WHAT MAKES AN ORPHAN DRUG?

Nigel Hawkes and **Deborah Cohen** investigate claims that drug companies are making easy profits by licensing existing treatments for rare diseases

Loopholes in legislation designed to provide treatments for rare diseases are being exploited by drug companies to generate huge returns for very little effort, British doctors have claimed.

In an open letter to the prime minister, 20 consultants and a patient group say that National Health Service patients are being denied access to a potentially life saving treatment since it was licensed under the European Union orphan drug legislation and its price increased by a factor of 40.

Little research was required of the US company BioMarin before it was awarded a European licence for amifampridine (Firdapse), a slightly modified version of 3,4-diaminopyridine, which is unlicensed but has been used for more than 20 years to treat two rare diseases, Lambert Eaton myasthenic syndrome (LEMS) and congenital myasthenic syndrome.

The licence granted for amifampridine covers only the first of these conditions, an autoimmune disease that causes muscle weakness that affects only about 150 patients in the UK at any one time. But the Medicines and Healthcare Products Regulatory Agency (MHRA) has told neurologists that now the drug is licensed they are obliged to use it for both LEMS and congenital myasthenic syndrome, an inherited condition with similar symptoms.

The rules allowed the company to rely on existing evidence of efficacy to gain a 10 year exclusive licence to market the drug. Treating a patient for a year with diaminopyridine costs £800-£1000 (€940-€1200; $1300-$1600) compared with £40 000-£70 000 for amifampridine, depending on dose. Some primary care trusts have refused to fund the drug because they argue that at this price it is not cost effective. In others that do fund it, the high cost is likely to have a knock-on effect, which could deny other patients the chance of treatment.

The amifampridine case is just one among many, charges Sam Richmond, a consultant neonatologist at Sunderland Royal Infirmary and a signatory of the open letter. "Drug companies are sweeping up useful little products that pharmacists have been producing in their back shop for years, which are available and cheap. They then turn them into something people can't afford, and present it as a good thing.

"This is not what the law was intended to do. If drug companies are undertaking research where nobody else was interested—and some are—then a monopoly may be justified. But if it's a product already in use, they should clear off, or sell at a price comparable with the existing price."

Daphne Austin, chair of the UK Commissioning Public Health Network, says: "It disgusts me, it really does. [Amifampridine] is one of a number of drugs that are not new but under the legislation have been licensed so that they can be sold for much more money, which is pure profit.

"The price set for the drug is indecent." Rather than contributing to patients' wellbeing, she says the arrival of amifampridine could do great harm. "As a direct effect of this drug's price, some patients will not get the care they would have done—either because their primary care trust won't fund it, or because it will and other patients' care has to be cut to find the money." She says that the extra cost of amifampridine in the UK is equivalent to that of kidney dialysis for 323 patients.

Licensing regulations

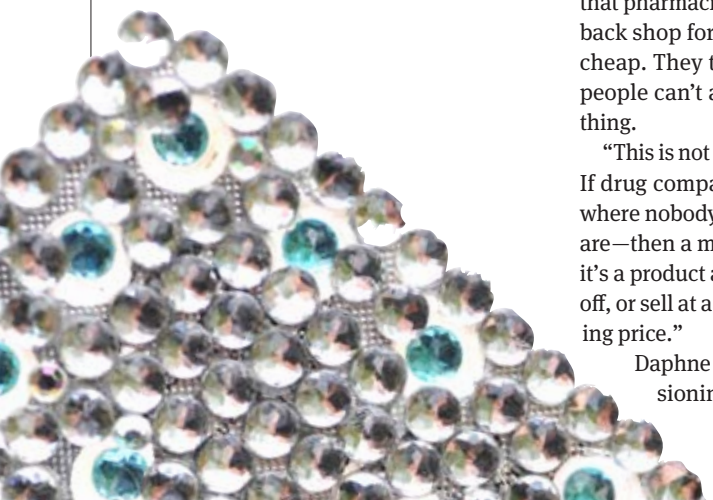
Critics of the way the legislation is being used direct much of their anger at the MHRA. It rules that if there is a licensed product available for any indication, a clinician cannot justify continuing to use an unlicensed product unless it offers a clinical benefit. A difference in price, no matter how large, does not provide such a justification, in the MHRA's view.

The MHRA also says that once a licensed medicine is available, companies making unlicensed products should cease to do so or face possible regulatory action. It allows a transitional period, but only to provide time for patients to be moved on to the licensed product. Furthermore, clinicians should not use an unlicensed medicine for other diseases—in this case, congenital myasthenic syndrome—when a licensed medicine will meet their needs, even if its licence does not cover that indication.

Others interpret the law differently. David Lock, a barrister who specialises in healthcare law, says there is no reason in principle why the NHS should be required to prescribe a more expensive licensed drug when a pharmacologically identical drug exists but is unlicensed. It depends, in his view, on primary care trusts refusing to fund the expensive drug.

If they have a choice, doctors must prescribe the licensed drug. But if that choice is denied by a decision of the primary care trust, he is confident that a doctor would be exposed to virtually no professional risk in following existing practice to prescribe the unlicensed alternative.

This assumes, of course, that the unlicensed alternative remains available—unlikely, in this case, since the MHRA gave compounders six months to stop producing diaminopyridine. (It has recently modified this instruction, permitting the production of 20 mg tablets, since BioMarin produces only 10 mg tablets of amifampridine. But this loophole would close if BioMarin started to produce 20 mg tablets.)



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Unintended effects

Orphan drug legislation began in the United States, in a laudable effort to encourage drug companies to develop medicines that would otherwise be uneconomic because of the small number of patients needing them. The US law was followed by similar legislation in Europe.

Both schemes offer a monopoly (usually seven years in the US, 10 in Europe) to the makers of orphan drugs that win a licence. Evidence of efficacy is much less demanding than for mainstream drugs, and often consists of little more than that already gathered by clinicians using unlicensed medicines in their day to day practice. Publicly funded health services provide the evidence for private companies to exploit for profit, generating drugs that those self same health services then can no longer afford.

Dr Richmond says that drug companies started asking questions of clinicians soon after the European legislation came into force in 2000. "A company called Orphan Europe wanted to know what drugs we were using off licence," he says. "Two drugs came up in the discussion, and they put them through licensing."

Orphan Europe acquired a licence for carbamylglutamate, the efficacy of which for treating a rare inherited defect of *N*-acetylglutamate synthetase had been identified as long ago as 1982. The treatment works well but must be continued for life. Carbamylglutamate unlicensed cost £11/g; the licensed product £262.90/g. The annual cost for a child increased from just over £4000 a year to more than £95 000, Dr Richmond reported in the *Lancet* in 2009.[1]

"It's a scam and it should be exposed as such," he had earlier told the *Guardian*.[2] "It would appear we have no alternative but to pay their outrageous prices or break the law." Orphan Europe responded in the same newspaper article that the price increases had been justified by the safety and quality of their product. "For ten years these physicians have been treating their patients with a chemical and they do not know what they have," Pierre Mambrini, a pharmacist employed by Orphan Europe, said.

Similar problems have arisen in the US. James Love, a lawyer who specialises in intellectual property, says that the 1983 act in the US started out as a limited measure but had become "an open ended entitlement, with zero transparency of the subsidies firms receive, which includes 50% of the cost of their clinical studies.

"The protection was given in cases where it was not needed, and it has raised the price of medicines, sometimes by an astronomical amount," he says. In evidence earlier this year to a Senate committee investigating paediatric diseases, he said that there were at least nine products that now cost more than $200 000 a year per patient, and the trend was for higher prices. Adult patients with Fabry's disease may pay over $700 a day for treatments they take every day of their lives.

The public, he says, finishes up paying twice for the medicines: first as taxpayers subsidising the cost of developing the drugs, then as consumers facing monopoly prices.

Easy profits

Orphan drugs offer returns to drug companies that can be eye watering. The fewer patients a drug treats, the more it tends to cost, because patients are so thinly spread that healthcare funders seldom have to pay for more than one or two. Shire Pharmaceuticals' Elaprase (idursulfase), a treatment for Hunter's syndrome, generated sales of $353m in the US last year even though only 500 Americans have the condition, *Forbes* magazine reported in February this year.[3]

Many orphan drugs are biological and cost more to produce, but others, such as diaminopyridine, are simple chemicals that can be readily synthesised by a competent pharmacist. There are few marketing costs because there are not many patients. And orphan drugs get many helping hands from licensing authorities anxious to ensure that patients with rare diseases do not miss out.

The hurdles that must be jumped to gain a licence for an orphan drug are set much lower than for other drugs. A study of 44 orphan drugs approved by the European Medicines Agency by the end of 2006 found that only 25 had been tested in randomised control trials, often on small numbers of patients and over short timescales.[4] Some drugs had been approved on the basis of the existing literature, others on data from trials with as few as 28 patients.

Silvio Garattini and colleagues from the Mario Negri Institute for Pharmacological Research in Milan, who carried out the study, say that clinical and public health needs "are poorly met by inadequately documented orphan drugs' efficacy and safety profiles." They criticise a lack of dose finding studies, inappropriate clinical design, surrogate end points, and weak proof of clinical benefit.

With amifampridine, BioMarin did not need to conduct any trials of efficacy or safety before licensing. They were granted the licence on the basis of experience with diaminopyridine prescribed by clinicians on a named patient basis and gave undertakings to conduct some further tests. The company argues that amifampridine

is a better drug than diaminopyridine because it is more stable and reliable.

A spokeswoman for the company said that the quality of diaminopyridine made by compounders was uneven. "A study by the University of Cardiff showed significant variability in the percentage of active drug in doses," she said. "In nine compounded formulations from different sources the dose of active drug varied from 22% to 125%."

But David Nicholl, a consultant neurologist at City Hospital and Queen Elizabeth Hospital, Birmingham, and a signatory of the open letter to David Cameron, said that clinicians had not noted that the stability or otherwise of diaminopyridine was a clinically important problem despite almost 30 years of use.

"Expert clinicians take the responsibility for informing patients about the drug and prescribing it," he said. "It has an excellent safety record."

The BioMarin spokeswoman said the company had acted at the request of the French government. "They said to us that patients with LEMS deserved the same protection as those with common diseases such as diabetes. Firdapse is a stable compound, offering more safety, greater availability and a consistent dose.

"The company has also set up a proper registry of patients taking the drug, so that they are investing in the future of their patients and any issues will be identified—with diaminopyridine there was no reporting protocol. Comparing Firdapse with diaminopyridine is comparing apples and pears."

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Adrian Quartel, medical director of BioMarin Europe, acknowledged that there had been concern about the price of the drug. He defended it by saying that BioMarin's survey of diaminopyridine in Europe had shown "severe problems" in some places.

"There was no commitment, no safeguards, no registry to capture incidents," he said. "Now we have all these, and most importantly, all the safety in place that the MHRA and EMEA require. All that tends to get lost in the argument over price."

In the UK, drug companies can set their own prices subject to a ceiling on profits, but in France the price of each drug is the subject of negotiation. "So in France we submitted a full review package and the price negotiated was only slightly below the UK price," Dr Quartel said.

He revealed that the company had been called in by the Department of Health "to explain ourselves" and had done so. "Afterwards we filled in the paperwork they asked us for, and the department said it was satisfied. So the department feels the price was reasonable; so does the French government."

Painful prices

Dr Austin says that it is "perverse" to use the orphan drug legislation for medicines that have been in use for many years. She points to the example of colchicine, which has been used to treat gout since the 19th century or even longer—the Greeks used the plant from which it is extracted for gout more than 3000 years ago—but which was nevertheless granted orphan drug status by the US Food and Drug Administration in July 2009. The FDA gave the US company URL Pharma three years of market exclusivity for this ancient drug under the trade name Colcrys.

To get this licence, URL Pharma did a small trial in 185 patients to confirm the drug's safety and efficacy, showing it had the same benefits and side effects as colchicine. Once it was granted exclusivity, the company brought a lawsuit seeking to remove other versions from the US market, and raised the price 50-fold, from $0.09 a pill to $4.85.

Aaron Kesselheim and Daniel Solomon, from Harvard Medical School, say that the reward "appears to be out of proportion to the level of investment." Writing in the *New England Journal of Medicine* in June this year, they add: "More important, there is no evidence of any meaningful improvement in the public health."[5] They estimate that Medicaid alone will have to find an extra $50m a year to pay for the drug. Since a form of colchicine is already licensed in the UK, it seems unlikely that similar problems will arise here.

Added value

The high prices for orphan drugs make possible a pricing strategy in which companies seek a licence for a niche product, and then once it is established they attempt to broaden the applications into more common diseases. "They go for subgroups of subgroups, then roll it out but the price is not renegotiated," says Dr Austin. "This is very specific to the orphan drug legislation."

The chief executive officer of BioMarin, Jean-Jacques Bienaime, said in October 2009 that the company would be seeking other indications for amifampridine in both the US and Europe. Among indications mentioned at the time was multiple sclerosis, but Dr Quartel told *BMJ* that this had been carefully examined and would not be proceeded with. "We have no plans to do that," he said.

The history of its acquisition of the drug is complex. Originally developed by the Assistance Publique Hopitaux de Paris (AP-HP), a group of 39 Paris hospitals, the rights were first acquired by EUSA Pharma, a company whose registered office is in the Oxford Science Park.

Huxley Pharmaceuticals, a private life sciences company founded and managed by Aceras Biomedical, a New York investment firm, then licensed the rights from EUSA Pharma and gained preliminary approval from the European Medicines Evaluation Agency for use of the drug for LEMS in October 2009. A week later Huxley was taken over by BioMarin.

Under the deal, BioMarin paid Huxley shareholders $15m upfront, with an additional $7.5m when the EU finally approved amifampridine. In addition, Huxley will be entitled to a further $36m in milestone payments if sales targets are met.

In a statement to *BMJ*, BioMarin said that when it purchased the intellectual rights they came with a preclinical safety and toxicology research package, and this was reflected in the price paid. Subsequently it has completed a clinical trial looking at how taking the drug with food affected the pharmacokinetics.

It also plans a double blind placebo controlled trial in patients with LEMS, a pharmacokinetic study in patients with renal impairment, and a further study into whether it causes heart rhythm disturbances.

"Our position has been straightforward," Dr Quartel said. "We really do care for the patients, we have all the safeguards in place, and the pricing is in line with other drugs. I know there has been a lot of noise in the neurological community, and we understand that. We want to work with them, but we have found it hard to engage. At no point have they contacted us about the allegations they have made."

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See EDITORIAL p 1059, ANALYSIS p 1084

Open letter to prime minister David Cameron and health secretary Andrew Lansley

Neurologists and paediatricians call for action on "massive" rises in the prices of orphan drugs

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We are writing to you as a group of clinicians treating patients with so called "orphan" diseases (and one representative of a patients' group) to express our concern at an unintended effect of the European Union's regulations on orphan drugs. The original purpose of this legislation, passed in 1999, was to encourage drug companies to conduct research into rare diseases and develop novel treatments. However, as the rules are currently enacted, many drug companies merely address their efforts to licensing drugs that are already available rather than developing new treatments. Once a company has obtained a licence, the legislation then gives the company sole rights to supply the drug. This in turn allows the company to set an exorbitant price for this supply and effectively to bar previous suppliers of the unlicensed preparation from further production and distribution.

We believe that this behaviour is not in the best interests of patients or the NHS but is undoubtedly significantly advantageous to drug companies. We have made representations to the Department of Health for England and the UK Medicines and Healthcare Products Regulatory Agency. In reply we have simply been quoted the rules, and no one seems willing to investigate the issues we are raising or to consider whether the system should be changed. We are asking you to identify the appropriate individuals who can act on this unacceptable situation.

One example of the effect of these rules is the drug 3,4-diaminopyridine (3,4-DAP). We have been using 3,4-DAP for more than 20 years to treat two rare diseases, Lambert-Eaton myasthenic syndrome and congenital myasthenic syndrome; both cause disabling muscle weakness of the limbs, body, eyes, and face, together with swallowing and breathing problems, which can be fatal. The drug improves muscle strength and is used either because other treatments haven't worked well enough or to avoid using drugs that can have serious side effects. Expert clinicians take the responsibility for informing patients about the drug and prescribing it. It has an excellent safety record. Until now 3,4-DAP has been produced by a small drug company on an unlicensed basis and costs between £800 (€945; $1285) and £1000 per patient per year.

The company BioMarin has now been issued with a licence to supply the drug (marketed as Firdapse) throughout Europe and has priced its product at £40 000 to £70 000 per patient per year—a 50-fold to 70-fold increase. BioMarin merely had to demonstrate that its drug works, using data generated from the unlicensed version. It has simply produced a slightly modified version (amifampridine) that meets regulatory standards and has been allowed to set the price at an exorbitant level with no clinically relevant advantage.

This high cost means firstly that some funders (primary care trusts) have refused to pay for the drug, because it doesn't fulfil cost effectiveness criteria. It also means that, where it is funded, no additional funding source has been identified, which must mean that patients in other areas are being deprived of NHS funding. The cost to the NHS is likely to be above £10m a year.

We urge you to instruct urgent review not only for the sake of our particular patients but also for the many other patients who are likely to be affected in the near future as other drug companies take advantage of this loophole. Extraordinarily, there is a website that lists other drugs that can be similarly exploited (www.fda.gov/ForIndustry/DevelopingProductsforRareDiseasesConditions/owtoapplyforOrphanProductDesignation/ucm216147.htm).

In the present economic situation it seems vital to ensure that systems are in place to prevent excessive commercial profits being made at the expense of patients and public spending. Although the pricing of 3,4-DAP is the most recent example of this trend,[1] massive price rises have been noted in treatments for other orphan diseases for years; examples include *N*-carbamylglutamate (for *N*-acetylglutamate synthetase deficiency), sodium phenylbutyrate (for ornithine carbomoyltransferase deficiency), ibuprofen and indometacin (for patent ductus arteriosus), caffeine citrate (for apnoea in preterm infants), and even nitric oxide (for pulmonary hypertension).[2 3]

We believe there to be sufficient grounds for the UK parliamentary health select committee to look at the pricing of orphan drugs, as the costs directly affect patients of all ages with a diverse range of conditions across the country. If an investigation were to find evidence of artificially high pricing, the Office of Fair Trading should consider pursuing the issue.

Legislation on orphan drugs, far from encouraging the development of new treatments for orphan diseases, is severely limiting the availability of existing treatments. We believe that the Medicines and Healthcare Products Regulatory Agency and Department of Health should not just state the rules but should act now to progress the issue of unfairness upwards, so as to instigate change.

Competing interests: All authors have completed the unified competing interest form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare no support from any organisation for the submitted work; JL has acted as a consultant to orphan drug manufacturers (Special Products Ltd and Swedish Orphan), has been paid travel expenses to attend professional meetings on orphan drugs, was on an educational advisory panel for the Orphan Academy, supported by Orphan Europe, and has chaired workshops for Swedish Orphan; and no other relationships or activities that could appear to have influenced the submitted work.

References are in the version onbmj.com

See EDITORIAL p 1059, ANALYSIS p 1084