i.e. reduce with) the total patient population across all these indications.⁶⁷ However, to the contrary, by means of accessing broader markets associated with multiple indications at very high prices, pharmaceutical firms have produced many true multi-billion euro 'blockbuster' or so-called 'nichebuster' products. The above-mentioned Opdivo (nivolumab) (BMS) is projected to become the largest selling orphan medicinal product in Europe with sales / costs rising from US\$ 523 million

⁶³ See, for example, Patrick Branch, John Gill, and Ray Fujii, 'New Realities of Drug Pricing and Access in Japan' (*L.E.K Consulting*, 2017) https://www.lek.com/sites/default/files/insights/pdf-

attachments/Japan_Drug_Pricing_Special_Report.pdf>.

⁶⁴ ibid.

 $^{^{\}rm 65}$ See, for example, Daniel and others (n 54).

⁶⁶ See, for example, European Commission notice (n 11) or Daniel O'Connor and others, 'Defining Orphan Conditions in the Context of the European Orphan Regulation: Challenges and Evolution (2018) Nature Reviews Drug Discovery https://www.nature.com/articles/nrd.2018.128.pdf>.

⁶⁷ See, for example, Kanavos and Nicod (n 34).

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per year in 2016 to US\$ 2.435 billion per year in 2022.⁶⁸ The multiply indicated Revlimid (lenalidomide) (Celgene) is projected to become the largest selling orphan medicinal product in the world with sales / costs rising from US\$ 6.974 billion per year in 2016 (c18% of which were in Europe) to US\$ 13.556 billion per year in 2022 (15% of which are projected to be in Europe).⁶⁹ Given their documented struggles with their pre-existing business models,⁷⁰ it is no surprise that these levels of profit earning potential have therefore attracted 'Big Pharma' to a new business model in what has recently been described as the "wicked hot" orphan disease field.⁷¹ The incentives therefore seem to have worked so well that instead of just 'nudging' orphan disease markets over the line into sufficient profitability for small to medium sized biotechnology firms, the leading worldwide pharmaceutical firms in 2016 (by orphan medicine sales) are leviathans: Novartis (US\$ 12.9 billion), Roche (US\$ 10 billion), Celgene (US\$ 9.1 billion), Bristol-Myers Squibb (US\$ 6.6 billion) and Shire (US\$ 5.4 billion).⁷²

So, although it is true that the orphan incentives provided under the Regulation and elsewhere have greatly increased the number of orphan medicines developed and marketed, which is positive news for orphan disease patients, this increase has often come, literally, at a very high and often unaffordable price: "...from a patient's perspective, an unaffordable treatment is no more effective than a non-existent treatment."⁷³ Orphan disease patients groups are understandably nervous that, even if there are problems with affordability, any interference with the orphan incentives could jeopardise the future hope of a continuing stream of orphan medicinal products.⁷⁴ However, whilst there ought to be enough resources in comparatively wealthy Europe to care for all, the high prices charged by pharmaceutical firms for orphan medicinal products will weigh heavily on already strained health care budgets and this only looks set to worsen.

It is projected that the near future rate of growth of the orphan medicine market (11.1% p.a.) will be more than twice that of the non-orphan prescription medicine market (5.3% p.a.), and total global sales / costs will reach US\$ 209 billion by 2022, representing 21.4% of all (non-generic) prescription medicines.⁷⁵ What can be done?

⁷³ Gagnon (n 52).

⁷⁵ Hadjivasiliou (n 27).

⁶⁸ Hadjivasiliou (n 27).

⁶⁹ ibid.

⁷⁰ See, for example, Gagnon (n 52).

⁷¹ "Wicked hot" description from Sarah Jane Tribble and Sydney Lupkin, 'Drugmakers Manipulate Orphan Drug Rules to Create Prized Monopolies' (*Kaiser Health Network*, 17 January 2017) https://khn.org/news/drugmakers-manipulate-orphan-drug-rules-to-create-prized-monopolies/>.

⁷² Hadjivasiliou (n 27) : "The image of the plucky small biotech striving to develop treatments for the rare diseases largely ignored by big pharma is long gone."

⁷⁴ See, for example, Sarantis Michalopoulos, 'Patients: Think Carefully Before Questioning Orphan Drugs' Incentives' (*Euractiv*, 12 October 2018) https://www.euractiv.com/section/health-consumers/news/patients-think-carefully-before-questioning-the-orphan-drugs-incentives/.

Conclusions and recommendations

The impact of the orphan medicinal product incentives under the Regulation has two very different faces. The incentives have undoubtedly contributed to a huge increase in the level of engagement of pharmaceutical firms with

High prices charged by pharmaceutical firms for orphan medicinal products weigh heavily on already strained health care budgets. What can be done?

orphan diseases, which has led to many new orphan medicinal products being introduced to the European market. Some of these are directed at symptomatic management whereas others are directed at outright cures. This outcome is a welcome one for those living with orphan diseases, although it has to be recognised that the vast majority of such diseases remain unaddressed.

However, no doubt to the dismay of the many scientists who helped discover and develop these new orphan medicinal products, both in the public sector and in pharmaceutical firms, these positive developments have been hugely overshadowed by commercial behaviour which has become often described as not just excessive but abusive (as with the CDCA example studied above in Box 3). There have been for a while articles in the academic literature and the popular press with titles along the lines of "What is wrong with Orphan Drug policies?"⁷⁶ or "It's time to reform the Orphan Drug Act."⁷⁷ Indeed, the architect of the original Orphan Drug Act in the United States, Senator Waxman, has candidly admitted that it is being used to profit driven ends for which it was never intended and has lamented the lobbying power of the pharmaceutical industry to defeat his attempts to amend the incentives review launched by the European Council in 2016 offers an opportunity to do better, and to remedy some of the defects that have become apparent in the last two decades. It will likely require co-ordinated action, both within the confines of the orphan medicinal product regime (in terms of the operation and amendment of the Regulation) and outside (in terms, for example, of competition law⁷⁹ and price control).

⁷⁶ See, for example, Côté and Keating (n 54) or Kanavos and Nicod (n 34).

⁷⁷ See, for example, Nicholas Bagley and others, 'It's Time to reform the Orphan Drug Act' (*NEJM Catalyst*, 2018) https://catalyst.nejm.org/time-reform-orphan-drug-act/.

⁷⁸ "Bush Pocket-Vetoes Orphan Drug Measure," CQ Almanac 1990, cited in Daniel and others (n 54); Waxman and Green (n 3).

⁷⁹ See, for example, Roos and others (n 34).

Medicines Law & Policy therefore makes the following recommendations:

The key theme in the following recommendations is reducing the possibility for excessive or abusive exploitation of the incentives provided under Regulation 141 / 2000 by increasing the transparency of the orphan medicinal product regime and therefore being better able to match commercial reward with development risk and cost.

- Fully operationalise Article 8 (2) of Regulation 141 / 2000 by defining the line between 'sufficient' and 'excessive' profitability and therefore between 'sufficient' and 'insufficient' (Return on Investment) ROI.⁸⁰ The ROI approach (stipulated in implementing Regulation 847 / 2000⁸¹, Commission guideline 2008/C⁸² and Commission notice 2016/C⁸³) should aim for the minimum return necessary to achieve the goals of the Regulation in encouraging the development of orphan medicinal products (and the 'how much can the market bear' approach to pricing should be rejected). This will introduce some much-needed transparency into the European institutions on the subject of pharmaceutical firms' business models (and questions about their efficiency and continuing viability). Although there is concern about discouraging pharmaceutical firms' engagement with this field, 'sufficient' profitability should surely be, by definition, just that.
- 2. The prevalence threshold of not more than five per ten thousand people in Article 3 (1)(a), equivalent to a maximum current EU patient population of circa 250,000, should be re-examined in the light of experience gained since 2000. This threshold defines the line between those orphan disease markets which are assumed to be insufficiently profitable (permitting the 'prevalence' route for orphan designation to be used) and those which have to be shown to be insufficiently profitable (requiring the use of the 'ROI' route for orphan designation). The unprecedentedly high prices charged for orphan medicinal products by some pharmaceutical firms have meant that orphan disease markets with < 10,000 patients can be made to produce 'blockbuster' profits. It is therefore clear that it does not make sense to set a prevalence threshold based on an assumption about profitability without considering pricing behaviour. As it stands, the threshold has been overly generous in letting sponsors access the incentives provided under the Regulation without having to show any evidence to support a case of insufficient profitability: only 1 out of the 2,302 applications for orphan medicinal product designation between 2000 and 2015 made use of the ROI route and was required to do so.⁸⁴ If the threshold were lowered, an equivalent number of applications for

 $^{^{\}rm 80}$ See, for example, Kanavos and Nicod (n 34).

⁸¹ Commission Regulation (n 10).

⁸² Commission Guideline (n 33).

⁸³ Commission Notice (n 11).

⁸⁴ European Commission (n 6).

orphan designation could still be made but a larger proportion of them would have to use the ROI route, supported by evidence that would justify the incentives being made available, and with the mechanism of Article 8 (2) available to restrain excessive profitability of the resulting orphan medicinal products.

- 3. A mechanism similar to the 'withdrawal clause' from the early drafts of the Regulation should be re-introduced to the present Article 8 (2). This could take various forms, for example:
 - (i) The prevalence route mentioned in Recommendation (2) could be removed altogether. All applications for orphan medicinal product designation would use the ROI route. Orphan exclusivity could therefore be removed in any cases where an orphan medicinal product proved sufficiently profitable.
 - (ii) Article 8 (2) could be amended in line with the text of the 'withdrawal clause' in the earlier drafts of Regulation 141 / 2000, such that orphan exclusivity could be removed irrespective of whether the prevalence or the ROI route had been used, in any cases where an orphan medicinal product proved sufficiently profitable or where the price charged for it was such that an unreasonable profit had been made, or where the price charged was unjustifiable.
 - (iii) Article 8 could be amended such that a shorter period of orphan exclusivity is initially provided, with an extension of that period being available if evidence shows that the necessary ROI has not yet been achieved.

The re-introduction of such a mechanism should provide a meaningful brake on the behaviour of pharmaceutical firms operating in the orphan disease field, certainly in those cases where orphan exclusivity extends beyond the life of their other IPRs and where there are other firms able and willing to compete. Although the information necessary for the assessment of ROI would have to be provided in all cases, the commensurately improved transparency of the orphan medicinal product regime should improve confidence that the incentives provided under Regulation 141 / 2000 were not being improperly exploited. The necessity of an 'affordable' price could be stipulated during the term of the orphan exclusivity (with potential consequences for the term over which a sufficient ROI may be achieved). At least some of the public health authority funds that were effectively freed up through the lowering of excessively priced orphan disease fields. Confidence would be also improved if Art 8 (2) were amended to permit suitable non-member state actors to be able to support the use of them by member states in terms of monitoring and reporting on the necessary information.

- 4. In particular cases where marketing authorisation (and orphan exclusivity) is granted for an orphan medicinal product which essentially 'formalises' the use of a product which has previously been used 'off label' or has been compounded by pharmacists,⁸⁵ such that the majority of the information required by the sponsor was already in the public domain, provision should be made to ensure that:
 - (i) the prior users can continue to make the same use of the product that they have before; and
 - (ii) the commercial reward accorded to the sponsor is matched to the relatively small development risk and cost.

The orphan incentives must be used to encourage the development and introduction of new and more effective orphan medicinal products, rather than being commercially mis-used to take away access to long standing and perfectly effective old ones. The 50- to 500-fold price rises of amifampridine phosphate and CDCA once they were subject to orphan exclusivity (Boxes 2 and 3) are striking examples where the rewards being reaped by pharmaceutical firms taking advantage of the incentives under the Regulation are out of all proportion to the risks and costs of development.

- 5. The mechanism of Article 8 (3)(a) should be revisited and rethought insofar as it may enable 'evergreening' to take place, improperly extending the effective exclusivity term for an orphan medicinal product beyond ten years.
- 6. Consideration should be given to providing for a 'claw-back' mechanism, such that if an orphan medicinal product turns out to be profitable above a determined threshold, any financial and other costed support incentives that were provided by the EMA during the orphan medicinal product designation and marketing authorisation processes, should be repaid to the EMA.⁸⁶
- 7. Consistent with the other briefing papers in this series, provision should be made so that, in situations where a compulsory licence (CL) has been granted for (or government use (GU) made of) a patent / SPC covering an orphan medicinal product, for example, on public health grounds, any equivalent orphan exclusivity is waived.

⁸⁵ See Dooms and Carvalho (n 55).

⁸⁶ See, for example, Olivier Wellman-Labadie and Youwen Zhou, 'The US Orphan Drug Act: Rare Disease Research Stimulator or Commercial Opportunity?' (2010) 95 Health Policy; Bagley and others (n 77).

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