

Negotiating the parallel imports rules

The final article in the series looks at the rules governing the sale of parallel-imported products. A thorough grounding in the procedures can help importers to maximise their market share by avoiding legal challenges to their trade, according to **Cathal Gallagher** and **Richard O'Neill**

To market a parallel-traded product, an importer needs an abbreviated marketing authorisation (PL[PI]) from the Medicines and Healthcare products Regulatory Agency (MHRA). The intricacies of applying for one are subtle and manifold. A good working knowledge of the procedure can help pharmacists not to transgress the Royal Pharmaceutical Society's fitness-to-practise regime by dispensing an inappropriate product that has been sourced outside the UK. A thorough grounding in the procedure can also help importers to maximise their market share. It is important that parallel importers keep their business practices within the letter of EU law, since challenges to the legality of their trade have been plentiful.

Potential challenges

Regulation 4A of the Medicines (Labelling) Amendment Regulations 1992 stipulates that all medicinal products in the UK must be labelled in the English language only, or in English plus one or more other languages, provided the same particulars appear in all the languages. For EU imports labelled in a language other than English, the importer must relabel the medicines to comply with the regulations, by repackaging the medicines or overlabelling the existing packaging.

The requirement for consistency of particulars between multiple languages, though statutory, has never been tested in the courts and does not, in practical terms, seem to encompass the name of the medicinal product as described in the standard labelling requirements in Regulation 4(1) of the Medicines (Labelling) Amendment Regulations 1992. Annex 3 of the World Health Organization's procedure for the selection of recommended international non-proprietary names for pharmaceutical substances¹ states that related groups of medicinal substances should, if possible, have a common stem. The stems are listed in Latin, English, French and Spanish. The common stem for medicinal substances classified as 3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors is *statinum* in Latin, *statin* in English, *statine* in French, and *statina* in Spanish. By this reasoning, *rosuvastatin* could be interpreted as French for rosuvastatin.

In cases where the brand name of a medicinal product differs between the UK and other EU countries, it is less obvious whether the packaging and the label, in a strict legal sense, need to contain "the same particulars".



There is a strong argument that they do not, since rosuvastatin, for example, is marketed in Italy as both Provasicor and Simestat. This would suggest that the Italian for Crestor is Provasicor or Simestat. This argument is largely irrelevant, because the MHRA is content to issue a product licence parallel import marketing authorisation in any name as long as patient safety is not compromised, and intellectual property rights are not infringed. Nevertheless, the need to contain the same particulars offers an opportunity for an innovator company to challenge the right of a parallel importer to change the brand name of its product, and possibly to forestall its imports.

Generic medicines

Manufacturers of generic medicines can apply to the MHRA for authorisation to market the same active ingredient under its non-proprietary name. They are not required to do a complete clinical trial to prove effectiveness and safety, as that will have been established for the drug already. However, they are required to show that the new product is equivalent to the original.

There is an economic incentive for the development of generic drug products. Typically, the innovator company will maintain the drug price at the original level or higher after its patent has expired to preserve cash-flow. Other companies can develop a

formulation of the drug and apply for marketing authorisation knowing that, even at a fraction of the selling price of the innovator's product, the company can make a good profit. During the patented period, the branded sector can market the product and its brand name extensively, so that when the patent expires the brand name is strongly associated with the generic name in many prescribers' minds. Because of this, the switch to a generic does not necessarily occur immediately after the patent expires, even if there is a significant cost reduction.

Trademarks

PL(PI)s, when granted, are issued by the MHRA in the name(s) applied for by the applicant. The licensing authority does not consider, and is not in a position to consider, whether the licence infringes trademark rights of third parties. However, the grant of a PL(PI) does not absolve the holder from the need to comply with others' trademark rights. To prevent infringements of trademarks, applicants should ensure that they are entitled to use the name in question. Just as generic lansoprazole capsules from a domestic source cannot be labelled Zoton capsules because that would infringe on a registered trademark owned by Wyeth, neither can PL(PI)-licensed lansoprazole be labelled Zoton.

The MHRA informs the holder of the UK product licence when it grants a PL(PI). According to European Court of Justice case law it is up to the trademark owner to check whether the presentation is such as to damage its reputation. The MHRA considers each application for a product name to ensure that the proposed name will allow the medicine to be taken safely and correctly, and has issued naming policy guidance with respect to umbrella segments of product names.

Modes of prescribing

Prescriptions for medicines can be classified in three ways: drugs prescribed and available generically where the pharmacist is reimbursed at the drug tariff price or the price of the generic; drugs prescribed generically where a generic is not available (principally because the proprietary medicine is under patent); and drugs prescribed and dispensed by proprietary brand name. In all cases, it may be possible for a branded drug or a parallel import to be dispensed against the prescription. Generic prescribing is encouraged by the NHS.

Each year, the NHS Business Services Authority (NHSBSA) provides health authorities with information about their potential savings from increased generic prescribing.² The information consists of a list of items prescribed by a GP practice that

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could have been prescribed generically, and the savings that would have been achieved by a total switch. There are financial incentives for GPs to prescribe generically under the general medical services (GMS) contract. Many drugs are prescribed generically even when not available in generic form.

Doctors make the final decision about the best way to treat patients, taking into consideration a variety of factors unique to the individual, such as their ability or willingness to comply with a particular course of medication. It is not unusual for doctors to prefer to prescribe branded medicines, even when a generic is available, because they are concerned that a change of medication could influence compliance with the course of treatment. It is not uncommon for patients to balk at the prospect of taking a generic equivalent. Additionally, patients with some conditions or sensitivities should not deviate from their regular medication for safety reasons and that limits the degree to which generic prescribing can take place.

Generic substitution

A prescription is defined as being written generically if the recommended international non-proprietary name (rINN) of the prescribed drug or the scientific name of the active ingredient is used. Generic dispensing occurs where a drug is prescribed and available generically and the dispenser is reimbursed for the generic drug.

In NHS hospitals, generic substitution has been carried out routinely for many years. In all but a few cases, pharmacists can dispense a brand rather than a generic, in accordance with hospital protocols. But community pharmacists are contracted by the NHS to dispense what is written on a prescription and are therefore prevented from initiating generic substitution without prior reference to the prescriber. The legal basis for this is s58(2)(b) of the Medicines Act 1968, which states that “no person shall administer (otherwise than to himself) any . . . medicinal product unless he is an appropriate practitioner or a person acting in accordance with the directions of an appropriate practitioner”.

The document “Professional Standards and Guidance for the Sale and Supply of Medicines”, issued by the Royal Pharmaceutical Society, prohibits a pharmacist from substituting any product for that named on a prescription, even if he believes that the therapeutic effect and quality of the other product are identical.³ Before the introduction of these professional standards and guidance documents in 2007, this guidance was provided by the Society in obligation (4)(1)(e) of its code of ethics and standards. The Council of the Society published an official statement on 12 July 1986 confirming that the rules of professional ethics “apply to imported medicines as well as those produced for the UK market”.

The Society’s rule that required a pharmacist, in response to a prescription for a medicinal product using its proprietary name, to

dispense only a product bearing that name, was challenged in the domestic courts. The Court of Appeal referred the case to the ECJ to determine whether the national rule was contrary to Article 30 of the Treaty of Rome.⁴ The effect of such a rule would be to prevent the pharmacist from dispensing a therapeutically equivalent product licensed by the competent national authority — then the Medicines Control Agency — but bearing a trademark or proprietary name applied in another member state that differs from the trademark or proprietary name appearing in the prescription.

Before the summer of 1986, about 50 products imported in parallel had brand names different from those of the equivalent products previously authorised in the UK. The importation of the products almost ceased after the Society published its statement. The court could not exclude the possibility that this rule was capable of hindering intra-community trade. For that reason it was deemed necessary to consider whether such a rule might be justified under Article 36.

The ECJ stated that the rules concerning the relationship between doctors and pharmacists, including the attending doctor’s freedom to prescribe, were matters for the national public health system. It was stated that, as long as those matters have not been regulated by community legislation, it is for the member states, within the limits laid down in Article 36, to decide on the degree to which they wish to protect human health and life and how that degree of protection should be achieved.

The court found no evidence to justify a conclusion that a rule banning pharmacists from substituting equivalent medicinal products went beyond what was necessary to achieve the objective of leaving responsibility for the treatment of the patient in the hands of the doctor treating him or her.

This ruling applies even where the difference in name between the domestically sourced and imported drug is small, as it often is. For example, the lipid-regulating drug simvastatin is called *simvastatine* in Spain and Italy. It is irrelevant that the therapeutic effect or quality of the drug is identical. It was noted, however, that there could only be psychosomatic reasons for a specific proprietary medicinal product to be prescribed rather than a generic product or any other proprietary medicinal product having the same therapeutic effect. In the NHS, prescribers are given the freedom, subject to certain exceptions, to prescribe medicinal products under their proprietary names, although they are encouraged to prescribe generically.

PL(PI) applications

Several options are available, each dependent on how the importer submitted their application for a PL(PI), when relabelling a parallel-imported proprietary medicine for sale in the UK. Each scenario will be examined with reference to Crestor, an on-patent drug first released in the UK on 29 March 2003,⁵ and

marketed in the EU under the brand names Crestor, Simestat and Provasicor.

In the first scenario the proprietary medicine is marketed under the same name in the UK and the country from which it is to be imported. Landmark Pharma Ltd applied for a PL(PI) for Crestor, imported from Italy, where the licence holder is AstraZeneca SpA, and manufactured in Germany by AstraZeneca GmbH.⁶ The licence was applied for under the brand name Crestor, and the packaging was relabelled in accordance with the Medicines (Labelling) Amendment Regulations 1992. In this case, the imported product can be dispensed against prescriptions for the generic and the branded product.

Where the proprietary name for the drug in the UK and in other member states differ, there are several possible outcomes, each of which has a different effect on the value of the import. Autumn Healthcare Ltd applied for a PL(PI), under the name Crestor, for Provasicor tablets imported from Italy, where the licence holder is AstraZeneca SpA. The tablets were manufactured in Germany by AstraZeneca GmbH.⁷ The imported product was labelled Crestor, which can be dispensed against prescriptions written generically or requesting the branded product.

Compare this to the application for a PL(PI) by B&S Healthcare Ltd for Provasicor, imported from Italy under the generic name, rosuvastatin.⁸ Having been granted a marketing authorisation under the generic name, the company was compelled to label the product with that name. The result is that the product can only be dispensed legally against prescriptions written generically, unlike Autumn Healthcare Ltd, which can have its (identical) product dispensed against any valid UK prescription for Crestor or rosuvastatin. In this case B&S Healthcare Ltd was unaware that it would be lawful for Provasicor to be licensed and labelled as Crestor as, in the light of the judgment in *R v Medicines Control Agency, ex parte Smith & Nephew*,⁹ it fulfilled the MHRA’s criterion of being made by the same company, or a member of the same group of companies, as the holder of the marketing authorisation for the UK product.

The MHRA grants the PL(PI) in the name applied for by the applicant, as demonstrated by the example of Autumn Healthcare Ltd. In that case it would be up to the marketing authorisation holder, AstraZeneca, to assert in the courts whether this adversely affected its trademark, but following *Boehringer Ingelheim and others v Swingward and another*,¹⁰ it is unlikely that such a legal challenge would be successful.

Where the proprietary name of a medicine in the UK differs from that of the country of origin,¹¹ and the product is presented by overlabelling the EU packaging, there is a strong argument that marketing the drug under its UK proprietary name violates Regulation 4C(1)(c) of the Medicines (Labelling) Amendment Regulations 1992. This has not been argued by any innovator companies to challenge the validity of PL(PI)

marketing authorisations issued in the UK.

Since the patent for Crestor in the UK is live, there is no difference between the drug tariff price for rosuvastatin and the Pharmaceutical Price Regulation Scheme price of Crestor. Importers that have labelled their products “rosuvastatin” are excluding themselves from the market for the percentage of prescriptions for the drug that are written non-generically. There is no difference in the monetary value of their product, but there is a reduction in the size of the market. However, for off-patent drugs, such as simvastatin, there is a significant price differential between branded and unbranded drugs, so importers of these products that label their product generically not only reduce their market size, but devalue their product.

Fitness to practise

Pharmacists have been subject to many sanctions by the Statutory Committee for transgressions involving generic substitution. In some cases the allegations have formed part of a “catalogue of misconduct”, including other breaches of the Code of Ethics and criminal activities.¹² However, several cases relating wholly to generic substitution illustrate the serious attitude taken by the Society to offences of this kind.

In 1998, a pharmacist, having pleaded guilty in Biggleswade magistrates’ court to two charges of labelling a medicine in such a way as to describe the product falsely, appeared before the Statutory Committee charged with two counts of dispensing generic cimetidine 800mg tablets as Tagamet.¹³ The prescriptions had been endorsed as Tagamet, and the PPA had paid the pharmacist at the higher rate afforded to the branded drug. This was deemed to constitute misconduct sufficient to issue a reprimand. The Council of the Society also alleged that the practice of generic substitution might not have been restricted to the cases taken to court. In delivering its verdict, the committee intimated that, had a continuous policy of generic substitution been confirmed, the pharmacist would have been struck off the Register of Pharmaceutical Chemists. However, because such an allegation could not be proven, a reprimand was reasoned to be a sufficient sanction.

In a similar case, another pharmacist failed to fulfil her responsibilities as the superintendent pharmacist of a retail pharmacy company, for the most part by effecting generic substitutions.¹⁴ The Council of the Society brought a seven-point complaint. Four of the seven points of complaint concerned alleged unlawful generic substitution. Generic sustained-release propranolol tablets were substituted for half-Inderal LA tablets, Orlept syrup for Epilim syrup (two allegations), and atenolol/chlorthalidone 100/25mg tablets for Tenoretic tablets. Gary Flather QC, the then chairman of the Statutory Committee, felt the need to explain why substitution of this kind was unacceptable. It confused patients: in this case the medicine within the packag-

ing was different from that named on the prescription and label. There was no consultation with a doctor, and the PPA was asked to pay for the prescribed item, which, in each case, was of greater value than the substituted medicine. No criminal charge was made regarding the alleged fraud. Each of the four allegations amounted to misconduct of sufficient “gravity” to render the pharmacist unfit to be on the Register. She was subsequently struck off. Given certain mitigating circumstances relating to the pharmacist’s gender and ethnicity, the committee agreed to hear an application for restoration to the register after “not less than 12 months”, should she wish it.

The importance of the application process for PL(PI) marketing authorisations in real situations is elegantly demonstrated by the case of a London pharmacist who dispensed Greek Voltaren tablets against a prescription for Voltarol tablets, and who was subsequently reprimanded by the Statutory Committee.¹⁵ A complaint from the Council of the Society alleged that the actions of the pharmacist amounted to misconduct rendering him unfit to remain on the Register. Both Voltarol and Voltaren are registered trademarks of the Swiss-based company Novartis AG. Voltarol Retard is the UK proprietary name for diclofenac sodium 100mg tablets in a 12-hour sustained-release formulation. An identical product is marketed by Novartis (Hellas) AEBE in Greece under the name Voltaren Retard. Both Novartis Pharmaceuticals UK Ltd and Novartis (Hellas) AEBE are wholly owned subsidiaries of Novartis AG. Had the application for a PL(PI) marketing authorisation been made under the name Voltarol, and subsequently relabelled as such, the pharmacist could have dispensed the product against the presented prescription. However, because the product dispensed was labelled by the importer as Voltaren, the Greek brand name, the pharmacist was acting contrary to Obligation 4.1(e) of the Society’s Code of Ethics and Standards in force at the time. The pharmacist’s contention that he thought he could dispense an identical parallel-imported product was dismissed by the chairman as “close to the most preposterous explanation one could ever hear from an intelligent person”. The chairman told the pharmacist that “[his] behaviour could never be tolerated in a profession as honourable and dignified as pharmacy”. However, had the parallel trader applied, as he was entitled to, to market the drug under its UK proprietary name, the pharmacist would have had no case to answer. This highlights the importance of a sound understanding of the legal aspects of parallel trade for the trader, and the pharmacist who will dispense his product.

Conclusions

Legal and professional requirements dictate that pharmacists in the community must dispense prescriptions in accordance with the directions of an appropriate practitioner. This precludes a pharmacist from substituting a

product for a named product without the approval of the patient and the prescriber. Although the NHS encourages suitably qualified healthcare professionals to prescribe proprietary medicinal products under their generic names, they are free to request both on- and off-patent drugs by their trademark names. It is common for prescribers to cite concern about reduced patient compliance, the reluctance to deviate from proven regular medication, and patient sensitivity to excipients when prescribing branded drugs, despite the availability of cheaper alternatives.

A PI can be dispensed when a prescription has been written generically. It can also be dispensed when a prescription has been written using a UK brand name, but only when the import has the identical brand name. Sanctions for pharmacists deviating from legal and ethical prescribing obligations can be severe, and have, in the past, included the issuing of reprimands and the removal of a pharmacist from the Society’s Register.

To maximise the value of imports, parallel traders must, where possible, apply for abbreviated PL(PI) marketing authorisations under the brand name of the drug in the UK. As long as the branded medicine has been licensed to a member of the same group of companies as the UK manufacturer, the MHRA will grant the PL(PI) in any name requested by the applicant, as long as it does not compromise patient safety. This holds regardless of the brand name of the medicinal product in the member state of its origin.

Notes and references

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