Orphan Medicinal Products in the European Union: *Briefing Document*



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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 €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.

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).

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).

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.

 $^{^{\}rm 70}$ 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.

- 1. 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

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.
- O. 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).

Further Reading

This document is part of a series of briefing papers; the rest of the series is available at https://medicineslawandpolicy.org/useful-resources/briefs/#EUReview.

- Koichi Mikami, 'Orphans in the Market: The History of Orphan Drug Policy' (2017) Social History of Medicine DOI: 10.1093/shm/hkx098
- Marc-André Gagnon, 'New Drug Pricing: Does it Make Any Sense?' (2015) 24 Prescrire International 192
- Medicines Law & Policy, 'The TRIPS Flexibilities Database', http://tripsflexibilities.medicineslawandpolicy.org
- 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>