



WeMeReC Bulletin
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Prolonging market exclusivity of medicines - implications for the NHS

The NHS puts a great deal of effort into managing the introduction of new drugs and assessing the impact of new formulations or new indications for drugs. However, the launch of new products often coincides with the expiry of patents for established drugs and, occasionally, with product withdrawals. These also need to be managed.

Concern over safety is the most common reason for a drug to be withdrawn from the market earlier than expected. However, a trend is emerging whereby pharmaceutical companies launch “new” or “improved” versions of successful products that are nearing the end of their patent lives. These are heavily promoted in efforts to protect the companies’ market share. In some cases, established products have then been withdrawn.

The rationale for this trend and the implications for the NHS are discussed here. Also outlined are points to consider when managing product withdrawals associated with this activity.

Background

While the wider application of new technologies to produce better medicines is welcomed, cases where they are used purely for commercial reasons should be recognised. Historically, companies have employed a variety of tactics to protect their market shares. These have included controlling the supply of the raw materials or arguing details of patent law, usually relating to manufacturing processes. There are sometimes opportunities within regulatory processes that can be used to extend patents (issues surrounding patent law are discussed on page 3). In addition, companies can often remain competitive by, for example, applying to change medicines from prescription to non-prescription status.

Summary

- There is a trend amongst pharmaceutical companies to attempt to prolong the period of market exclusivity of innovative products by developing “new” or “improved” versions and, in some cases the original product has then been withdrawn from the market.
- Three of the methods used to produce “new” or “improved” products are chiral switching, switching to active metabolites, and the development of new formulations, such as modified-release products. The evidence for superiority of these products at the time of launch is often weak.
- Patients who are stabilised on therapies with well-established safety profiles are often being switched to “black triangle” products that confer no clinical advantage.
- The direct financial impact of this trend on the primary care drug budget in Wales could potentially amount to millions of pounds per year. The NHS depends on both research-based and generic drug companies and the impact on both, in terms of future profitability, must be considered.
- There are implications for the NHS in terms of the workload generated in managing changes in drug therapy, and for patients who are being subjected to those changes.

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When new versions of products are launched, sometimes along with new or different indications or licences, they can be:

- ♦ **new formulations** of existing medicines, such as modified-release preparations
- ♦ **chiral switches**; single enantiomers rather than racemic mixtures of drug molecules
- ♦ **active metabolites** of parent compounds.

New formulations

For many years drug companies have marketed new formulations of their products by, for example, using modified-release technologies to produce versions that require less frequent dosing. In the past these newer formulations have usually been marketed alongside the original products and market forces have influenced the uptake of each. New formulations that supercede older products can extend the life of a branded product significantly. Such formulation changes can make it difficult for other companies to market alternatives once an original patent expires; an example of this occurred with ciclosporin when Novartis switched the formulation from *Sandimmun*[®] to *Neoral*[®].

Recently, Pfizer marketed a modified-release version of doxazosin and then discontinued the corresponding strength of the conventional-release product prior to patent expiry. They claimed that this decision was influenced by the fact that the modified version was better and cheaper and that withdrawing the original formulation reduced the likelihood that patients would be supplied with the wrong product.¹ There is a view that forcing changes in patients' drug therapy reduces the likelihood that prescribers will intervene at later stages to switch patients to generic versions of a product for purely financial reasons.

Chiral switches

Many commonly used drugs are administered as racemates, or 50:50 mixtures of enantiomers. Enantiomers are types of optical or stereoisomers.² These molecules are chiral; they are non-superimposable mirror-images of each other, or “left-handed” and “right-handed” versions of the same molecule. Enantiomers are specified as S- or R-isomers depending on their chemical configuration. Alternatively, they are denoted as (+) or *d* for dextrorotatory, and (-) or *l* for levorotatory, depending on the direction in which they rotate polarised light.

Pharmacological receptors may also be chiral, so a “left-handed” drug will only fit a “left-handed” receptor. Selective binding of enantiomers with receptors can lead to different enantiomers having different pharmacokinetic properties. Potential advantages of chiral switching can include a simpler dose-response relationship, lower dose requirements, minimisation of toxicity, and reduced potential for drug interactions.² While these switches can be used to great advantage in the development of medicines, such as the use of penicillamine or levodopa, they can also be used to extend the market exclusivity of products. In many instances there is a lack of appropriate comparative studies that allow prescribers to determine whether any potential advantages are evident in clinical use.

Examples of drugs originally licensed as racemates that are now marketed as single isomers include:

- ♦ esomeprazole, the S-isomer of omeprazole
- ♦ escitalopram, the S-isomer of citalopram

New indications and licence changes

In the case of esomeprazole, AstraZeneca has tried to establish a distinct identity for the single isomer by obtaining a licence that differs from that of the racemic drug. Esomeprazole is licensed for use at 40 mg for conditions that have traditionally been treated with 20 mg of omeprazole. This is despite claims that the S-isomer has greater activity. The indications for esomeprazole that are specified in its licence are limited in comparison with other proton pump inhibitors (PPIs) but initial marketing was heavily based on a “new” indication for use “when needed” to prevent recurrence of symptoms of gastro-oesophageal reflux disease. The company points out that indications for new medicines are often limited until clinical experience is gained and that experience with PPIs supports use of higher levels of acid suppression.

Metabolite switching

Another approach is switching to the active metabolite of a drug and, preferably, to the more active isomer of that metabolite.² The substitution of terfenadine with its metabolite, fexofenadine, is an example that improved safety by minimising cardiac toxicity. Other non-sedating antihistamines, such as desloratadine (a metabolite of loratadine), were developed as the market for antihistamines expanded into non-prescription sales.

New markets

As with levocetirizine, the (-)-isomer of cetirizine, desloratadine replaced loratadine as an antihistamine available on prescription. Both the original drugs are now available generically and

have been available and marketed as non-prescription products. However, at the time, the decision made by Schering Plough to withdraw loratadine from prescription sales before its patent expiry was controversial.¹

Patent Law

In the EU, patent protection is usually granted for a maximum period of 20 years. Given that considerable time elapses before a patented drug can be fully researched and licensed for use, companies try to maximise the period of market exclusivity before a patent expires. To compensate companies for the development process, a Supplementary Protection Certificate can be issued. This can extend the time period covered by a basic patent and thus the period of market exclusivity.

Companies applying for marketing authorisation to produce and distribute a generic version of a medicine are required to demonstrate “essential similarity” to the original product, that is, that it has the same active ingredient, pharmaceutical form and clinical effect. This is usually done by reference to the data relating to the original product that was submitted to the licensing authority. However, currently in the UK a 10-year period of

data exclusivity with respect to a marketed product can be awarded, such that data filed to support an application for registration of a new chemical entity is protected.³ (This period differs from that in the USA and can vary across the EU). In a ruling by the European Court of Justice, new therapeutic indications, dosage forms, doses and dosage schedules do not give the innovator a right to additional data exclusivity.^{3,4} Unfortunately, situations in which the original product itself has physically changed or improved were not covered.

Currently in the UK, if marketing authorisation is withdrawn in respect of an original product (even though the data exclusivity period may have expired), this act may prevent the licensing of any generic version of that product. Existing legislation is being challenged and a review of EU pharmaceutical law may help clarify the situation, however, codes of practice that will address these situations may take years to come into effect.⁴

Implications for the NHS

It is estimated that within 12 months of a generic version of a drug entering the market, a large proportion of the original product's market share can be lost. With successful products this can represent a significant proportion of a company's revenue. In 2002, citalopram accounted for 30% of spending on selective serotonin re-uptake inhibitors in primary care in Wales⁵ and was estimated to account for 80% of Lundbeck's revenue.⁶ Escitalopram was launched that year, the same year the patent on citalopram expired. Omeprazole accounted for 47% of spending on PPIs (or 42% of spending on ulcer-healing drugs). £1.7 million (or 5% of the PPI budget) was spent on esomeprazole.⁵ However, omeprazole is now available generically and prices are beginning to fall.

Traditionally the savings realised by prescribing generically have helped offset the general increase in drug expenditure. Delaying generic competition has direct effects on budgets but may also affect the profitability of generic manufacturers. There are other important implications for patients and NHS staff when tactics involving product withdrawals or switches are employed by companies. Points for

consideration are outlined on page 4. If medication changes are undertaken because of a product withdrawal, changing again when a generic version becomes available requires the investment of considerable additional resources, not least of which involves ensuring the clinician/patient relationship is not compromised.

Importantly, as with any new chemical entity that is licensed, many of these new products have “black triangle” status. Unless there is clear evidence of clinical benefit, the ethics of forcing patients to switch from products with established safety profiles to products of this status are questionable.

Finally, a patent holder has been granted exclusive rights to profits from a product for many years, and in the case of medicines in the UK, the NHS is the main bearer of the cost of this monopoly. The patent holder expects their rights to be upheld and the government to support them in defending those rights if necessary. The question has been raised - is it not then reasonable to expect companies to refrain from using controversial methods to protect their market share when a patent expires?¹

Points to consider when managing product withdrawals

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| What is the reason for the withdrawal? | Are there concerns about efficacy or safety, or are the reasons for withdrawal commercial? |
| Do current prescribing patterns indicate that the withdrawal presents a problem? | How much of the product is prescribed in terms of volume and cost? This may need to be considered at a local, regional or an all-Wales level. |
| Will there be a generic equivalent available? | <p>Have any product licence applications been submitted to the Medicines and Healthcare products Regulatory Agency for a generic equivalent of the original product? (Note: this information can only be released with the applicant's consent.)</p> <p>Unless withdrawn for safety reasons, it is not unreasonable to assume that there will be generic entrants to the market for commercially viable products. The likely timing of the availability of the generic preparation (if known) will affect what, if any, interim measures are put into place. If stocks of the original product are sufficient, larger amounts of the drug could be prescribed short-term to keep the patient supplied until a generic preparation becomes available.</p> |
| Is the original product still available without a prescription or as a parallel import? | Where there are products available "over the counter", they can be dispensed against prescriptions for generic products. This applies even if the brand name is included in Schedule 10 or 11 of the NHS General Medical Service Regulations. However, this could have cost implications. Similarly, parallel imports can be used if readily available. |
| Are there medicines that are suitable alternatives? | <p>Have local (or regional or national) prescribing groups issued any guidance?</p> <p>What is the evidence for the comparative efficacy and safety of any alternatives? Consider, for example, whether the indications, age groups covered, and drug interactions are comparable.</p> <p>What do the alternatives cost; is there information on cost-effectiveness?</p> <p>Are the alternatives generic or proprietary and, if applicable, when do their patents expire?</p> <p>Is the manufacturer recommending switching patients to another product?</p> <p>What is the impact of any change on patients? Is treatment still necessary? Will any changes be beneficial or are there associated clinical risks? Will changes be accepted by the patient?</p> <p>Will any indirect costs be incurred? Will the need to change patients' management affect the healthcare team workload? Will appointments for review and counselling be necessary and if so, with whom? Will records need amending? Will stock levels need to be reviewed?</p> |

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