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Making medicines evergreen

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examine how drug companies maximise profits after patents expire and show why regulatory agencies, policy makers, and prescribers need to be alert to the use of these techniques

Over the next three years the drug industry is projected to lose about £5.4bn in UK revenue as exclusivity rights on major brands expire.[1] To prevent or mitigate losses from sales of cheaper generic versions, drug companies use a range of "evergreening" strategies to maintain market share. Many of these involve minor modification or reformulation of drugs that do not necessarily provide additional benefit for patients.

In 2011 the NHS spent £13.6bn (€17bn; $21bn) on medicines, of which about £10bn was spent on branded or proprietary products.[1] In an assessment of drugs that accounted for about a fifth of the primary care prescribing budget, the National Audit Office identified over £200m of unnecessary spending on branded products.[2] Greater awareness of evergreening techniques could save money and avoid exposing patients unnecessarily to new drugs with inherently uncertain risk-benefit profiles.

The profit cycle of drugs

Developing drugs is risky, costly, and time consuming. It takes 12-14 years[3 4] and costs nearly $900m (£560m; €700m)[5] to bring a drug to market. Protecting pharmaceutical intellectual property and maximising its commercial exploitation are therefore crucial to recoup these costs. Patents are central to this, providing exclusive rights to commercialise an invention for a limited period, usually 20 years from filing. Because obtaining marketing authorisation (previously known as a product licence) is a lengthy process that delays commercialisation, provisions exist to extend exclusivity rights to partially compensate for this.

Once exclusivity rights over a medicine have expired, others may produce and market it as a generic (non-proprietary) product. The licence terms of the generic usually reflect those of the branded product, to which it must be pharmaceutically equivalent. However, since generic manufacturers need not repeat expensive clinical trials, they can sell the drug more cheaply and take market share from the branded product. For example, when Zocor (simvastatin) faced generic competition, its sales collapsed despite increasing simvastatin prescriptions (fig 1). Annual spending on Zocor in England fell from over £250m to about £2m in only two years.[6]

Evergreening strategies

Build a strong brand

Brand names are accessible and memorable, whereas generic names can be cumbersome. Brand names are also actively marketed, unlike generic names. However, except in a few circumstances,[7] drugs should be prescribed generically. This reduces risk because an active substance has only one generic name (which is unique and globally recognised) but may have many brand names. Generic prescribing also allows the pharmacist to dispense the cheapest form available.[7] Conversely, in primary care, if a branded drug is prescribed, only that brand can be dispensed, regardless of whether this is important. Seventeen per cent of UK primary care prescriptions specify a brand,[8] partly because companies have succeeded in embedding brand names into medical language and encouraging their use in prescription writing. For example, co-amoxiclav, marketed under the familiar brand name Augmentin, has faced generic competition since 1999. Twelve years on, despite Augmentin costing twice as much as generic co-amoxiclav (£8.00 versus £3.25 for a 21 tablet pack),[9] the branded product still accounts for 6% of co-amoxiclav prescriptions and 12% of their cost (fig 1 (right)).[6]

Encouraging brand affinity among patients is also valuable. In this respect, manufacturers benefit from producing tablets with distinctive appearances, which they protect using trademark rather than patent law.[10] For example, Viagra (sildenafil) tablets have a distinctive blue diamond design that generics manufacturers would not be allowed to imitate. Patients identify tablets by appearance, and the size, shape, and colour may affect the way they perceive them to work.[10] Having associated the branded tablet with a particular effect, patients are often reluctant to move away from this, and may perceive others as less effective.

Although direct to consumer marketing is not permitted in the UK (unlike in the US), medicines are usually identified by their brand name in media coverage. In the early 2000s, for example, the combined oral contraceptive Yasmin was promoted to healthcare professionals as having unique lifestyle benefits. The advertising claims were disputed[11] and later retracted[12] but received attention in the popular press. Anecdotally, there is affinity for this product among some patients and healthcare practitioners that seems to have arisen more from its marketing than the evidence. At £14.70 per three cycle pack, Yasmin is more expensive than other combined oral contraceptives (mean £5.48 per pack).[9] In 2011, Yasmin accounted for 15% of primary care combined oral contraceptive prescriptions and 41% of their cost.[6]

Modify the drug to keep the patent

Drug manufacturers can extend the patent of existing medicines by modifying them so that they become eligible for protection by new patents. To obtain marketing authorisation for these follow-on products, the manufacturer needs to

prove efficacy, safety, and quality but does not have to show superiority over existing medicines.

Follow-on products are often introduced while the manufacturer still has exclusive rights over the original product. The follow-on product is often initially cheaper than the original, encouraging prescribers and hospital formularies to adopt its use. Occasionally, the original product may even be withdrawn, forcing a wholesale prescribing shift. Having established a patent (or hospital formulary) on the follow-on product, it becomes more difficult to take advantage of generic forms of the original medicine once they become available. Follow-on drugs can be created in several ways.

Chemical tricks

Molecules that have asymmetric (chiral) centres exist in mirror image forms called enantiomers. When medicines comprise a mixture of enantiomers, follow-on products may be developed by marketing one of the enantiomers in pure form. This is known as chiral switching.

Although enantiomers may differ in their effects and handling in the body, the differences may not be clinically important. Omeprazole is a mixture of R and S enantiomers. Esomeprazole is the S-enantiomer only. Although the R-enantiomer is more rapidly metabolised, such that a lower proportion reaches the systemic circulation, once in gastric parietal cells both forms are converted into the same (non-chiral) active metabolite.[13] In general, the same clinical effect can be achieved more cheaply by using a higher dose of omeprazole than by using esomeprazole.

Drugs that are converted into their active form in the body offer another route to making follow-on drugs. Metabolite switching is the strategy of developing a follow-on product based on an active metabolite. Although there may be advantages to administering the active molecule directly, this is not always the case. For example, desloratadine (Neoclarityn) is the active metabolite of loratadine (Clarityn). The two drugs are similarly effective. In 2001, the manufacturer stopped supplying prescription packs of Clarityn to pharmacy wholesalers. Only over the counter packs, which were priced higher, remained available. In informing general practitioners of this change, the manufacturer advised them to prescribe desloratadine instead.[13] This caused a mass prescribing shift to desloratadine, which was sustained even after cheaper generic loratadine became available (fig 2).

Structurally related but non-identical molecules may produce similar effects but can be covered by different patents. For example, pregabalin and gabapentin are closely related.[13] Both are effective in focal epilepsy and neuropathic pain. In 2004, after generic forms of gabapentin had taken market share, Pfizer launched pregabalin (Lyrica). The new drug was priced to be competitive with generic gabapentin, which facilitated its adoption into formularies and guidelines[14] (the rationale for which has been questioned[15]). The price differential between pregabalin and gabapentin has since widened: Lyrica 600 mg/day costs £64.40 per month, while generic gabapentin 1800 mg/day costs £17.91.[9] However, in 2011, pregabalin still accounted for 43% of primary care gabapentin/pregabalin prescriptions and 80% of their cost.[6]

Reformulation

An active substance is usually combined with other substances to generate a final product (such as a tablet). The formulation influences how the drug is absorbed. Slowing absorption by reformulating the medicine as a modified release preparation may be beneficial if, for example, it reduces dosing frequency and thereby improves adherence.

Towards the end of its patent term, the α blocker doxazosin (Cardura) was reformulated as a modified release preparation, Cardura XL. Although their release characteristics differ, both formulations are administered once daily and they are similarly effective. When Cardura XL was introduced, the commonly used Cardura 4 mg tablet was withdrawn.[13] Prescribers were advised instead to use Cardura XL, which was dosed differently. This resulted in substantial spending on Cardura XL, despite generic doxazosin entering the market a short time later (fig 3). The monthly cost of Cardura XL 8 mg/day is £9.98, while the equivalent generic doxazosin 4 mg/day costs £1.31.[9]

Combinations

Fixed dose drug combinations can offer benefit through synergistic activity (such as trimethoprim with sulfamethoxazole), assured adherence to co-prescription (long acting β agonists with inhaled corticosteroids), and convenience

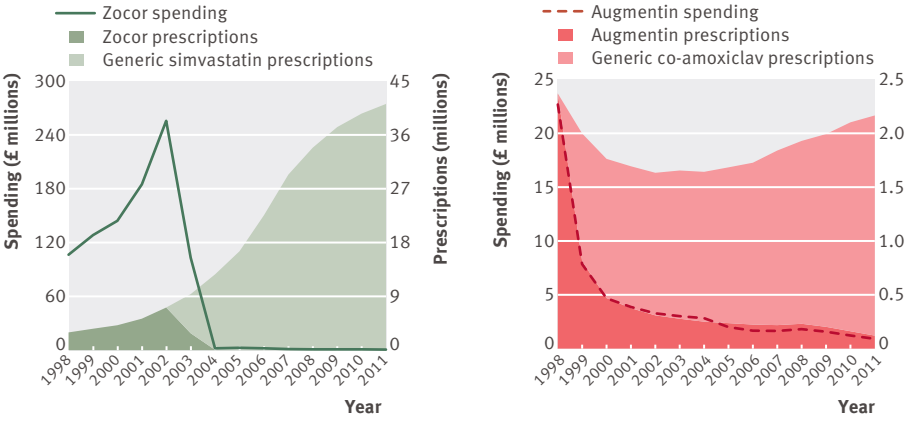

Fig 1 | Generic competition usually leads to a collapse in market share and revenue for the original branded product. However, when a brand name is embedded in medical language (such as Augmentin), it may help sustain market share (right)[6]

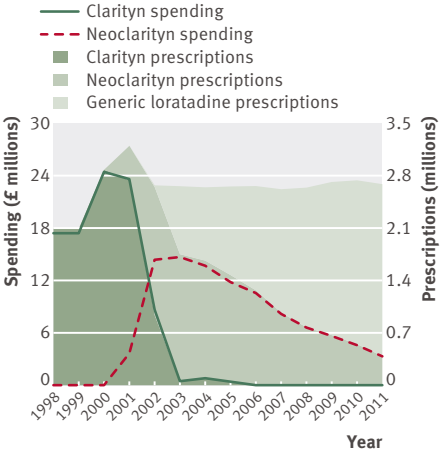

Fig 2 | Replacement of loratadine while it was under patent resulted in mass prescribing shift to the follow-on product desloratidine, helping to resist the effect of generic competition[6]

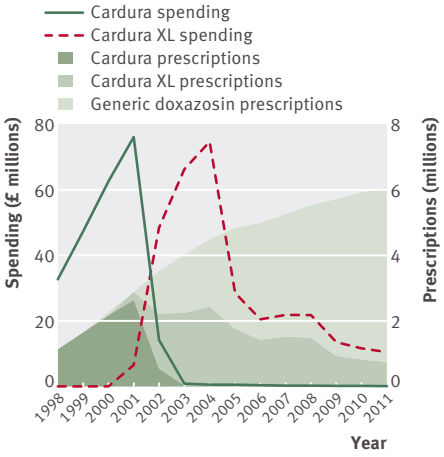

Fig 3 | Replacement of doxazosin (Cardura) tablets with a modified release preparation (Cardura XL) helped retain market share after the release of generic tablets

(combination antiretroviral drugs). However, the value of some combinations may be questionable, particularly when their cost is weighed against that of the constituent drugs. For example, Fosavance, a combination of alendronic acid and colecalciferol, may not remove the need for separate daily calcium supplementation.[13] Weekly Fosavance plus daily calcium carbonate costs £24.83 per month, whereas weekly generic alendronic acid with daily calcium carbonate-colecalciferol costs £3.02 per month.[9]

Licence for a new condition

Medicines are often found to be useful in conditions other than those for which they were originally licensed. The General Medical Council (GMC) advises that medicines may be prescribed outside their licensed indications (off-label) only if there is no equally effective licensed alternative[16] (although proposed changes may allow off-label prescribing if supported by authoritative clinical guidance[17]). Subject to presenting supporting evidence to the regulator, manufacturers can have new indications added to their product's licence. However, it may be more valuable to restrict this to the licence of a follow-on product. Then, when exclusivity rights on the original medicine expire, generics based on this will not be authorised for use in the new indication.

For example, the antipsychotic drug paliperidone is the main active metabolite of risperidone. Both are similarly effective in schizophrenia,[18 19] but the monthly cost of paliperidone 6 mg daily is £97.28, compared with only £1.88 for generic risperidone 4 mg.[9] Paliperidone is also marketed as the only medicine approved for the treatment of schizoaffective disorder (schizophrenia with significant mood disturbance).[20] As risperidone and paliperidone are pharmacologically and clinically similar, it seems unlikely that risperidone would be any less effective in this indication. However, since paliperidone is more specifically licensed for this indication, prescribers may feel compelled to use this over the cheaper product.

Change the dosage

Different dose regimens may also hinder generic substitution. For example, if a reformulation is dosed differently from generic forms, brand name prescribing may be unavoidable. Additionally, if novel dosage regimens are developed, it may be possible to protect them with new patents. For example, donepezil is an acetylcholinesterase inhibitor used in Alzheimer's disease. Four months before its patent protection expired, the US Food and Drug Administration approved a new 23 mg daily dose. Generics will be available only in 5 mg and 10 mg multiples, so 23 mg cannot be administered except by using the branded product. This dosage is associated with marginal improvement in efficacy, of doubtful clinical importance, but with substantially more side effects.[21]

Hallmarks of evergreening—when to be suspicious of a new medicine

- It is described as an isomer/enantiomer (its name may be prefixed lev-, dex-, or es-), active metabolite, or analogue
- It is a modified release or fixed dose combination product
- It is promoted over the drug it supersedes on the basis of theoretical advantages, perhaps with some non-clinical data, but not substantiated by robust clinical evidence
- It is promoted as being less expensive than the drug it supersedes, but the price comparison fails to take account of their different patent expiry dates

Is it all bad?

Maximising the commercially exploitable lifespan of medicines generates revenue that supports an important industry and helps sustain pharmaceutical innovation. Moreover, incremental development of medicines may yield benefit for patients. However, it is not risk free, especially when the benefit is marginal or non-existent. Evergreening invariably increases the cost of healthcare, and may expose patients to medicines that are no more effective but for which there is less clinical experience. Importantly in this context, many adverse drug reactions are not detected during development (when trials typically involve a few thousand carefully selected participants) but come to light only when the medicine is used in practice.

Who protects the public and advises clinicians?

Medicines regulators assess the efficacy, safety, and quality of medicines largely in isolation. Comparative effectiveness and cost effectiveness are assessed after the drug is licensed, and here, the National Institute for Health and Clinical Excellence dominates. NICE appraisals are informative and rigorous. However, they are also slow, often conducted long after licensing, and rarely for evergreen medicines. Independent sources, such as the *Drug and Therapeutics Bulletin* and the Cochrane Collaboration, have an important role in informing prescribers, as they examine a wider spectrum of medicines. Ultimately, decisions on the use of these medicines are taken locally by primary care commissioning groups, hospital drugs and therapeutics committees, and individual prescribers. With little time to review the literature themselves, prescribers often rely on information provided by manufacturers, with all its inherent biases.

The way forward

We define an evergreen medicine as one that seeks extended protection from market competition, or resistance to its effects, without providing additional benefit for patients. Many argue that such medicines should not be licensed. However, we are not persuaded that this would be workable or even wholly beneficial. Cumbersome regulation may have unintended consequences that stifle investment for innovation. That said, regulators and policy makers must be alert to evergreening and take care not to reinforce it. The overly constraining GMC guidance concerning off-label prescribing could be argued to do this.

To counter evergreening, assessments of comparative effectiveness should be conducted for all types of new drugs, not just those that are novel or high profile. However, the best controls will be those that work at a local and operator level. Prescribers should know when it is and, more commonly, is not appropriate to prescribe drugs by brand name. This requires that medical students are appropriately trained and assessed in pharmacology and prescribing, and that practitioners receive continuing education and feedback. Prescribers, primary care commissioning groups, and drugs and therapeutics committee members should be alert to the hallmarks of an evergreen medicine (box). They should be wary of purported advantages over its predecessor unless supported by appropriate evidence from clinical trials. When no such data exist, the older drug should usually be preferred because there will be more extensive data on its safety. Finally, those who manage formularies for NHS organisations should be sceptical of apparent cost savings associated with follow-on drugs. If they fail to take account of earlier patent expiry of the older product, they may find the savings are short lived.

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