

# Birth of the parallel medicines trade

In the first of a series on parallel imports, Cathal Gallagher and Richard O'Neill examine the history of the parallel trade in medicines and outline the landmark European law cases that have set the criteria for the licensing of these products throughout the EU

The dispensing of parallel imports (PIs) generates heated debate among patients, prescribers and pharmacists.<sup>1-3</sup> Many people will have come across PIs, but their legal standing is little understood among those who most frequently encounter them.

A PI is a legitimately produced medicinal product imported into the UK from another EU member state without the permission of the owner of the intellectual property rights that attach to the product in its country of origin. The intellectual property rights for a medicine are typically owned by its manufacturer (the holder of the manufacturing authorisation). PIs are imported into one member state from another and placed on the market, outside the formal channels of the manufacturer or its licensed distributor.

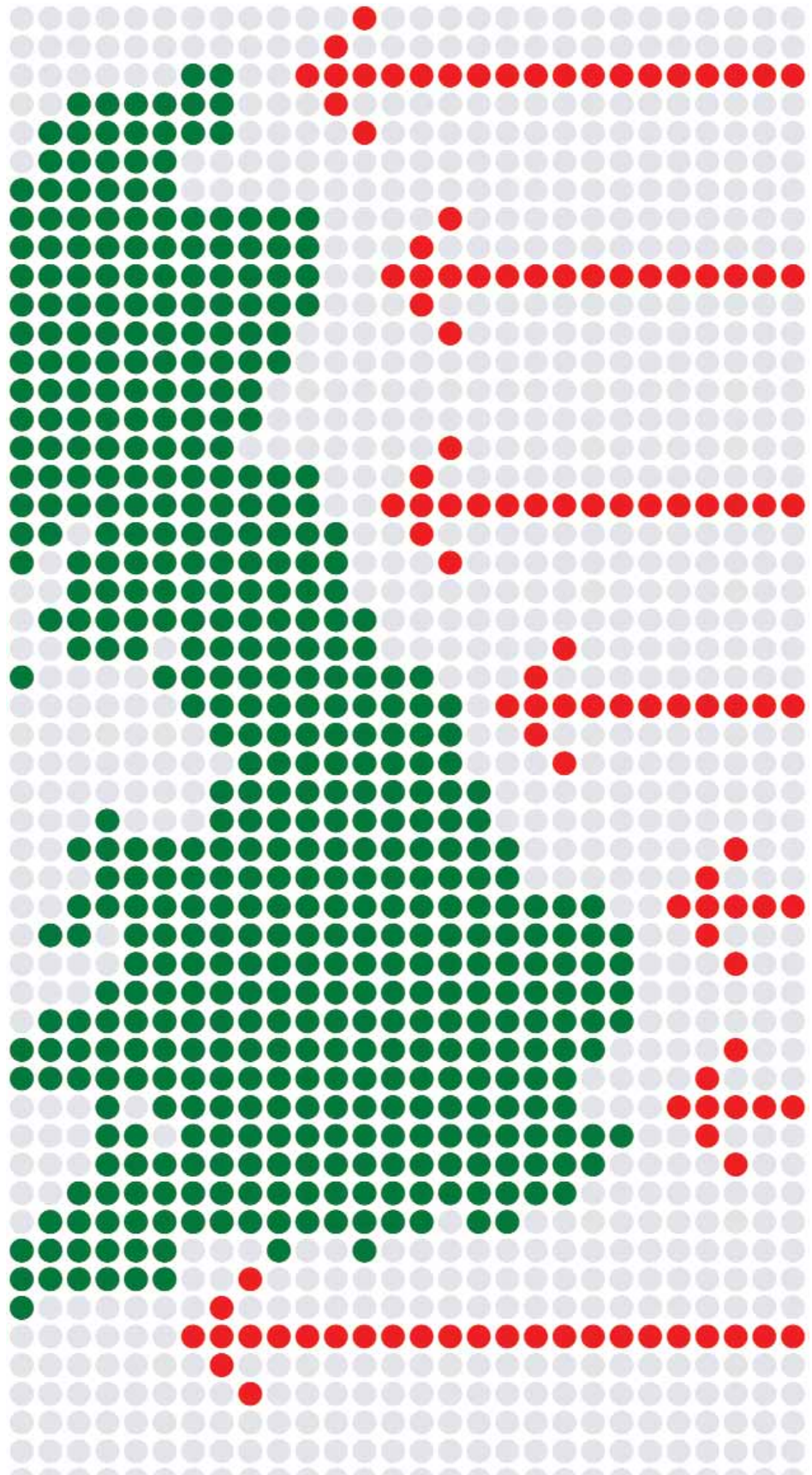
Parallel imports tend to occur when price levels for similar products between two member states are significantly different. This creates an incentive for traders to buy products in the member state where they are priced lower and sell them in the member state where they are priced higher.

A modified form of licensing procedure may be considered for a PI provided it is covered by a valid marketing authorisation (MA) in an EU member state, has no different therapeutic effect to that of its UK-licensed equivalent, and is made by (or under licence to) the UK manufacturer or the same group of companies. This article will examine the genesis of the parallel trade in medicines and visit the landmark EU cases that set the criteria for the licensing of these products.

## Opinions on parallel trade

The financial benefits of parallel trade to patients and the NHS are hotly contested by stakeholders, such as drug manufacturers, parallel distributors and health insurers. Parallel distributors argue that parallel trade promotes competition by forcing down prices of domestically sourced counterparts; and that through parallel trade, savings are realised, helping to keep down the burgeoning costs of public healthcare expenditures in the EU.<sup>4</sup>

The York Health Economics Consortium study,<sup>5</sup> commissioned by the European Association of Euro-Pharmaceutical Companies (EAEPC), confirmed that the UK market for parallel-distributed pharmaceuticals is one of the largest in Europe, and was worth over €2bn in 2002. Overall, the total direct savings from the parallel trade of



pharmaceutical products in 2002 were estimated by the study to be €342m. The authors estimated that these savings were realised by the UK Government via lower hospital medicine prices and the clawback mechanism applied to pharmacies.

The study also found evidence that parallel trade generates indirect savings by creating competition, thus forcing pharmaceutical manufacturers to reduce prices of domestically sourced products. These results are borne out by a report from the University of Southern Denmark, commissioned by the EAEP, which revealed that parallel imports saved €237m in 2004.<sup>6</sup>

Pharmaceutical manufacturers oppose parallel trade, contending that, in the absence of adequate intellectual property protection, research and development investment will decline, hampering the development of new medicines, contrary to the interests of patients and society. The pharmaceutical industry views parallel trading as a significant problem for the UK economy. It claims it erodes the home base of one of our most successful industries and leads to the export of jobs.

The alleged unfairness of the situation was illustrated by GlaxoWellcome in a report on the parallel import of medicines into the UK submitted to a House of Commons Select Committee on Trade and Industry in 1999.<sup>7</sup> It highlighted the Pharmaceutical Price Regulation Scheme (PPRS) agreed between the Department of Health and the pharmaceutical industry, which regulates the price of medicines by capping the profit that companies can make on their sales to the NHS. This system is designed to allow companies a sufficient return to fund R&D spending. However, the resulting prices are higher than those in member states whose pricing policies make no allowance for R&D investment. This, claimed Glaxo, creates an unfair price differential. Moreover, it argued that pharmacists' reimbursement arrangements provide a financial incentive to dispense parallel imports. The net result is that parallel imports into the UK are at a level that is undermining industry's ability to invest in R&D, contrary to the aims of the PPRS.

### Legal basis for parallel imports

The legal basis for the parallel trade in medicines can be traced back to Article 30 of the Treaty of Rome 1957, which prohibits quantitative restrictions on imports and all measures having equivalent effect between member states of the EEC.<sup>8</sup> Furthermore, Article 31 of that treaty declares that member states shall refrain from introducing between themselves any new quantitative restrictions or measures having equivalent effect, and Article 32 requires that, in their trade with one another, member states shall refrain from making more restrictive the quotas and measures having equivalent effect existing at the date of the entry into force of the treaty. In effect, the treaty allows neither direct restrictions, such as a complete ban, nor indirect restrictions, such as laws favouring the sale of

home-produced products, over those imported from other EU member states. However, Article 36 states that the provisions of Articles 30 to 34 shall not preclude prohibitions or restrictions on imports or exports justified on "grounds of the protection of health and life of humans, animals or plants". This is accompanied by the qualification that such "prohibitions or restrictions shall not... constitute a means of arbitrary discrimination or a disguised restriction on trade between member states".

Ironically, given the UK's position as one of the most common destinations for parallel-traded medicines, these issues were first raised in a case involving the export of medicines from its shores. Criminal proceedings were instituted by the district of Rotterdam against Dutch importer Adriaan de Peijper.<sup>9</sup> Mr de Peijper was accused of having infringed Netherlands public health legislation by supplying pharmacies in that member state with medicinal preparations that had been imported from the UK without the consent of the Netherlands authorities and by failing to have in his possession the product-marketing approval documents.

### Questions for interpretation

He did not deny the matters of which he was accused, but argued that he could not comply with the rules because he was unable to obtain the required documents. He said the medicinal products in question were made by a British producer. Mr de Peijper bought them from a wholesaler established in the UK and then imported them "in parallel" into the Netherlands. He contended that neither the said manufacturer, nor the representative of that manufacturer in the Netherlands, would furnish the help that was necessary if he was to obtain the above-mentioned documents.

The *kantonrechter* (county court judge) of Rotterdam referred two questions concerning the interpretation of the Treaty of Rome to the European Court of Justice (ECJ) on 29 September 1975.<sup>10</sup> The main purpose was to find out whether the rules that required Mr de Peijper to provide such documents were contrary to community law because they constituted a measure having an effect equivalent to a quantitative restriction, and whether these rules may fall within the exception specified in Article 36 in favour of restrictive measures justified on grounds of the protection of health and the life of humans.

The ECJ was asked to rule on whether the imposition of a rule by national authorities requiring the production of documents identical to those already lodged with them by the domestic manufacturer was equivalent to a quantitative restriction, when the pharmaceutical product was of identical qualitative and quantitative composition to a domestically sourced product. It was ruled that if the public health authorities of the importing member state already possess, as a result of importation on a previous occasion, all the pharmaceutical particulars relating to the medicinal preparation in question, it is unneces-

sary, to protect the health and life of humans, for the authorities to require a second trader to produce the same particulars again.

The second question referred to the ECJ was whether the answer given to the first question would apply to a case where the process of manufacture and the qualitative and quantitative composition of the imported medicine were different from those of the domestically procured medicinal preparation bearing the same name. This question was formulated to address instances where the differences between one and the other product were of such minor importance that it would be likely that the manufacturer was applying these differences with the conscious and exclusive intention of using them to prevent or impede parallel trade of their product. The court ruled that its first answer would apply in such cases.

The court reasoned that the legal authorities of the importing member state would be entitled to require the manufacturer, when it applies for a marketing authorisation, to state whether it produces several variants of the medicinal preparation under the same name for different member states and, if it does, to produce similar documentation for the other variants too, identifying the differences between all these variants. Only if the documents showed that there were differences which could alter the therapeutic effect would there be a justification for treating the variants as different medicinal products.

The court believed that as the relevant documentation (in this case batch records) was already held by one set of authorities, they should co-operate in making these available on a reciprocal basis, and that member states should develop a presumption of conformity. If parallel-traded and domestic versions were slightly different it was up to the authorities to investigate whether this was therapeutically significant. The only measures which a national regulatory authority were justified in taking as regards parallel trade, the court said, were those intended to verify that such products were identical with the version marketed in that country by the domestic trade mark owner, or that the difference had no therapeutic effect.

### Abbreviated marketing authorisations

In effect, the ECJ ruled that national rules or practices that mean some traders can import the products, while others are barred from doing so, constitute a measure having an effect equivalent to a quantitative restriction within the meaning of Article 30 of the Treaty of Rome. The court said that such rules or practices do not fall within the exception specified in Article 36 if the health and life of humans can be as effectively protected by measures that do not restrict intra-community trade so much.

The court held that Article 36 cannot be relied on to justify rules or practices that contain restrictions primarily concerned with lightening the administration's burden or reducing public expenditure, unless this burden

or expenditure clearly would exceed the limits of what can reasonably be required.

After the *de Peijper* judgment, the European Commission produced a text outlining the basic principles for an abbreviated form of an MA for parallel-traded medicines.<sup>11</sup> The commission recommended that the information supplied by the importer should be sufficient to ensure that the medicine is covered by an existing authorisation in the country of destination. In effect, this means that the parallel-traded version must contain the same active ingredient(s); be administered to patients through the same route; have the same therapeutic effects; and have a common origin.

This text also set out the minimum amount of information that the importer must provide, including the product name and where it is sourced; the name and address of the holder of the full marketing authorisation (in the member state of origin and in the member state of destination); the name and address of the parallel trader; the product's marketing authorisation number in the source country; the product's summary of product characteristics; and specimens or mock-ups of the product in the form in which it will be sold in the member state of destination.

On 22 December 1986, these recommendations were adopted into EU legislation by Community Directive 87/21/EEC. This affirmed that an applicant for an MA would "not be required to provide the results of pharmacological and toxicological tests or the results of clinical trials if he can demonstrate that either the proprietary medicinal product is essentially similar to a product authorised in the country [of] application and that the manufacturer has consented to [data] on the original proprietary medicinal product being used for the purpose of examining the application in question; or . . . that the constituent or constituents of the proprietary medicinal product have a well established medicinal use, with recognised efficacy and an acceptable level of safety".

The necessity for a medicine that is subject to an abbreviated parallel import marketing authorisation (PL(PI)), to be manufactured by the same company in the concerned member states was the subject of a case in the English courts. *Smith & Nephew* markets the proprietary medicinal product *Ditropan* (oxybutinin) in the UK pursuant to an agreement concluded in 1982 with the US company *Marion Merrell Dow* (MMD). Until 1997, the product was manufactured in the UK on behalf of *Smith & Nephew* by *Boots Pharmaceuticals Ltd*. The application for a marketing authorisation for *Ditropan* was submitted to the Medicines Control Agency (MCA) by *Smith & Nephew* in 1982 on the basis of data and other information supplied by MMD.

### Marketing authorisation

Since the MCA, which was the regulatory body for the UK at that time, considered that information to be insufficient, *Smith &*

*Nephew* was required to perform additional clinical studies and, according to the High Court, to change the formulation of the proprietary medicinal product from that which had been manufactured by MMD in the US. As a result, a marketing authorisation was not granted until January 1991.

On 8 October 1992, the pharmaceutical importer *Primecrown* submitted an application for an authorisation under the PL(PI) procedure for the purpose of making parallel imports of a variant of *Ditropan* sold in France by *Laboratoires Debat*. The MCA rejected that application on the ground that there was no link between *Smith & Nephew* and *Laboratoires Debat*. On 22 February 1993 *Primecrown* made a further application to the MCA for an authorisation under the PL(PI) procedure for the purpose of importing and selling, in the UK, *Ditropan* marketed in Belgium by MMD Belgium pursuant to a Belgian marketing authorisation. In a document signed on 8 July 1993, the pharmaceutical assessor appointed by the MCA concluded that the Belgian *Ditropan* was identical in formulation to *Smith & Nephew's* *Ditropan*. On 24 August 1993 the MCA granted the authorisation sought by *Primecrown*, erroneously taking the view that the requisite link existed between *Smith & Nephew* and MMD Belgium for the application of the PL(PI) procedure. The MCA considered that the case raised no public health problems at that time.

### Product specifications

In a letter sent to the MCA on 7 September 1993, MMD stated that, although it knew of and controlled the specifications for *Ditropan* manufactured in Belgium, such was not the case for the specification for *Ditropan* manufactured in the UK. MMD stated that *Smith & Nephew* was a separate legal entity from the MMD group of companies and that MMD merely provided it with the ingredient oxybutynin hydrochloride. It concluded that it could not confirm that the product specifications for *Ditropan* manufactured in Belgium were identical to those for *Ditropan* manufactured in the UK. When it became aware that the requisite link for the purposes of the PL(PI) procedure did not exist between *Smith & Nephew* and MMD Belgium, the MCA withdrew the marketing authorisation granted to *Primecrown*.

On 26 January 1994 the High Court granted *Smith & Nephew* leave to bring proceedings for judicial review of the MCA's decision of 24 August 1993 authorising *Primecrown* to import Belgian *Ditropan* into the UK. Simultaneously, *Primecrown* applied to the High Court under section 107(2) of the Medicines Act 1968 for an order quashing the MCA's decision to withdraw authorisation.

The High Court referred to the ECJ the question of whether the licensing authority in one member state was entitled to grant a marketing authorisation for a medicinal product, which is sought to be imported from

another member state, in circumstances where the product was not made by or under the control of the company, or group of companies, holding the marketing authorisation in the member state into which it was to be imported.<sup>12</sup>

The ECJ found that it would be contrary to Article 3 of Directive 65/65/EEC for a national authority, in the context of an application for a marketing authorisation, to use information supplied by an independent company, without its agreement, in support of an application for a marketing authorisation concerning another proprietary medicinal product. In other words, if it is concluded by the Medicines and Healthcare Products Regulatory Agency (MHRA) that both UK- and EU-sourced products are manufactured by independent companies pursuant to agreements concluded with the same licensor and that those two products, though not identical in all respects, have been manufactured according to the same formulation, using the same active ingredient, and having the same therapeutic effects, then the imported product must be treated as being covered by the latter MA.

If, however, the MHRA concludes that the proprietary medicinal product to be imported does not satisfy those criteria, as would be the case if no such licensing agreement existed between the independent companies, a new MA would be required. That authorisation can be issued only in accordance with the conditions laid down in Articles 3 and 4 of Directive 65/65/EEC, as amended by Directive 87/21/EEC.

### Judicial review

A PL(PI) is granted for five years, but normally remains in force only so long as both the UK marketing authorisation and the EU marketing authorisation to which it relates remain in force. If either of these is revoked, the PL(PI) will automatically fall. If a marketing authorisation is withdrawn, it may be possible to continue to market the product in the UK, but only if the PL(PI) satisfies the strict criteria that the ECJ has set for the survival of PL(PI)s in these circumstances.

The case in question stemmed from an application for judicial review of two decisions of the MCA.<sup>13</sup> A member of a group of pharmaceutical companies (*May & Baker Ltd*), obtained marketing authorisations from the MCA, in compliance with Council Directive 65/65/EEC for a medicinal product called *Zimovane* (zopiclone). It appointed an agent (*Rhône-Poulenc Rorer Ltd, RPR*) to manufacture and market that product in the UK. After some years, the agent developed a new version of *Zimovane* containing the same active ingredients as the old product, but with different excipients that, they claimed, made it more beneficial to public health.

The MCA varied the authorisations, so allowing the marketing of the new version in the UK, and subsequently revoked the authorisations under which the old version had been marketed. Thereafter, only the newer

version was marketed in the UK, although the older product continued to be marketed in other member states.

Before the revocation, parallel import licences for the old version had been granted, and the MCA decided to treat those licences as still valid. May & Baker and RPR sought a judicial review of the MCA's decisions claiming that, in the absence of any subsisting marketing authorisations of the old version in the UK, imports of that version into the UK were not parallel imports, so it was contrary to UK legislation and community law to treat them as such. The MCA contended that, had it treated the two versions of Zimovane as different products and required the parallel importers of the old version to apply for marketing authorisations under Directive 65/65/EEC, it would have created an unjustifiable restriction on imports contrary to Article 36 of the Treaty of Rome. The matter was referred to the ECJ,<sup>14</sup> where RPR also claimed that the particular benefit to public health provided by the new version would not be achieved if the old version was present on the UK market.

The ECJ ruled that, where it was sought to import a medicinal product from one member state into another, it was permissible for the person seeking to do so to obtain a PL(PI) licence in that member state without meeting all the requirements of Directive 65/65/EEC, if the product was the subject of a marketing authorisation granted in the first member state and of an authorisation that had ceased to have effect in the second member state; or the product was the subject of a marketing authorisation granted in the second member state, but not in the first. The ECJ said it was also permissible where both medicinal products had the same active ingredients and therapeutic effect, but did not use the same excipients and were manufactured by different processes, provided that the competent authority in the second member state was able to verify the product complied with quality requirements and could ensure pharmacovigilance. The court stated that authorisations referred to must be granted to different members of the same group of companies and that companies within the same group as the holder of the authorisation must continue to manufacture and market the product in (an)other member state(s).

PL(PI)s are subject to the provisions of the Medicines (Standard Provisions for Licences and Certificates) Regulations 2004 (as



amended). The PL(PI) holder must also take reasonable steps to keep informed of changes to the MAs on which his licence depends and notify these changes to the MHRA.

For the purposes of EU law, the product is marketed in the UK under the UK marketing authorisation for the reference product mentioned in the PL(PI). This does not affect the status of the PL(PI) as a UK marketing authorisation, but where the holder of the marketing authorisation for the reference product has to vary his marketing authorisation, the PL(PI) holder will have to vary the PL(PI) as well. The PL(PI) holder must take reasonable steps to keep himself informed of variations in the EU marketing authorisation(s) on which his licence depends and report these to the licensing authority, although in most cases it will not be necessary for a PL(PI) holder to vary the PL(PI) if the EU marketing authorisation is amended.

The licence holder must inform the licensing authority of any changes that he proposes with regard to the source of his product supplies and arrangements for repackaging the product by him or on his behalf, and vary the PL(PI) to reflect this. If required, the PL(PI) holder must seek approval to market the varied product by asking for a variation to that PL(PI) licence. No batch of a varied product may be marketed in the UK until the variation has been approved by the licensing authority.

Conversely, the MHRA is required to ensure that the PL(PI) is kept in line with the relevant provisions of the appropriate MA, and notify the PL(PI) holder of any action necessary as a result of a variation to the UK marketing authorisation.

## Conclusions

Each criterion for licensing a parallel import — the product in question is covered by a valid MA in an EU member state, has no different therapeutic effect to its UK equivalent, and is made by the UK manufacturer or the same group of companies — has been arrived at following legal challenges that have gone to the ECJ. A sound knowledge of the statutory law surrounding PIs, but also of the cases whence it stemmed is invaluable to pharmacists and importers alike. In the next article in this series, we will discuss recent challenges to the legality of the parallel trade in medicines as a primer to avoiding the common pitfalls of importing and dispensing medicines from outside the UK.

## Notes and references

- Freudenberg R. Do not blame counterfeits on parallel trade (letter). *Pharmaceutical Journal* 2006;277:666. 2006.
- Birkby RJ. Number of doses differ (letter). *Pharmaceutical Journal* 2007;278:459.
- First recall of parallel trade counterfeits ordered. *Pharmaceutical Journal* 2007;278:635.
- Kanavos P, Holmes P. The economic impact of parallel trade. In: Irvine B (editor), *Pharmaceutical Parallel Trade in the UK*. The Institute for the Study of Civil Society, 2005.
- West P. Benefits to payers and patients from parallel trade. York: York Health Economics Consortium, May 2003.
- Parallel imports saved UK €237m in health care costs in 2004, says European report. *Pharmaceutical Journal* 2006;276:744.
- Select Committee on Trade and Industry, Eighth Report. 29 June 1999.
- The Treaty of Rome 1957.
- Kantongerecht Rotterdam, Sentence of 29 September 1975 (74310/74).
- Officier van Justitie v de Peijper [1976] ECR 613.
- Commission communication on parallel imports of proprietary medicinal products for which marketing authorisations have already been granted. C115/5. Official Journal of 6 May 1982.
- R v The Medicines Control Agency, ex parte Smith & Nephew Pharmaceuticals Ltd [1996] ECR I-5819.
- R v Medicines Control Agency, ex parte Rhône-Poulenc Rorer Ltd (No.1) (Queen's Bench Division) [1998] CLY 2659.
- R. v Medicines Control Agency, ex parte Rhone Poulenc Rorer Ltd (C94/98) [2000] All ER (EC) 46.