Intellectual property and chirality of drugs

Israel Agranat and Hava Caner

Chirality has emerged as a key issue in drug design, discovery and development. Chiral switches are drugs that are already approved and claimed as racemates but that have been redeveloped as single enantiomers. The legal state of the art of patentability of chiral switches, as derived from US and European precedents, is reviewed. The issues of intellectual property in the pending chiral switches of the blockbuster drugs ibuprofen, fluoxetine and omeprazole are analysed.

The issue of chirality has emerged as a major theme in drug design, discovery and development[1–6] as stereoisomer distinction is a significant component in many pharmacological events. The advances in chiral technology and the ability to produce enantiomerically pure compounds have an important impact on drug design, research and development and on the strategies and policies of the pharmaceutical industry[7–9]. In May 1992, the US Food and Drug Administration (FDA) issued a policy statement for the development of new stereoisomeric drugs[10], whereas the European Union (EU) Committee on Proprietary Medicinal Products (CPMP) released its guidelines on the investigation of chiral active substances in December 1993 (Ref. 11). The FDA statement was not an edict[12] and although the FDA would prefer the development of only one form of a chiral drug, it indicated that it might still be possible to develop a chiral drug as a racemate. However, the FDA statement of official recognition of the chiral drug issue served as an incentive to the current move to single enantiomer drugs[12]. The scientific and regulatory considerations in the development of chiral drugs in the US, the EU, Canada and Japan have been reviewed[13–15].

It has been recently concluded that the racemate-versus-enantiomer debate is coming to an end*. An in-depth clinical perspective of this debate was presented in 1998†. Likely advantages of using stereochemically pure drugs are that: (1) the total dose could be reduced, (2) the dose–response relationship would be simpler, (3) a source of interobject variability would have been removed and (4) toxicity from the inactive stereoisomer would be minimized*. These pharmacodynamic and pharmacokinetic factors have led to an increasing preference for single enantiomers*. Indeed, single enantiomer drugs continue to take an increasing share of the market with worldwide sales of these drugs surging by 21% between 1996 and 1997 up to almost $90 billion[6].

There are two principal scenarios in chiral drug development: the first is the *de novo* development of an enantiomerically pure chiral drug; the second is a switch from an existing racemic drug to the single enantiomer(s) of that drug[14].

'Chiral switches' are chiral drugs that are already approved as racemates but that have been redeveloped and launched as single enantiomers[6,8]. The term 'chiral switches' is preferable to 'racemic switches' because the switch is from a racemic drug ($E_{1,2}$) to the corresponding enantiomer(s) (E_1 and/or E_2). The definition of a chiral switch can be broadened to include chiral drugs that are already approved as mixtures of diastereomers (e.g. epimers) but that have been redeveloped and launched as single enantiomers, or single enantiomers (E_1) that have been redeveloped and launched as the corresponding enantiomers (E_2).

Although, in 1997, the prospects for chiral switches seemed bleak[5], in 1998, the outlook for chiral switches was upbeat[6]. If the two enantiomers of a chiral drug are

*Caldwell, J. (1997) Molecular Chirality 1997, 26–27 October, Nagoya, Japan, pp. 3–6.
† Eichelbaum, M. (1998) 10th International Symposium on Chiral Discrimination, 30 August – 2 September, Vienna, Austria, L21.

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sufficiently pharmacologically different, it might be possible to obtain a patent for one or both enantiomers, in addition to a pending (or expired) patent for the corresponding racemate. Very often, the two enantiomers of a chiral drug are not protected by patents, whereas the corresponding racemic drug is protected.

Intellectual property law concerns the legal rights associated with creative efforts or commercial reputation and goodwill[16]. The law deters others from copying or taking unfair advantage of the work or reputation of another, but should this happen, the law provides a method for remedial action. A patent right is created by a government grant[17] and, because it gives its owner a monopoly, is the form of intellectual property *par excellence*. A patent can be granted in respect of a new invention that is capable of industrial applicability and gives the inventor a monopoly right that can last for 20 years[16]. Article I, Section 8, Clause 8 of the US Constitution (1787) states that 'Congress shall have the power…to promote the Progress of Science and useful Arts, by securing for limited Times to Authors and Inventors the exclusive Right to their respective Writings and Discoveries.' The prerequisites for patentability are that the protection claimed is novel, inventive and of industrial applicability, and that the supporting description is sufficient for the application[18–21]. In the USA, the bulk of the legislature relating to the implementation of statutory provisions concerning patents can be found in the Patent Act of 1952, Title 35, United States Code (USC)[22]. In the context of patentability of single enantiomers in a chiral switch scenario, attention should be drawn to Sections 101 (Invention patentable), 102 (Conditions for patentability: novelty and loss of right to patent), 103 (Conditions for patentability: non-obvious subject matter), 112 (Specification) and 156 (Patent term extension)[23] of Title 35 USC. In Europe, the relevant legislation is embodied in the European Patent Convention (EPC; in force since 7 October 1997)[24]. In the present context, attention should be drawn to Articles 52 (Patentable inventions), 54 (Novelty), 56 (Inventive step), 57 (Industrial application) and 83 (Disclosure of the invention) of the EPC.

Chiral switch – a selection invention *par excellence*

A selection invention is an invention that selects a group of individually novel members from a previously known class, on the basis of superior properties[20,25]. The patentability of enantiomer(s) in a chiral switch is an extreme case of the patentability of a selection invention.

Selection patents are governed by the I.G. Farben rules[20,25,26], going beyond the normal requirements for validity. These rules are as follows: (1) the advantage from the selection must be substantial; (2) the whole of the selected members must possess it; (3) the special characteristic selected must be peculiar to the selected group, in the sense that it 'must not be one which those skilled in the art will expect to find in a large number of members' of the original class; (4) the special property must be defined in clear terms in the specification[25,26]. Certain special considerations might apply to selection inventions. When the earlier disclosed class of compounds is small, as for a racemate, it can be argued that a general disclosure of the class is equivalent to a specific disclosure of each of its members, thereby rendering every member of the class no longer novel. In the UK, the House of Lords held in the DuPont (Witsiepe)[27] judgement that the disclosure of a class, even a very small class, whether the disclosure is in general terms or by enumeration of its members, is not disclosure of the individual members so as to make them no longer new[27].

In any ordinary selection case, the question is not of novelty but one of obviousness (lack of inventive subject matter), utility and sufficiency of description, these in the ordinary way[25]. In the UK, the test of obviousness in a selection patent is whether it is obvious to any skilled person in the state-of-the-art existing at the date of the patent, and whether any substances described within the claim would be likely to present a sufficient improvement over those previously made, therefore justifying the expenditure needed for their investigation. If the answers to this test are not obvious, then the invention should be patented, as long as it can be properly claimed[25]. The test of obviousness in a selection patent for the European Patent Office (EPO) is whether the improvement is surprising and, hence, whether it involves an inventive step within the meaning of Article 56 EPC (Refs 20,24,28). If the cited prior art shows that the technical problem is the selection of the novel agent from a known class, then it can generally also be subsequently agreed that the problem consists in selecting the surprisingly improved agent.

The above criteria, including the I.G. Farben rules[25,26] and the DuPont (Witsiepe)[27] precedent, also apply to selection patents involving chiral switches. In England in 1971, it was held that publication of the existence of an optically active compound is not publication of the separated optically active forms, even though any chemist would appreciate that each form must exist and could be produced[29]. This case could have been treated as a selection invention, but it was not. In a chiral switch, if a company first patents a specific group of compounds to obtain a 20-year monopoly, and then attempts to obtain a further 20-year monopoly for selecting a preferred group of them, this might be seen as an abuse of patent rights[20]. For this reason, in the public interest, selection inventions, especially those representing selection from a relatively small class of

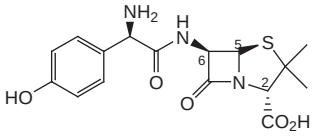


Figure 1. *Amoxycillin (Beecham Group Limited's amoxycillin application).*

compounds (e.g. chiral switches), should be examined carefully to ensure patents are not granted too readily[20].

The patentability of a single enantiomer in a chiral switch raises the question of a *prima facie* obviousness. Prior art compounds (e.g. racemates) that are structurally similar to the claimed compound or drug in question could render the latter obvious and therefore unpatentable. The US Federal Circuit ruled in *re Dillon*[30] that 'This court…reaffirms that structural similarity between claimed and prior art subject matter, proved by combining references or otherwise, where the prior art gives reasons or motivation to make the claimed compositions, creates a *prima facie* case of obviousness, and that the burden (and opportunity) then falls on an applicant to rebut the *prima facie* case. Such rebuttal or argument can consist of a comparison of test data showing that the claimed composition possesses unexpectedly superior properties or properties that the prior art does not have'[17,18,30].

In 1980, the Court of Appeal in England gave an important judgment on the validity of the selection patent of the antibacterial drug amoxicillin[31] (Fig. 1). The amoxicillin case was litigated on the basis of the Patents Act 1949 which preceded both the Patents Act 1977 and the EPC (Ref. 24). The patent in suit involved a selection invention of one enantiomer from a previously claimed group of nine semisynthetic penicillins. These originated from three structural isomers, each one giving rise to two epimers and their 1:1 mixture.

The opinions of the Lord Justices[31] deserve a separate report. The final judgement of the Court of Appeal illustrates the legal difficulties involved in a chiral switch selection patent litigation, especially with respect to the principle of obviousness.

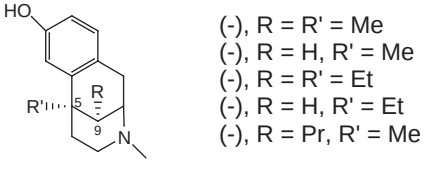


Figure 2. N-*Methylbenzomorphans (re May and Eddy).*

The patentability of chiral switches – patent law precedents

US precedents

Re Adamson and Duffin[32] (US Court of Customs and Patent Appeals, US CCPA) is considered to be the leading US precedent concerning chiral switches. The patent application claimed the making, separating and the specific therapeutic activity of the (−)-isomers of 1-cyclohexyl-1-phenyl-3-piperidinopropan-1-ol and 1-cyclohexyl-1-phenyl-3-pyrrolidinopropan-1-ol. The appellants demonstrated that the (−)-isomers of these compounds have higher spasmolytic activity than the (+)-isomers or the racemic mixture whilst only having slightly higher toxicity than the same quantity of the racemate. The US CCPA ruled that the claimed compounds were unpatentable over the cited prior art reference, in view of the *Karrer Organic Chemistry Textbook* which emphasized the fact that 'the physiological properties of two antipodes [stereoisomers] can differ considerably'. The US CCPA found obviousness in the appellants' claim for the superior spasmolytic activity of the (−)-isomers. Despite the Adamson and Duffin precedent, the US CCPA decided that enantiomers of known racemates can be considered as novel *per se*, and have allowed the patenting of enantiomers in certain chiral switch scenarios.

In *re May and Eddy*[33] (US CCPA), the appellants claimed in their application that the salts of the (−)-isomers (R = H) and the α-(−)-isomers (R = Me, Et, Pr) of *N*-methylbenzomorphans (Fig. 2) exhibit a unique combination of neuropharmacological properties, such as an analgesic potency comparable to that of morphine, coupled with non-addictiveness and the absence of other side-effects. All of the claims in this application were rejected by the examiner and the US Patent Authority (PTO) Board of Appeals under 35 USC Section 103 (Conditions for patentability: non-obvious subject matter)[22]. However, the US CCPA have found that some methods-of-use claims differ critically from the rejected obvious claims in that they describe the use of a novel compound. As recognized in *re Williams*[34], 'the novelty of an optical isomer is not negated by the prior art disclosure of its racemates…It was totally unexpected that appellants' (−)- and α-(−)-*N*-methylbenzomorphans would exhibit such a combination of properties (analgesic potency comparable to morphine coupled with non-addictiveness) and, concomitantly, could be used to effect non-addictive analgesia'[33]. The court stated that 'those properties which would have been expected must be balanced against the unexpected properties'[33]. The court based its opinion on *re Albrecht*[35], where it had been stated that 'we are of the opinion that a novel chemical compound can be nonobvious to one having ordinary skill in the art not withstanding

that it must possess a known property in common with a known structurally similar compound.' The CCPA reversed the rejection on 11 out of the 13 remaining claims[33].

European precedents

The leading European precedent on chiral switches is the Enantiomers/Hoechst[36] decision of the *European Technical Board of Appeal* (TBA) on European Patent 2800B2 (application date 20 December 1978) entitled *Optically active α-phenoxypropionic acid derivatives*. The TBA wrote[36]:

> Long before the contested patent's priority date, it was generally known to specialists that, in physiologically active substances (e.g. herbicides, insecticides and growth regulators, but also pharmaceuticals and food stuffs) with an asymmetrical carbon atom enabling them to occur in the form of a racemate or one of two enantiomers, one of the latter frequently has a quantitatively greater effect than the other or than the racemate. If – as here – the aim is therefore to develop agents with increased physiological activity from a physiologically active racemate the obvious first step – before any thought is given, say, to synthesizing structurally modified products – is to produce the two enantiomers in isolation and test whether one or the other is more active than the racemate. Such tests are routine. Under established Board case law, an enhanced effect cannot be adduced as evidence of inventive step if it emerges from obvious tests. Since, in the present case, tests with the enantiomers were obvious in view of the task at hand, discovery of the claimed effect of the D-enantiomers compared with corresponding racemate does not involve an inventive step. (Point 8.4.1 of the Reasons for the Decision[36].)

The Enantiomer/Hoechst decision of the TBA (Ref. 36) also considered the question of 'whether a known claimed formula evidently containing a (single) asymmetric carbon atom destroys the novelty not only of the compound in the form of a racemate, but also of its enantiomers', without mentioning the enantiomers at all (Point 6 of the Reasons for the Decision). The TBA held that 'the novelty of the D- and L-enantiomers is not destroyed by the description of the racemate'[36,37].

The chiral switch of the inhalation anaesthetics isoflurane and desflurane – patent specification of enantiomers

The chiral inhalation anaesthetics, isoflurane and desflurane (Fig. 3), are clinically administered as synthetic racemic mixtures[38]. The absolute configurations of isoflurane and desflurane, first determined in 1992–1993, are still considered controversial[39].

In 1993, Sepracor Inc. (MA, USA) was granted two consecutive US Patents, 5114714 (Ref. 40) and 5114715 (Ref. 41), which claimed that both (*R*)- and (*S*)-isoflurane and both (*R*)- and (*S*)-desflurane can induce and maintain anaesthesia and are associated with less-adverse effects than the corresponding racemates (Box 1). These patents contain no data on the chiroptical properties of the enantiomers, and the absolute configuration descriptors (*R*) and (*S*) in these patents were devoid of supportive evidence.

The present context raises the question of what are the necessary prerequisites for patent specification of enantiomers. One of the grounds upon which a patent might be revoked by the courts for invalidity is insufficiency. 'Insufficiency means something which is insufficiently described…If you cannot achieve the promised result because of deficiencies in the information given in the specification, there is insufficiency'[42]. From this point of view, the two Sepracor applications for patents were probably applications without sufficient evidence, and thus did not fulfil the requirements of Title 35 USC Section 112 (Specification)[22]; see also Article 83 EPC (Disclosure of the invention)[24]. It can therefore be suggested that experimental evidence, such as chiroptical properties, absolute configuration(s) and/or NMR data should all be included in the patent specifications of enantiomers.

The strategy of complementary pairs of patents of enantiomers

Consider the two enantiomers E_1 and E_2 of a racemic drug $E_{1,2}$. The two Sepracor US Patents 5114714 and 5114715 (Box 1)[41] are a complementary pair of patents for the two enantiomers of isoflurane and desflurane‡. In the first patent, the claim is that E_1 is pharmacologically superior to $E_{1,2}$. In the second patent, the claim is that E_2 is pharmaco-

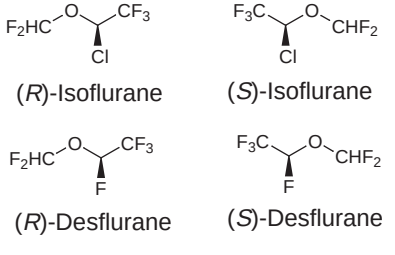


Figure 3. *The enantiomers of isoflurane and desflurane.*

‡Agranat, I., Biedermann, P.U. and Caner, H. (1997) AFMC International Medicinal Chemistry Symposium, AIMECS '97, 27 July – 1 August, Seoul, Korea, p11.

Box 1. The complementary pair of Sepracor's US patents of the enantiomers of the inhalation anaesthetics isoflurane and desflurane

US 5114714 (Ref. 40)
Inventors: J.W. Young and S. Brandt
Assignee: Sepracor Inc., MA, USA
Claim 1: A method of inducing and maintaining anesthesia while diminishing the concomitant liability of adverse effects associated with the administration of racemic isoflurane or desflurane, comprising administering by inhalation to a warm-blooded animal including a mammal in need of anesthesia an amount sufficient to induce and maintain anesthesia but insufficient to cause said adverse effects, of (*R*)-isoflurane or (*R*)-desflurane, wherein when (*R*)-isoflurane is administered said amount contains about 90% or more by weight of (*R*)-isoflurane and about 10% or less by weight of (*S*)-isoflurane, or when (*R*)-desflurane is administered said amount contains about 90% or more by weight of (*R*)-desflurane and about 10% or less by weight of (*S*)-desflurane.

US 5114715 (Ref. 41)
Inventors: J.W. Young and S. Brandt
Assignee: Sepracor Inc., MA, USA
Claim 1: A method of inducing and maintaining anesthesia while diminishing the concomitant liability of adverse effects associated with the administration of racemic isoflurane or desflurane, comprising administering by inhalation to a warm-blooded animal including a mammal in need of anesthesia an amount sufficient to induce and maintain anesthesia but insufficient to cause said adverse effects, of (*S*)-isoflurane or (*S*)-desflurane, wherein when (*S*)-isoflurane is administered said amount contains about 90% or more by weight of (*S*)-isoflurane and about 10% or less by weight of (*R*)-isoflurane, or when (*S*)-desflurane is administered said amount contains about 90% or more by weight of (*S*)-desflurane and about 10% or less by weight of (*R*)-desflurane.

logically superior to $E_{1,2}$. A second party might discover that E_1 is pharmacologically superior to E_2. However, the utility of E_1 is already claimed by the original patent and is covered. This is probably an example of a discovery and not of an invention and thus, the chances that the second party will be able to obtain a patent for his claims are very small. Nevertheless, it is not sufficient to claim that, for a given chiral drug, enantiomers E_1 and E_2 both have superior pharmacological effects compared with the corresponding racemic drug $E_{1,2}$ (e.g. lack of adverse effects), without claiming that E_1 is superior to E_2 (or *vice versa*). The examiners of patents should consider these arguments before granting the patent(s) in a chiral switch scenario. Indeed, the examiners of the EPO have so far declined to grant complementary pairs of patents on enantiomeric drugs.

This therefore gives rise to the question of whether complementary pairs of patents of enantiomers are false or true. Such patents might, in principle, be true, if diastereomeric interactions are involved, such as the homochiral interactions, $E_1 \cdots E_1$ and/or the heterochiral interactions, $E_1 \cdots E_2$ (Ref. 43). The example of the complementary pair of patents on the enantiomers of isoflurane and desflurane is not a rarity, but is rather an illustration of a strategy. A list of international patent applications (WO) of complementary pairs of patents, all submitted by Sepracor, includes applications claiming the following pairs of enantiomeric drugs: (*S*)- and (*R*)-terodiline, (−)- and (+)-pantoprazole, (−)- and (+)-zileuton, (−)- and (+)-ketoconazole, (+)- and (−)-doxazosin, (+)- and (−)-cetirizine, (−)- and (+)-sibutramine, (−)- and (+)-pirbuterol, (*S*)-(−)- and (*R*)-(+)-ondansetron, (−)- and (+)-cisapride and (−)- and (+)-zopiclone. In those cases in which a company holds intellectual property rights to single enantiomers and pair of enantiomers in a chiral switch scenario, the original proprietor of the patents of the corresponding racemate (or other interested parties) might be obliged to negotiate with that company with the object to obtain licences for use of the subject matter covered by these patents.

The chiral switch of the analgesic, ibuprofen

The chiral switch of ibuprofen (Fig. 4) is an illustration of the insecure intellectual property climate towards chiral switches[16]. Racemic ibuprofen is a well-known non-steroidal anti-inflammatory drug (NSAID) having analgesic and antipyretic activity. It was first launched in 1969 as a prescription drug for the treatment of pain and inflammation associated with rheumatic diseases. It has been known since 1976 that the pharmacological activity of ibuprofen resides in its (*S*)-enantiomer. Furthermore, (*R*)-ibuprofen undergoes a biologically fortuitous metabolic chiral inversion to (*S*)-ibuprofen with no other covalent change in the molecule[1,44,45].

The European Patent EP 0324007 B1 for (*S*)-ibuprofen[44], entitled *A pharmaceutical composition containing (*S*)-(+)-ibuprofen substantially free of its (*R*)-(−)-antipode*, was filed on 8 July 1988 and published as WO 89/00421, which then claimed priority over the US Patent Application 071914 (dated 10 July 1987). This latter application led to US Patent 4851444 (granted 25 July 1989) entitled *Onset hastened/enhanced analgesia*. The patent, EP 0324007 B1 (dated 14 November 1994), was opposed by seven companies based on Articles 100 [grounds for opposition: (a) not patentable, (b) not sufficient, (c) other matters], 102 (Revocation or maintenance of the European patent) and 123 (Amendments) of the EPC (Refs 24,47). The Opposition Division of

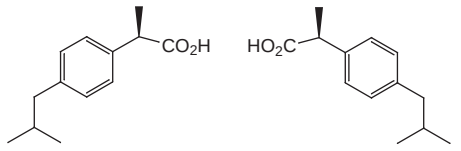


Figure 4. *The enantiomers of ibuprofen.*

the EPO preferred not to address the arguments relating to novelty and inventive step under Article 100(a) EPC nor to the sufficiency of disclosure under Article 100(b) EPC (Ref. 47). One of the opponents (The Boots Company plc, Nottingham, UK) argued that the application did not limit the mode of administration or the type of carrier/diluent. The requirement that the carrier/diluent 'permits release of the mixture so as to obtain hastened-onset of analgesia' was not disclosed initially so that it was open to objection under Article 100(c). The Opposition Division of the EPO decided on 4 November 1997 that EP 0324007 B1 should be revoked under Article 102(1) EPC because all the requests submitted were contrary to Article 100(c) EPC (Refs 23,47), which pertains to the changes made in the claims during the prosecution of the original patent application[47]. A notice of appeal on the decision of the Opposition Division to the European TBA was filed by the patent proprietor on 25 March 1998. Notwithstanding the patent dispute, (*S*)-(+)-ibuprofen (Dexibuprofen) was launched as a prescription drug in Austria in 1994 as Seractil® by Gebro Broschek under a licence from PAZ (Frankfurt-Main, Germany), which had developed the single enantiomer drug as far as gaining approval for marketing authority. (*S*)-(+)-Ibuprofen was also launched in Switzerland in late 1997 as DexOptifen® by Spirig AG (Egerkingen)[45] and Spirig AG has subsequently applied for patents on formulations of tablets of (*S*)-(+)-ibuprofen for rapid release, for the treatment of rheumatic diseases. (For a review of the pharmacodynamics, pharmacokinetics and toxicity of ibuprofen, see Ref. 45.)

The chiral switch of the antidepressant drug fluoxetine hydrochloride

Fluoxetine hydrochloride is a selective serotonin reuptake inhibitor[48], marketed under the trademark Prozac™ by Eli Lilly and Company (IN, USA), for the treatment of depression. This compound is among the many which appear in Eli Lilly's US Patents 4018895 (19 April 1977), 4194009 (19 March 1980) and 4314081 (2 February 1982) as being potent, selective blockers of serotonin reuptake. Fluoxetine is a racemate of the two enantiomers (*R*)-(−)-fluoxetine and (*S*)-(+)-fluoxetine (Fig. 5). The biological and pharmacological activity of each enantiomer has been found to be essentially the same[49]. Under these circumstances, Eli Lilly probably did not consider it advantageous to seek patents for the individual fluoxetine enantiomers as antidepressants. Nevertheless, Sepracor was able to obtain US Patent 5589511 (Ref. 50) on 31 December 1996 and US Patent 5648396 (Ref. 51) on 15 July 1997 claiming the use of (*S*)-(+)-fluoxetine and (*R*)-(−)-fluoxetine for the clinical treatment of migraine headaches and depression, respectively.

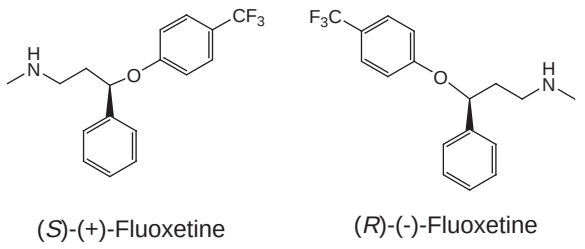
The summary of the invention of US Patent 5589511 includes the following paragraph[50]:

> It has been discovered that the (*S*)-(+) isomer of fluoxetine does not have certain side effects, including causing nervousness, anxiety, insomnia, and adverse psychological effects; has a fast onset of action and an increased response rate. It has also been discovered that with the use of the (*S*)-(+) isomer of fluoxetine it is possible to avoid other activities of the racemic compound which would be unwanted effects when treating a patient suffering from depression. Thus, the (*S*)-(+) isomer of fluoxetine is useful for methods of treating depression and in the compositions used thereof where these detrimental effects will be avoided…In addition, it has been discovered that the (*S*)-(+) isomer of fluoxetine is useful in the treatment of migraine headaches.

The summary of the invention of US Patent 5648396 includes the following paragraph[51]:

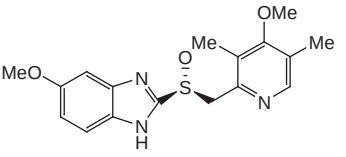
> It has been discovered that the (*R*)-(−) isomer of fluoxetine is an effective antidepressant and appetite suppressant, which because of its short half life and short duration of action, will not be accumulated in a patient's body, thus decreasing the incidence of adverse effects seen with the racemic mixture of fluoxetine. It has also been discovered that the (*R*)-(−) isomer of fluoxetine is useful in the treatment of migraine headaches…In addition to its short half life and short duration of action decreasing adverse effects, using the pure (*R*)-(−) isomer of fluoxetine will also decrease the adverse effects associated with the racemic mixture of fluoxetine.

These two paragraphs are reminiscent of a complementary pair of patents, although the claims of these patents lack this complementarity. It should be noted that Eli Lilly succeeded in obtaining patents on the single enantiomers of the metabolites of fluoxetine, (*S*)-norfluoxetine and (*R*)-norfluoxetine. On 5 October 1993, Eli Lilly obtained US Patent



(*S*)-(+)-Fluoxetine (*R*)-(-)-Fluoxetine

Figure 5. *The enantiomers of fluoxetine.*



(*S*)-(+)-Omeprazole

Figure 6. *(S)-(+)-Omeprazole.*

5250571 (Ref. 52) entitled *(S)-Norfluoxetine in methods of inhibiting serotonin uptake*. In addition, Eli Lilly obtained US Patent 5250572 (Ref. 53) on 5 October 1993 entitled *(R)-Norfluoxetine in method for occupying serotoninic receptors*, and US Patent 5356934 (Ref. 54) on 18 October 1994 entitled *Selected serotonin subtype receptor agonist to treat sleep apnea*. Such patents, claiming single-enantiomer-metabolites of a previously claimed racemic drug, might serve as a defence against obtaining intellectual property rights in chiral switches of the original racemate. The enantiomers and metabolites of fluoxetine are examples of improved chemical entities of marketed drugs[55].

On 7 December 1998, Eli Lilly and Sepracor announced that they had entered into a licence agreement that will enable Lilly to develop exclusively and commercialize globally (*R*)-fluoxetine[56]. According to Sepracor, (*R*)-fluoxetine is currently in Phase I clinical development in the US as a short-acting drug giving increased flexibility in the treatment of depression, whilst (*S*)-fluoxetine is currently in Phase II clinical development for the potential prevention of migraine headaches.

The chiral switch of the anti-ulcer drug omeprazole

The racemic drug, omeprazole, is the first and the leading gastric proton-pump inhibitor used clinically as an anti-ulcer agent[57], becoming the world's highest selling drug in 1997 ($5 billion)[6]. The chirality of the (*S*)-enantiomer of omeprazole (Fig. 6) stems from the presence of a stereogenic sulphur atom in a sulphoxide group. The absolute configurations of the enantiomers of omeprazole have been determined by X-ray crystallography[58]. The mechanism of action of omeprazole as an active H^+/K^+-ATPase inhibitor has been depicted in terms of the 'omeprazole cycle', which involves achiral intermediates[57]. However, there still remains the question of whether one enantiomer of omeprazole is more susceptible to acid-activation and has improved pharmacokinetic and metabolic properties that will give an improved therapeutic profile (e.g. a lower degree of interindividual variation) compared with omeprazole and with its other enantiomer.

Omeprazole was first described in US Patent 4255431 and in European Patent 5129 (both patents being granted in 1981). Omeprazole is, in addition to the substance patent, protected by several other patents including those covering formulation, use, intermediates and processes. These latter patents expire in most markets between the year 2005 and 2016. On 11 February 1998, Astra AB (Södertälje, Sweden) announced that it had received the first patent in the US for perprazole, the (*S*)-(−)-enantiomer of omeprazole. This US Patent 5714504 (Ref. 59), entitled *Compositions* and dated 3 February 1998, is a formula patent, which means that Astra AB has protected the manufacturing process of perprazole. Claims 6 reads[59]: 'A method of inhibiting gastric acid secretion comprising the oral administration of a pharmaceutical formulation comprising a therapeutically effective amount of a pure solid-state alkaline salt of the (−)-enantiomer of 5-methoxy-2[[(4-methoxy-3,5-dimethyl-2-pyridinyl)-methyl]sulfinyl]-1- benzimidazole and a pharmaceutically acceptable carrier'. On 7 July 1998, Astra AB obtained US Patent 5776765 (Ref. 60) entitled *Method of preparing a pharmaceutically active enantiomeric or enantiomerically enriched sulfoxide compound by enantioselective bioreduction of a racemate sulfoxide compound*. This US patent does not refer explicitly to perprazole. Patents on perprazole do not need to prevent generic drug companies from launching their own versions of omeprazole in 2001 (Ref. 6). However, the chiral switch of omeprazole to perprazole might play a role in generic defence strategies of Astra AB (Ref. 6).

It will be interesting to follow the expected patents of perprazole pertaining to its superior pharmacological activity (as compared to omeprazole) and the legal developments that might ensue. On 8 October 1998, Astra AB presented favourable preliminary results from clinical trials involving 11,000 patients on short-term treatment for reflux oesophagitis demonstrating significant clinical superiority of perprazole over omeprazole. Astra AB has recently claimed that new clinical trials in 'acid-NSAID' disease have shown that omeprazole is a rational first-line

therapy for the management of 'acid-NSAID' disease[61]. A double-chiral switch of omeprazole with ibuprofen to perprazole with (*S*)-ibuprofen will be an attractive future challenge in intellectual property law.

Conclusion

The issues of intellectual property involved in chiral switches are by no means straightforward, and the legal picture of patentability in a chiral switch scenario is far from being unequivocal. The barriers of *prima facie* obviousness and lack of novelty have to be overcome. The players and spectators of chiral switches are eagerly anticipating the final decisions and guidelines of the patent courts in the pending litigations of the chiral switches of ibuprofen[47], ketoprofen[§] and cisapride[**].

It is hoped that the patent authorities will take into consideration the argument that sufficient experimental evidence should be included in the patent specifications of enantiomers. In view of the growing demand for single enantiomer drugs, which are essentially free from enantiomeric impurities, emphasis should be drawn to the purity of the claimed single enantiomers[8,36,37#,§§]. Following the case of dexfenfluramine[¶¶], which was approved as a single-drug prescription appetite suppressant for long-term use and marketed as REDUX™ (Ref. 63) and has now been withdrawn[64], a continuation in the collaboration between the patent authorities and the regulatory authorities towards an extension of a patent in a chiral switch scenario is recommended. The patent authorities should scrutinize applications for patents in chiral switches that involve enantiomerizations or epimerizations, or both, of the claimed single-enantiomer drugs. In addition, diastereomeric, enantiomer–enantiomer interactions should be given more consideration to allow mixtures with optimal therapeutic profiles to be obtained[65].

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International Conference on Harmonisation of Technical Requirements for Regulation of Pharmaceuticals for Human Use (ICH). *Guidance on specifications: Test procedures and acceptance criteria for new drug substances and new drug products: chemical substances*[62]. This draft guidance contains a decision tree establishing the identity, assay and chiral impurities procedures in a new drug product containing a chiral drug substance.

§ European Patent Application 89900973.2, EP 0346431 B entitled '*Onset hastened-enhanced analgesia using (S)-(+)-ketoprofen*', filed on 16 November 1988 as WO 89/04658, claiming a priority from US Application of 17 November 1987 [Inventors: Sunshine, A. and Laska, E.M. Proprietor: Bayer Corporation (NJ, USA). Opponent: Menariny International Operations Luxembourg SA (Luxembourg)].

** European Patent Application No. 93918153.3 (EP 651639 A1) entitled *Methods of using (+)-cisapride for the treatment of gastro-esophageal reflux disease and other disorders*, filed as WO 9401111 on 20 January 1994 (Applicant: Sepracor Inc. MA, USA).

†† European Patent Application 93916996.7 (EP 649307 A1) entitled *Methods of using (−)-cisapride for the treatment of gastro-oesophageal reflux disease and other disorders*, filed as WO 9401112 on 20 January 1994 (Applicant: Sepracor Inc.).

§§ In the Erythro-compound/Novartis decision[37], the European Technical Board of Appeal (TBA) examined, *inter alia*, the question of whether the feature of an erythro:threo ratio of 99.5:0.5 or higher, which in fact represents a specific degree of chemical purity (in particular diastereomeric purity), constitutes a 'new element' importing novelty to the claimed subject over a previous citation which disclosed the preparation of the same racemic erythro-compound without specifying its purity. The TBA decided that 'the degree of diastereomeric purity given in the claim cannot be accepted as a new element distinguishing the claimed subject-matter from the state of the art as disclosed' in the previous citation. Furthermore, the TBA held that 'in general a document disclosing a low molecular chemical compound and its manufacture makes normally available this compound to the public in the sense of Article 54 European Patent Convention (EPC) in all desired grades of purity' (Point 7 in the Reasons for the Decision).

¶¶ The chiral switch of the anti-obesity drug fenfluramine into its (*S*)-(+)-enantiomer dexfenfluramine illustrates a collaboration between the US Patent Authority (PTO) and the Food and Drug Administration (FDA) in a patent term extension, in accordance with 35 USC Section 156 (Refs 22, 23). Dexfenfluramine was considered to be one of the few successful realizations of the chiral switch strategy (see footnote *). However, dexfenfluramine, launched in the US on 12 June 1996 was withdrawn by the FDA and the manufacturers, along with fenfluramine and 'fen-phen' (a combination of fenfluramine and phentermine) on 15 September 1997 as a result of significant side-effects involving fenfluramine and dexfenfluramine (US Department of Health and Human Services, Interim Public Recommendation, November 1997). The intellectual properties aspects of this chiral switch will not be analysed here.

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