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- News Doctors are warned not to prescribe generic pregabalin for pain control (*BMJ* 2015;350:h3119)
- Views & Reviews: Margaret McCartney: Second use patents—why do we have to prescribe branded Lyrica for pain? (*BMJ* 2015;350:h2734)
- Feature: Why have UK doctors been deterred from prescribing Avastin? (*BMJ* 2015;350:h1654)

Pfizer steps up battle to defend control of pregabalin

Pfizer's actions over its biggest blockbuster drug Lyrica sparks confusion

Pfizer has launched a charm offensive on UK doctors, after accusations of profiteering and concerns over increased paperwork for prescribers, and has taken to the courts to defend exclusive control over the main use of its valuable pain drug pregabalin.

The US pharmaceutical giant has written to the medical press to emphasise to doctors its desire to continue investing in research and development in patients' interests, while arguing that its top selling drug should remain partly protected from competition, despite the expiry of the original patent.

Berkeley Phillips, Pfizer's UK medical director, and Seema Patel, its medical director for established UK pharma business, apologised to doctors for confusion and said, "Our intention was neither to cause confusion, nor add to your workload." But they insisted on the need to defend the company's intellectual property rights.

The letter follows concern among doctors in recent weeks after they received circulars from the NHS cautioning that they should seek to prescribe pregabalin by using its brand name (Lyrica) when they prescribe the drug to treat pain.[1] Pfizer had cautioned commissioning groups that to do otherwise could be "unlawful."

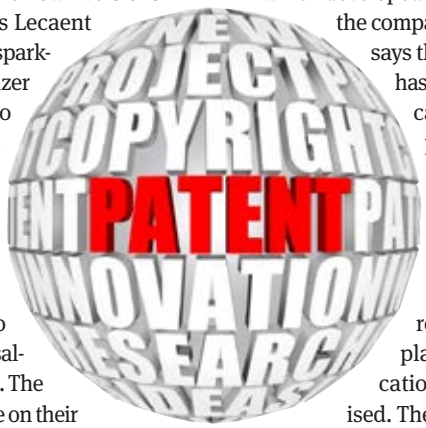
The actions highlight the large financial sums at stake, unusual aspects of the patent system, and limitations in the way prescribing operates in the United Kingdom. "This is a massive case in intellectual property terms," says one of the lawyers who is involved. "Lots of law firms are watching it. We have never had a case like it."

Pfizer's latest move came after the primary patent that the company held on the pregabalin molecule expired at the end of last year, spurring several manufacturers of generic drugs to launch cut price versions targeted at its indications for epilepsy and generalised anxiety disorder.

However, Pfizer continues until 2017 to hold exclusivity under a "secondary use" patent it was subsequently granted on pregabalin when the drug is prescribed for the treatment of neuropathic pain.

"Skinny labels"

Actavis and Dr Reddy's, two generic drug manufacturers, have launched their own versions of the drug (brand names Lecaent and Alzain, respectively), sparking a legal riposte from Pfizer that has already gone to appeal and is scheduled for fresh hearings at the end of June.



Consilient Health has also offered its branded version (Rewisca), which requires pharmacists to order the drug from wholesalers under tight supervision. The generic manufacturers state on their websites that their product is only for the two indications that are no longer covered by patents, using a "skinny label" that does not include the pain treatment authorisation also granted on the drug by British regulators.

However, the British system, which encourages generic prescribing to maximise use of the cheapest version of drugs, offers no easy way to make a distinction between the different indications for which the drug is used.

> Lots of law firms are watching it. We have never had a case like it

UK and other authorities have long granted "second" or "further medical use" patents to drug companies, designed to provide financial rewards for continued research into their wider application. Drug companies argue that without such a process they would have no incentive to fund further long, costly, and uncertain research trials and regulatory approvals.

There are some precedents for skinny labels, which have allowed generic manufacturers in the past to officially sell drugs only for off-patent uses while in practice being able to benefit from sales for the small additional indications that technically remained under patent.

But no previous examples are on the scale of pregabalin. Pfizer estimates that in the UK 80% of the drug's total prescriptions are for neuropathic pain. The income involved is substantial. The NHS last year spent nearly £250m (€340m; $380m) on Lyrica. Worldwide, the drug is the company's most important, generating sales of $5.2bn in 2014, up substantially on previous years.

Pregabalin was originally licensed to Parke-Davis, which later became part of Pfizer and which developed the drug for epilepsy. But the company tested other uses and says that from the late 1990s it has invested in about 50 clinical trials involving 12 000 patients to evaluate its use for neuropathic pain.

Drug industry executives argue that without the incentive of second indication patents, such research would never take place, and new drug applications would not be authorised. The alternative is that drugs are prescribed "off label," based more on hunches than rigorous trials—allowing their use without large scale systematic testing of benefits or risks.

Not just a Lyrica issue

"This is not just a Lyrica issue, it's an industry issue," said Pfizer's Phillips. "We are all for discovering new molecules, but increasingly, with our knowledge around science, mechanisms, and pathways, we will go back and test medicines in new conditions. If second patents are not protected, companies are not going to be able to invest in that sort of research, and patients will suffer."

The industry has recently been exploring ways to improve collection of data on the use of drugs by indication. The absence of such data on prescription forms today eases doctors' paperwork, encourages prescribing of lower cost drugs, and ensures the privacy of patients. But it makes it difficult for legitimate researchers to understand usage levels, follow how far guidance, such as that of the National Institute for Health and Care Excellence, is being followed, and to adapt pricing.

Whatever the outcome of the Pfizer legal battle with its generic rivals, the case has sparked fresh debate over incentives for research and the trade-off between minimising administration while collecting information more systematically on prescription by indication.

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PAID FOR BY THE NHS, TREATED PRIVATELY

John Appleby looks at how much non-NHS providers contribute to NHS care

Fig 1 | NHS inpatients treated by NHS and non-NHS organisations, 2006-07 to 2013-14[2]

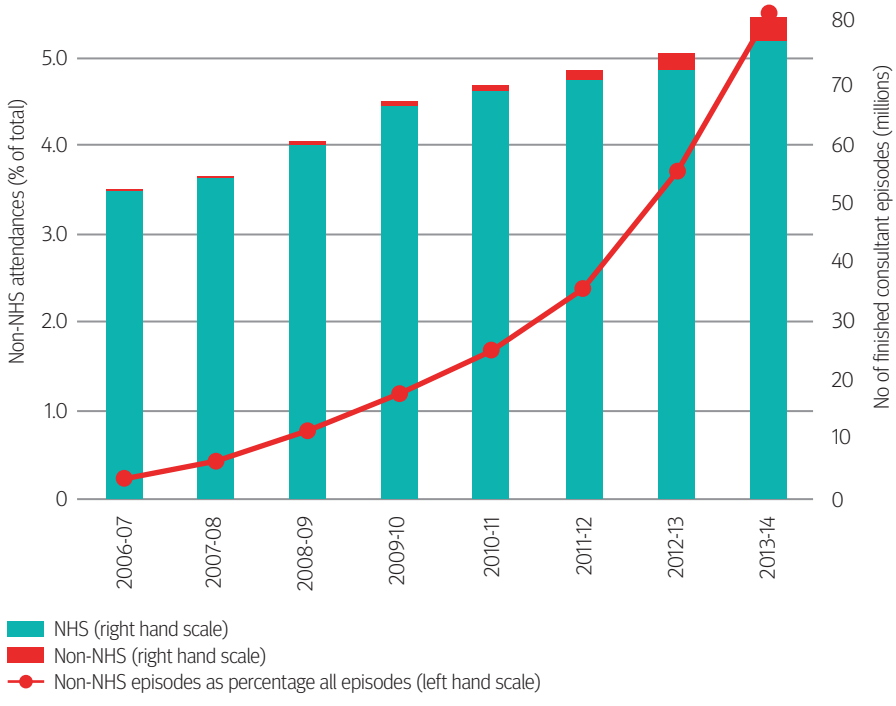

Fig 2 | NHS outpatients treated by NHS and non-NHS organisations, 2006-07 to 2013-14[2 3]

Central to the 1990 reforms of the NHS was the idea that by separating purchasers of care from providers, with the purchasers holding the money (but no services) and the providers services (but no money), the transactions that would need to take place would drive up quality and efficiency.[1] Health authorities would be active purchasers of care on behalf of their resident populations. And in this "internal market" there would be freedom to shop around for the best deals from any organisation willing to supply, whether state owned or independent sector.

There have been several reboots of the original idea since then. Internal market 2.0 from the 2002 Labour administration emphasised patient choice and encouraged more private providers of NHS secondary care through financially favourable contractual terms. Internal market 3.0—the reforms of the last government's Health and Social Care Act—reasserted the basic market model with a twist of EU procurement law and revamped commissioning staff (I characterise).

Nevertheless, the central theme remains. So, after a quarter of a century of purchasers having the freedom to purchase from, or patients the ability to choose, NHS or independent sector providers what's happened? How many patients is the private sector treating on behalf of the NHS?

Unfortunately, NHS data systems (hospital episode statistics) have only recently started to produce some decent figures on this. As figure 1 shows, over the seven years since 2006-07, the proportion of NHS patients treated by non-NHS providers has risen from around 0.5% (73 000) to 2.6% (471 000) of all inpatient episodes (which totalled over 18 million in 2013-14). For outpatient care (fig 2), the proportion treated by non-NHS providers has risen faster—from 0.2% (123 000) to 5.5% (4.5 million).

In terms of the type of inpatient activity carried out by non-NHS providers (and ignoring audiology, where it is 34%, but on very low numbers), trauma and orthopaedics top the list at around one in eight episodes of care (fig 3). For inpatient work 88% of the market is covered by seven private providers, with Ramsay Health Care accounting for a quarter of all non-NHS provider inpatient episodes (fig 4).

As a proportion of the NHS's total secondary care activity, the contribution of the non-NHS sector has been and remains very small. But it could grow. If rates of growth since 2006-07 continue over the next 20 years, non-NHS providers could account for one in five of all outpatient attendances and approaching one in 10 inpatient episodes paid for by the NHS. But is the observed rate of growth genuine? Some of

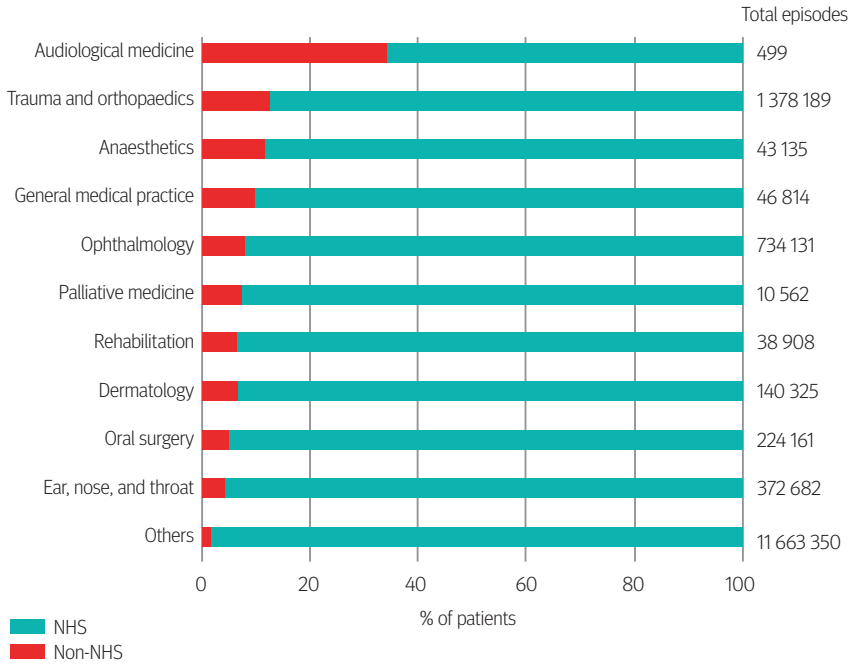

Fig 3 | Percentages of NHS inpatients treated by NHS and non-NHS providers by specialty, 2013-14[2]

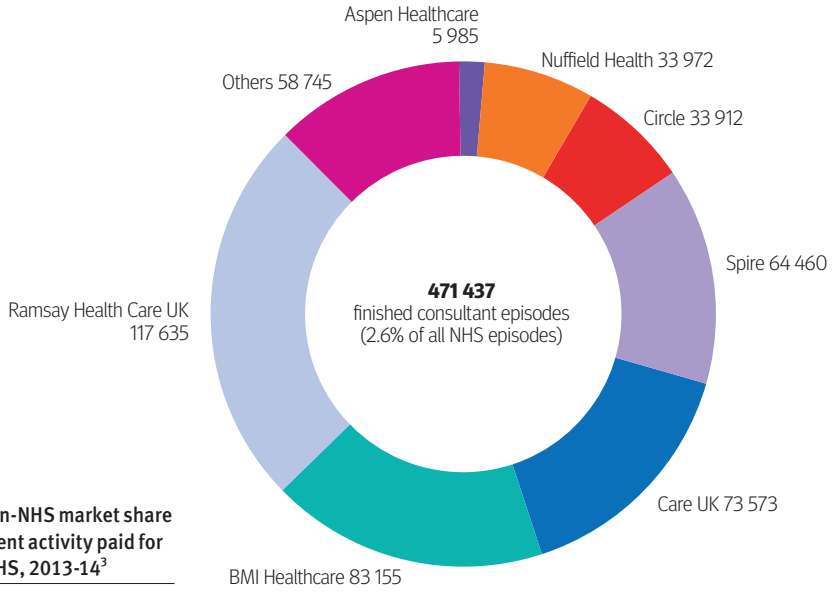

Fig 4 | Non-NHS market share of inpatient activity paid for by the NHS, 2013-14[3]

If rates of growth continue over the next 20 years, non-NHS providers could account for one in five of all outpatient attendances and approaching one in 10 inpatient episodes paid for by the NHS

the observed growth in non-NHS activity is likely to be the result of better reporting rather than actual growth in work done. If so, predictions for the next 20 years should be based on a lower rate of growth.

And even if non-NHS providers were to increase their share of NHS paid work, would this matter? (How much does it matter that general practice and community dentistry are non-NHS services?) As Duckett suggests, ownership of the means of production isn't really the issue.[4] What matters for the quality of patient care and the efficiency with which it is delivered applies regardless of ownership: the quality of management, the incentives organisations and individuals face, the regulatory environment, etc.

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ANSWERS TO ENDGAMES, p 35

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STATISTICAL QUESTION
Uncertainty in sample estimates: standard error

Statements *a* and *b* are true, whereas *c* is false.

ANATOMY QUIZ
Computed tomography angiogram of the thoracic vessels

A: Trachea
B: Aortic arch
C: Bronchial artery
D: Right main pulmonary artery
E: Right lower pulmonary artery branch (interlobar artery)

CASE REVIEW
A man with rust coloured urine and normocytic anaemia

1 Haematuria, menstrual contamination, haemoglobinuria, and myoglobinuria will cause dark urine that is positive for blood on urine dipstick testing. Red cells will be absent on microscopy in haemoglobinuria and myoglobinuria. Food dyes, drugs, porphyria, alkaptonuria, and obstructive jaundice can all cause dipstick negative urine discoloration.
2 Cardiac haemolysis related to previous surgical intervention, microangiopathic haemolytic anaemia, and arteriovenous malformations.
3 Haemoglobinuria and acute kidney injury as a result of mechanical haemolytic anaemia caused by turbulent flow at his dysfunctional mitral metallic heart valve.
4 In cases of mechanical haemolysis, measure the patient's platelets and interpret the results alongside history and examination findings. Investigate those with a history of valve replacement and new murmur for infective endocarditis with three sets of blood cultures, transthoracic echocardiography, and transoesophageal echocardiography.
5 Surgery to replace or repair the affected valve is the definitive treatment for a paravalvular leak that causes severe symptoms and the need for repeated blood transfusions. Patients should be made safe for surgery with warfarin reversal, optimisation of fluid balance, correction of anaemia, and management of acute kidney injury and heart failure.