Orphan drug pricing may warrant a competition law investigation

EU legislation offers an exclusive marketing period as an incentive for companies to develop drugs for rare diseases. But pricing for orphan drugs hinders access and may warrant a competition law investigation, say **Jonathan C P Roos**, **Hanna I Hyry**, and **Timothy M Cox**

Orphan drug legislation in the European Union has promoted the development of treatments for very rare diseases by bestowing 10 year marketing exclusivity. This market monopoly is one of the benefits that comes under the European Union's Regulation EC No 141/2000 (see web table 1) and has enabled manufacturers to charge what many consider "exorbitant" prices for orphan drugs[1] (table 1).

These necessary drugs, which are very costly, profoundly affect the wellbeing of patients who[2] struggle to persuade national health systems, operating under significant constraints,[3] to finance their treatment.[4 5] Orphan drug costs already consume 5% of the Belgian national drug budget[6] and are predicted soon to consume 6-8% of healthcare budgets of larger EU countries such as France[5]—an unsustainable position.

Current high pricing thus hinders access to treatment[7] and contravenes the aim of the Orphan Regulation: "Patients suffering from rare conditions should be entitled to the same quality of treatment as other patients."[8]

Why are orphan drug prices so high in Europe?

The regulation did not create an oversight body to regulate prices and protect consumers from market abuse, by contrast with other state sanctioned monopolies (for example, OFWAT regulates water prices in England [9]). However, if the product is deemed sufficiently profitable, the exclusivity period can be reduced to six years under Article 8(2). But a recent EU commissioned investigation has noted fears that it could "substantially" reduce investment incentives.[10] Thus this "claw-back" provision seems never to have been invoked and is unlikely to be in the future.

The EU has delegated responsibility for pricing and reimbursement to member states,[11] whose individual health authorities have usually only limited power to negotiate orphan prices.[5] Typically, companies avoid downward price referencing between countries by first marketing in member states where launch prices are unrestricted, such as the UK, Germany, or France.[5 12 13] In France the price is fully reimbursed during the trial phase.[5] Companies thus have an incentive to set a high initial price—which in practice remains unchanged after formal authorisation.[5] This practice can confound the efforts of other countries, such as Belgium, Spain, Greece, and Italy, which attempt to control prices.[5 12 13] Companies prefer to donate drugs[14] rather than perhaps sell at discounted rates to individual countries. Giving product away free can help to avoid the downward price referencing associated with differential pricing.[15] Once a drug is available elsewhere, even at a high price, national health authorities find themselves under intense public pressure to provide these long awaited treatments.[16]

The overall effect is harmonisation of pricing across the EU by reduced cross-country price referencing and inter-country imports.[5] A study commissioned by the EU found that prices varied only by a factor of 1.6, principally attributable to taxation.[5]

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The problem of high prices has prevailed since introduction of the regulation, and no solution hitherto has been found. However, a potentially powerful mechanism for controlling prices has been overlooked.

Does orphan drug pricing contravene competition law?

The aim of competition law is to protect consumers. A commonly known provision concerns the regulation of collusive behaviour such as the operation of cartels (Article 101 of the Treaty on the Functioning of the European Union). Another, Article 102, prohibits: "abuse by one or more undertakings of a dominant position within the internal market or in a substantial part of it ... Such abuse may, in particular, consist in: (a) directly or indirectly imposing unfair purchase or selling prices or other unfair trading conditions...."[17]

Although it is not an offence to be dominant, such a position places a special responsibility on a company not to allow its conduct to impair competition.[18 19 20] In the case of orphan drugs, the granting of market exclusivity by statute does not remove the company from the ambit of Article 102.[21 22] Table 2 shows the four conditions that

Table 1 | Orphan drugs and their approximate costs

Drug	Orphan disease	Approximate cost for typical patient per year (patient weight in kg)	Date of orphan marketing authorisation
Imiglucerase	Gaucher disease type I	£93 000 (70 kg)	23 May 1994 US
Agalsidase alfa	Fabry disease	£130 000 (70 kg)	4 May 2001 EU
Idursulfase	Mucopolysaccharidosis II (Hunter disease)	£413 000 (48 kg)	8 Jan 2007 EU, 24 Jul 2006 US
Alglucosidase alfa	Pompe disease	£268 000 (70 kg)	29 Mar 2006 EU, 28 Apr 2006 US
Sapropterin	Phenylketonuria	£102 000 (70 kg)	8 Jun 2004 EU
Eculizumab	Paroxysmal nocturnal haemoglobinuria	£250 000	17 Oct 2003 EU, 19 Mar 2007 US

Price calculations based on unit costs obtained from *British National Formulary*.
US=United States, EU=European Union.

Table 2 | Elements of Article 102 of the Treaty on the Function of the European Union

Article 102 element	Application in orphan drug context
(1) Market dominance must be established by showing ability to (a) prevent effective competition (b) behave independently of customers/consumers	The manufacturer of an orphan drug is undoubtedly in a dominant position by virtue of its market exclusivity, which prevents effective competition (a). Even a market share of 50% can give rise to a presumption of dominance, so an orphan drug manufacturer's market exclusivity is likely to amount to dominance.[20 23-25] The persistence of high drug prices despite the concerns of patients, doctors, and health authorities suggests independence from consumers and customers, thus fulfilling (b)
(2) Must pertain to whole or substantial part of internal EU market	As the orphan marketing exclusivity applies throughout the EU, an orphan drug company occupies a dominant position in the entire internal (meaning EU-wide) market. A monopoly in even one member state is likely considered a substantial part of the internal market, in particular where the company enjoys a statutory monopoly. Even if this pan-EU criterion were not met, a company would remain subject to corresponding national antitrust legislation of individual member states (eg, Chapter II of the UK Competition Act 1998 which was successfully invoked to end market abuse by an orphan drug company in the UK)[26-29]
(3) Must affect interstate trade	The abuse of a dominant position must affect trade between member states. Behaviour of the given company need not in fact have affected interstate trade; it is sufficient that it is capable of having such an effect. Thus, even if an orphan company were found to abuse its position in only one member state, interstate trade would probably be threatened, since the regulation envisages sales throughout the EU[28 30 31]
(4) The market position must be abused	The fourth and perhaps most difficult question is whether abuse in fact takes place. This is discussed at length below

Table 3 | Approaches to determining if a price is fair

Investigative approach	Application in orphan context
Consideration of competitors' charges on similar products or services[25]	In the absence of a competitor's drug (owing to the unique monopoly situation), an investigation would not be able to draw a direct comparison with competing prices
Economic value of the service or product[35]	Similarly, this is typically determined by the differential with competitors' prices[9 35] and would therefore not apply in the orphan setting
Company's profit margin on drugs sold[36]	An investigating authority might focus on the fact that some orphan companies are thought to make profits of more than 90% on their bestselling medicines[2] and their margins are generally thought to be greatly ahead of more "mass market" therapies.[38] For example, the price of an orphan drug did not materially change after production costs were presumably substantially reduced after switching from purification from human placentas to in vitro recombinant expression of the cognate protein[14]
Return on investment[37]	Rare diseases necessitate a higher price per patient for reasonable returns, but the influx of the largest pharmaceutical companies into the orphan market suggests that returns may be unusually lucrative (see table 2)
Manufacturer's cost base[36]	The European Court of Justice[9 25] and the UK Competition Appeal Tribunal[36 39] have previously held that it is permissible to use a comparison between costs and pricing, rather than returns on investment, to determine whether a price is excessive

Table 4 | Price setting for orphan drugs compared with non-orphan drugs

Drug price determinant . . .	. . . in the orphan drug context
Prevalence (the less prevalent a condition the more it costs to treat per capita)	Orphan drug pricing correlates to some extent with disease prevalence.[5] However, the relation is not linear and exceptions exist. For example, arsenic trioxide is priced similarly to bosentan even though acute promyelocytic leukaemia and primary pulmonary hypertension differ almost tenfold in prevalence.[5] Indeed, the price of drugs for diseases with similar prevalence can vary by up to a factor of seven[5]
Production costs	Companies do not typically disclose production costs but they do not appear to feature strongly in orphan price setting. Changes in production methods have apparently not led to an analogous reduction in consumer price, despite substantial savings in costs and a likely substantial rise in profit margins[40]
Molecular complexity	Complexity of the compound does not seem to readily correlate with orphan prices.[5] Arsenic trioxide (consisting only of three oxygen and two arsenic atoms and in regular production since the 18th century)[41] was re-priced as an orphan agent at $50 000 for one year's therapy (currently approximately £13 000 in the UK).[42] Sapropterin, a simple orphan molecule with a molecular weight of 314.17 Da (C9H15N5O3-2HCl), which can be used to treat phenylketonuria, retails at around £102 000 per year. This is similar to the price charged for enzyme replacement therapy for Gaucher disease, even though the latter's structures are much more complicated, with molecular weights in tens of kilodaltons, and with pH sensitive three dimensional structures, as well as the need for post-translational modification of glycans for targeting to lysosomal compartments. Moreover, monoclonal antibodies, probably of equal molecular and manufacturing complexity, can retail at less than £10 000 (adalimumab) or over £230 000 (eculizumab)
Need to recover investment	That orphan drug companies very readily recoup their investments at the current high price levels is suggested by the large influx of mainstream pharmaceutical companies into this niche area through, for example, a hostile takeover bid.[43-45] Recovery of investment seems to be faciliated by the relatively low development costs: it has been suggested that by 1992 a biotech company's annual profits on the original enzyme replacement therapy for Gaucher disease exceeded $200m compared with the cost of developing the drug, which a federal study estimated to have been less than $30m[46 47]
Perceived medical benefit	Therapeutic benefit does not seem to play a part in pricing. Efficacy frequently remains under investigation as a condition of marketing authorisation for rare disorders. As an example, highly effective enzyme replacement therapy for Gaucher disease is priced at a lower level than that for Fabry, even though the therapeutic benefit of the latter is less clear[48 49]

must be met for a company to breach Article 102.

As to the first condition—establishment of market dominance—orphan drug companies may even be classified as "super-dominant" because of their unusually large market share.[9 32 33] Under these circumstances of overwhelming dominance,[19 34] the manufacturer's responsibility is considered to become greater, since market abuse is more likely, as well as potentially more harmful.[9 32 33]

Are orphan drug prices abusive?

Article 102 states that "directly or indirectly imposing unfair purchase or selling prices or other unfair trading conditions" constitutes abuse. Under competition law, behaviour can be abusive, even where there is no intention of infringement.[9]

But neither Article 102, nor case law, has conclusively defined "unfair." Traditionally difficult, this is ultimately for an investigating authority or court to determine with reference to pricing data. The possible approaches an investigation can take are outlined in table 3.

In evaluating fairness, authorities may also examine the basis on which orphan drug prices are set. Non-orphan drug prices are typically based on (1) the price of competing drugs, (2) the need to recover investment, (3) production costs, (4) disease prevalence, (5) molecular complexity, and (6) the perceived medical benefit. An EU commissioned study, by contrast, has deemed orphan drug price setting "highly arbitrary"[5] and referred to the "black box of pricing"[5] owing to the lack of transparency in the process. Despite the limited information in the public domain, a provisional analysis (table 4) seems to support the independent study's conclusion of arbitrariness in orphan price setting.

Our experience in treating orphan diseases is biased towards lysosomal disorders, and the examples given here are principally drawn from this field. As academics, with access only to incomplete, publicly available data, we are not in a position to determine whether any particular breach of Article 102 has taken place, and make no judgment in this regard. This is a "complex" question of fact[9] for a court or competition authority, such as the European Commission, to investigate and determine.

Can companies abuse their dominance by means other than pricing?

Our analysis suggests that in this field, pricing may warrant investigation by a competition authority. Were such a body to look into this issue, conceivably it might also wish to look into matters other than pricing, for market abuse can take other—often more subtle—forms.

For example, an orphan company has been held to have offended the UK's competition law by bundling services so as to retain control of the home delivery and infusion assistance markets.[29] Similar anti-competitive practices have been highlighted in the commission's report into the non-orphan drug sector.[11]

The consequences of Article 102 infringement

Infringement of competition law has serious consequences: the commission can impose a fine; require the company to stop the infringing behaviour[50] or, in extreme cases, break up the company.[51] Furthermore, consumers are able to seek an injunction and damages in national courts,[52] enabling individual patients, patient groups, and healthcare providers to seek redress.

The prospect of regulatory action could motivate a constructive dialogue on acceptable pricing levels

Responsibilities under Article 102 become greater (so that a finding of abuse becomes more likely) where a company is super-dominant.[9 19 32-34] In this setting, regulators consider the special characteristics of the product and market.[9 32 33] Heightened responsibility to refrain from abusive practices would probably be expected given that orphan drugs are life saving or life prolonging necessities, rather than regular commodities.

How might companies respond?

Orphan drug companies may argue that their prices are proportionate and justified objectively because they are set at a level the market will bear.[22] This argument may be questioned since, in a market with legally sanctioned exclusivity, each company is the market; there are no other participants.

As noted, through compassionate use programmes, some companies donate free orphan products for severely ill patients in countries that cannot afford to pay.[14] Though highly laudable, potential or notional beneficence would not excuse market abuse should it be found. Some have suggested, with reference to the non-orphan sector, that such donations can be a means to avoid the downward price referencing discussed earlier.[15]

Companies contend that large profits allow them to invest in innovative treatments for other rare diseases,[14] but investment is common pharmaceutical business practice. Furthermore, the research underlying many innovative drugs has often been started in publicly funded universities and research institutes.[44] Development requires direct involvement of patients, their encouragement, willingness to take risks, and material funding from their charitable organisations.

The high cost of manufacturing biological drugs has also been invoked to justify high pricing[53]; but manufacturing costs correlate poorly with price and ought not to be materially higher than for other biological agents retailing at a fraction of orphan prices.

Companies could argue that the Commission should not intervene, because their monopoly period is limited compared with those of utility companies, which could last indefinitely. However, orphan drugs can be life altering—in the 10 year exclusivity period, patients (including children) may die or become seriously debilitated. By contrast, a utility would not be expected to have such a drastic effect on an individual.

Competition law has at times been controversial: companies have argued that the law penalises the superior product or business model, which resulted in their success and dominance. In the orphan context this argument is specious because dominance is attained by competition to be first into clinical development rather than have a better product or price.

As orphan drugs near the end of their exclusivity periods, competing entrants will match or only slightly undercut the prices of the dominant company to maximise revenue for their shareholders. In conversation, orphan company executives have estimated that five or more competing products will be required before prices are substantially reduced—a state of affairs unlikely be attained in the highly specialised orphan arena for some time to come.[54] As Article 102 can also be applied to positions of collective dominance, it will remain helpful to those who care for patients with rare diseases.

Can the Article 102 route realistically reduce prices?

Without competition in the market, citizens must rely on regulators to control excessive pricing. For the reasons outlined in web table 2, the Article 102 investigation route could offer the most direct and effective mechanism to curb excessive pricing even if no abuse is ultimately found.

Although the commission has previously been reluctant to pursue investigations based purely on excessive pricing (it is notoriously difficult to define a fair purchase price[55] and we presume particularly so in the "synthetic" orphan market), we contend that the ethical imperative is in no way decreased by the difficulty of the task. Indeed, rare diseases have been identified as a "priority area" for community action.[8]

High prices entail direct human costs: they may preclude treatment or burden patients with guilt and, especially in times of economic hardship, induce fears that funding for treatment will be withdrawn.[56]

We note, however, that a finding of abuse under Article 102 or its national equivalents, could have severe repercussions for an industry that is instrumental in bringing innovative treatments to patients for whom no therapy has previously been available. A sufficient profit motive must be preserved to ensure that the industry continues to attract the necessary capital to fund drug development.

We conclude by suggesting that while competition law potentially offers a direct and effective route to address the difficult problem of orphan drug pricing, it may also inspire a less contentious resolution: the prospect of regulatory action could motivate a constructive dialogue on acceptable pricing levels, and even result in further EU orphan legislation.

Jonathan C P Roos medical doctor, Department of Medicine, University of Cambridge, Cambridge CB2 2QQ, UK
Hanna I Hyry lawyer, Department of Medicine, University of Cambridge, Cambridge CB2 2QQ, UK
Timothy M Cox professor of medicine, Department of Medicine, University of Cambridge, Cambridge CB2 2QQ, UK
Correspondence to: T M Cox **ec432@medschl.cam.ac.uk**

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Contributors and sources: JCPR is a medical doctor with a research interest in orphan diseases. TMC is a physician who cares for patients with rare disorders. HIH is a lawyer with a background in philosophy, politics, and economics. The views expressed here are our own and do not represent the view of any firm, company or charitable trust. HIH and JCPR contributed equally to this work. HIH conceived the idea of applying Article 102 to the orphan funding problem. All authors have contributed to the legal, scientific, market and clinical analysis and their application to the orphan context. All three authors wrote the paper. TMC acts as guarantor for this work.

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