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feature

The strategy of enantiomer patents of drugs

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Enantiomer patents (ENPTs), constituents of chiral switches, claim single enantiomers of chiral drugs previously claimed as racemates. In this article, the strategy of ENPTs and recent court decisions and trends in case law worldwide are highlighted. ENPTs are challenged frequently (e.g. anticipation, obviousness, double patenting and insufficient disclosure), even though the novelty of enantiomers is not destroyed by the description of racemates. For establishing inventiveness (nonobviousness), the description in ENPTs should include superior pharmacological and/or pharmaceutical properties of enantiomer vis-á-vis racemate, above the expected 2:1 ratio. ENPTs were 'obvious-to-try' (unless taught away) since the mid-1980s. General concern about evergreening by ENPTs is not justified. ENPTs should be evaluated on a case-by-case basis. ENPT litigations are especially susceptible to settlements.

Introduction

The three top-selling drugs for 2008 – Lipitor (atorvastatin calcium), Plavix (clopidogrel bisulfate) and Nexium (esomeprazole magnesium), with total sales of $30 billion [1] – are single-enantiomer drugs. Each of these compounds is claimed in an enantiomer patent – a patent that claims a single enantiomer of a chiral compound that has been claimed previously in the corresponding basic patent (also referred to as the broader patent) as a racemate or as a mixture of diastereomers (including epimers). Illustrative claims of the basic and enantiomer patents of atorvastatin calcium are given in Box 1. Innovator (brand-name) companies establish enantiomer patents with priority dates notably later than those of the corresponding basic patents. Consequently, the expiration dates of the enantiomer patents are later than those of the corresponding basic patents. Generic companies often challenge the validities of enantiomer patents on grounds of lack of novelty (including anticipation), obviousness, lack of utility, insufficiency of disclosure, invalid selection, false suggestion, misrepresentation and double patenting. Here, we highlight the strategy of enantiomer patents in drug discovery and their important role in disputes between brand-name and generic companies and point out recent trends in the case law of patentability of enantiomers.

Enantiomer patents and their corresponding basic patents are constituents of the strategy of chiral switches of drugs [2]. A chiral switch is the development of a single enantiomer from a chiral drug that has been developed (and often approved and marketed) previously as a racemate or as a mixture of diastereomers. The development of the blockbuster selective serotonin re-uptake inhibitor (SSRI) antidepressant Lexapro/Cipralex (escitalopram oxalate), the (+)-(*S*)-enantiomer of the racemic SSRI drug Celexa/Cipramil (citalopram hydrobromide), is a manifestation of this strategy. A chiral switch does not necessarily imply that a racemate has been marketed previously. Lipitor and Plavix have never been marketed as racemates, so the chiral switches in these situations are operating at the level of the intellectual property [3]. By contrast, the chiral switches leading to Nexium and Lexapro/Cipralex were derived from the blockbuster racemic drugs Losec/Prilosec (omeprazole) and Celexa/Cipramil, respectively (Fig. 1).

The enantiomer patents of the majority of chiral switch drugs – Lipitor, Plavix, Nexium, Lexapro/Cipralex, Levaquin/Tavanic (levofloxacine), Xopenex (levalbuterol hydrochloride), Focalin (dexmethylphenidate hydrochloride), Altace (ramipril), Seractil (dexibuprofen), Xyzal (levocetirizine dihydrochloride), Lunesta (eszopiclone), Nuvigil (armodafinil) and Aderall XR (Fig. 1) – have been challenged in various patent jurisdictions. Table 1 gives a list of recent cases involving enantiomer patents. In the USA, enantiomer

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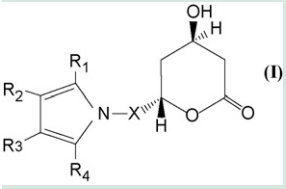
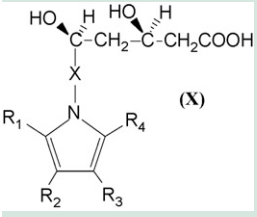
BOX 1

Illustrative claims of basic and enantiomer patents of atorvastatin calcium.

Basic patent	Enantiomer patent
EP 0 247 633 B1 **Priority date** 30/05/1986 (US 4,681,893[a]) **Claim 1** A compound of structural formula I  (I) wherein X is $-CH_2-$, $-CH_2CH_2-$, $-CH_2CH_2CH_2-$ or $-CH_2CH(CH_3)-$; The claim then goes on to set out possibilities for the various R_1, R_2, R_3 and R_4 groups; Or a hydroxy acid or pharmaceutically acceptable salts thereof, derived from the opening of the lactone ring of the compounds of structural formula I and having the formula X  (X) **Claim 3** A compound as defined by claim 1 having the name *trans*-(±)-5-(4-fluorophenyl)-2-(1-methylethyl)-*N*,4-diphenyl-1-[2-(tetrahydro-4-hydroxy-6-oxo-2*H*-pyran-2-yl)ethyl]-1*H*-pyrrole-3-carboxamide. **Claim 6** A pharmaceutical composition, useful as a hypocholesterolemic agent, comprising a hypocholesterolemic effective amount of a compound in accordance with claim 1 in combination with a pharmaceutically acceptable carrier.	**EP 0 409 281 B1**[b] **Priority date** 21/07/1989 (US RE 40,667[c], publication date: 17/03/2009) **Claim 1** The hemicalcium salt of [R-(R*,R*)]-2-(4-fluorophenyl)-β,δ-dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)-carbonyl]-1*H*-pyrrole-1-heptanoic acid. **Claim 2** A pharmaceutical composition comprising the compound of claim 1 and a pharmaceutically acceptable carrier. **Claim 3** Use of the compound of claim 1 for the preparation of a pharmaceutical composition useful for treating hypercholesteremia or hyperlipidemia. **Claim 4** A process for preparation of the compound, according to claim 1 which comprises. . . **Claim 6** Use of the compound prepared according to claim 4 for the preparation of a pharmaceutical composition useful for treating hypercholesteremia or hyperlipidemia.

[a] The US CAFC interpreted claim 1 as including both the racemate and each of the corresponding single enantiomers [57].
[b] This patent was invalidated by the England and Wales Court of Appeal for lack of novelty and obviousness [26].
[c] The original enantiomer patent US 5,273,995 was invalidated by the US CAFC [57] and later reissued: US RE 40,667.

patents have often been challenged under Paragraph IV certification (in which the generic applicant must certify that the relevant patent or patents of the brand-name drugs are invalid or will not be infringed) according to the Hatch–Waxman Act (1984) [4], which established the modern system of generic drugs and includes incentives to challenge patent claims that stand in the way of entry of generic drugs into the market.

Enantiomer patents as selection patents

An enantiomer patent is often considered a selection patent, in which a single enantiomer is selected from the corresponding basic patent. The *locus classicus* describing selection patents has been the UK decision (1930) in re I.G. Farbenindustrie A.G.'s Patents [5] (the *IG rules*). In the context of chemical compounds, in general terms, a selection patent is one whose subject matter (compounds) is a fraction of a larger, known class of compounds that was the subject matter of a prior patent (the originating patent, also referred to as the genus patent) [5]. The seminal speech of Lord Diplock in The House of Lords (in a license case concerning the invention of amoxycillin; Fig. 1) characterized the type of invention according to the doctrine of selection patents [6]: 'The inventive step in a selection patent lies in the discovery that one or more members of a previously known class of products possess some special advantage for a particular purpose, which could not be predicted before the discovery was made' [6]. The specification must describe 'the special advantages that the selected members of the class possess' [6]. The House of Lords held that 'the size of the group or class is not itself decisive as to a question of prior publication of an invention related to a selected member or members,

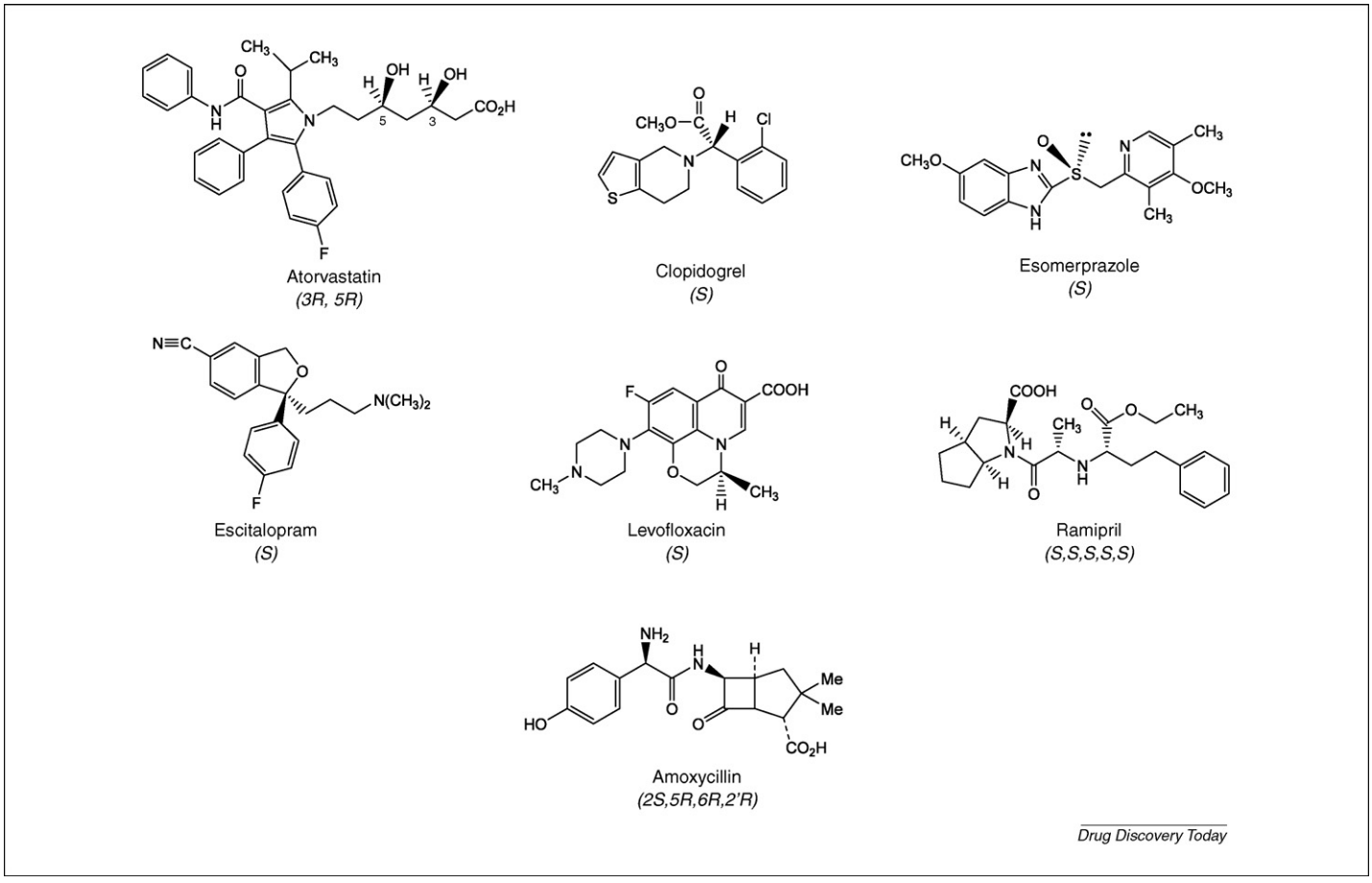


FIGURE 1

Chemical structures of representative single-enantiomer drugs claimed in enantiomer patents. Lipitor is atorvastatin calcium, Plavix is clopidogrel bisulfate, Nexium is esomeprazole magnesium, Lexapro/Cipralex is escitalopram oxalate, Levaquin/Tavanic is levofloxacin and Altace is ramipril.

although it may be relevant to a question of obviousness' [7]. 'A selection patent might be claimed for one or several out of a class of 10 million or for one out of two (cf. the selection of one out of two epimers of a synthetic penicillin combination)' [7].

The UK case law of selection patents has been modified recently by the England and Wales High Court (Patents) (EWHC) and Court of Appeal (EWCA) [8,9]. The EWCA regards the *IG rules* as not part of the living law; the European Patent Office (EPO) does not use them [9]. According to the EPO jurisprudence, which is to be preferred (in the UK) [9], a selection of a group of compounds from a broader group can involve an inventive step if those selected compounds achieve a particular technical result that would not be achieved by the other members of the broader group, although not if the selection was based on an arbitrary choice [9]. A selection, which makes a real technical advance in the art, is patentable [9].

In an enantiomer patent, the selection is often of one single enantiomer from a small group (or subgroup) of three, consisting of the corresponding racemate and its enantiomers (cf. Lipitor and Plavix) claimed in the basic patent. The amoxycillin enantiomer patent (the 'Epimer patent') involved a selection invention [6] of one enantiomer [the (2*S*,5*R*,6*R*,2′*R*)-epimer] from a previously claimed (in the 'OMP patent') group of nine semi-synthetic penicillins [6,10]. These originated from three constitutional isomers (ortho-, meta- and para-hydroxy penicillins), each one giving rise to two epimers (2*S*,5*R*,6*R*,2′*R*/2*S*,5*R*,6*R*,2′*S*) and their 1:1 mixtures (the 'inclusive clause') [10]. The Supreme Court of Canada has recently held that the Plavix patent (CA 1,336,777) is a valid selection patent [11]. The genus patent (CA 1,194,875)' claims all derivatives of general formula I as well as the two enantiomers and the racemic mixture. It is a broad claim for a class or a genus. The claim in the '777' patent is specific. It claims only the (+)-enantiomer of the racemate. This is a typical selection patent' [11]. The Federal Court of Canada, however, held recently that the enantiomer patent of escitalopram (CA 1,339,452) is not a selection patent (allegedly from US patents 4,136,193 and 4,650,884) [12]. 'If the subject matter of either prior US patent were worked, the result would be a racemate, not an enantiomer . . . so the selection patent argument falls for lack of prior disclosure' [12]. Interestingly, the court held that if escitalopram is a selected patent, it is invalid [12]. Is the claim of a racemate *ipso facto* a claim of its enantiomers? The Canadian court did not accept the proposition that a disclosure and claim of a racemate in a prior patent is automatically a disclosure and claim of the enantiomer [12]. In a recent decision in the Lipitor patent litigation [13], the Federal Court of Australia Full Court held that the basic patent of Lipitor (AU 601,981) claimed the racemate, as well as the (+)-enantiomer and the (−)-enantiomer, so the selection of the (+)-enantiomer in the enantiomer patent (AU 628,198) was a selection of one out of three. The Full Court eventually revoked the enantiomer patent (*vide infra*) and validated the basic patent [13], so Lipitor was 'saved' (albeit for a shorter period).

TABLE 1

Some recent cases involving enantiomer patents

Drug	Patent (Court, year)	Decision
Cipralex (escitalopram oxalate)	EP (UK) 0,347,066 (EWHC [37], 2007)	Claim 1 (a product claim to the specific enantiomer) and claim 3 (to pharmaceutical composition containing the enantiomer) invalidated: insufficiency; claim 6 (a process claim to a method for the preparation of the enantiomer) validated
	EP (UK) 0,347,066 (EWCA [14], 2008)	Patent validated
	EP (UK) 0,347,066 (UKHL [53], 2009)	Patent validated
	EP (NL) 0,347,066 (DCH [19], 2009)	Patent revoked: lack of inventive step
	EP (DE) 0,347,066 (BGH [41],2009)	Patent validated
Lexapro (escitalopram oxalate)	US RE 34,712 US (CAFC [54], 2007)	Patent validated
	AU 623,144 (AU FCA [55], 2008)	Patent validated
	AU 623,144 (FCAFC [20], 2009)	Patent validated
	CA 1,339,452 (FC [12], 2009)	Patent validated
Lipitor (atorvastatin calcium)	EP (UK) 0,409,281 (EWHC [56], 2005)	Patent revoked
	EP (UK) 0,409,281 (EWCA [26], 2006)	Patent revoked: lack of novelty and obviousness
	US 5,273,995 (US CAFC [57], 2006)	Patent revoked: improper claim 6 (to atorvastatin calcium) dependency on claim 2 (to atorvastatin acid) (Box 1)
	AU 628,198 (FCAFC [13], 2008)	Patent revoked: false suggestion and misrepresentation
	CA 2,021,546 (FC [25] 2008)	Patent revoked: not valid selection patent
Plavix (clopidogreal bisulfate)	AU 597,784 (FCA AU FCA [58], 2008)	Patent invalidated: lack of novelty and/or inventive step (except claims 2 to 5 to salts of clopidogrel)
	AU 597,784 (FCAFC [59], 2009)	Patent invalidated: lack of novelty and/or inventive step
	CA 1,336,777 (SCC [11], 2008)	Patent validated
	US 4,847,265 (US CAFC [46], 2008)	Patent validated
Nexium (esomeprazole magnesium)	EP 0,652,872 (EPO TBA [60], 2006)	Patent revoked: lack of inventive step
Altace (ramipril)	US 5,061,722 (CAFC [22], 2007)	Patent revoked: obviousness
Levaquin (levofloxacin)	CA 1,304,080 (FC [24], 2006)	Patent validated
	CA 1,304,080 (FCA CA FCA [61], 2007)	Patent validated
Tavanic (levofloxacin)	EP (UK) 0,206,283 (EWHC [36], 2008)	Patent validated
	EP (UK) 0,206,283 (EWCA [21], 2009)	Patent validated

Abbreviations: BGH, Federal Court of Justice of Germany; CAFC, US Court of Appeal for the Federal Circuit; DCH, District Court of the Hague; EWCA, England and Wales Court of Appeal; EWHC, England and Wales High Court; FC, Federal Court (Canada); FCA CA FCA, Federal Court of Appeal (Canada); AU FCA, Federal Court of Australia; FCAFC, Full Federal Court of Australia – Full Court; HCA, High Court of Australia; SCC, Supreme Court of Canada; TBA, EPO Technical Board of Appeal; UKHL, United Kingdom House of Lords.
Links to Courts' Decisions: BGH, (http://www.bundesgerichtshof.de/entscheidungen/entscheidungen.php); CA FCA, (http://decisions.fca-caf.gc.ca/en/index.html); CAFC, (http://www.cafc.uscourts.gov/dailylog.html); EWCA, (http://www.bailii.org/ew/cases/EWCA/Civ/); EWHC, (http://www.bailii.org/ew/cases/EWHC/Patents/); FC, (http://decisions.fct-cf.gc.ca/en/index.html); FCA AU FCA, (http://www.austlii.edu.au/au/cases/cth/federal_ct/toc.html); FCAFC, (http://www.austlii.edu.au/au/cases/cth/FCAFC/); HCA, (http://www.austlii.edu.au/au/cases/cth/HCA/); SCC, (http://scc.lexum.umontreal.ca/en/index.html); TBA, (http://www.epo.org/patents/appeals/search-decisions.html); UKHL, (http://www.bailii.org/uk/cases/UKHL/); USSC, (http://www.supremecourtus.gov/opinions/opinions.html).

Novelty (including anticipation)

When considering the novelty of an enantiomer patent, it is settled jurisprudence in the EPO that a disclosure of a racemate does not in itself amount to the disclosure of each of its enantiomers [14,15]. Likewise, in the USA, 'the novelty of an optical isomer is not negated by the prior art disclosure of its racemate' [16]. The US courts concluded that a prior art disclosure of a racemate does not anticipate the individual enantiomers of the racemate [17]. According to EPO case law, a prior disclosure does not take away the novelty of a claim to a specific compound, unless the compound is disclosed in 'individualised form' [8,9,15]. The only technical teachings prejudicial to novelty are those that disclose a substance as an inevitable result of a prescribed method or in specific 'individualised form' [8,9,15]. Thus, the disclosure of the racemate will be harmful to the novelty of an enantiomer of the same only if there is a direct and unambiguous disclosure of this very compound in the form of a technical teaching [18]; for example, when the state of the art includes enantiomers – however designated (D, d, L, l, or + or −) – which are specifically named and can be produced. That it is theoretically possible to resolve a known racemate into the individual enantiomers is not relevant for the assessment of the novelty of an enantiomer *vis-á-vis* a racemate [19]. The Federal Court of Australia Full Court also held (in the escitalopram patent case) that the disclosure of a racemate does not necessarily amount to a disclosure of the individual enantiomers [20]. In the basic patent claiming the racemate (citalopram), there were no clear and unmistakable directions to obtain the enantiomers [20].

The UK Court of Appeal, in the escitalopram patent litigation, considered the issue of anticipation as a challenge on the ground of novelty [14]. To anticipate a patent, the prior art must disclose the claimed invention and (together with common general knowledge) enable an ordinary skilled person to perform it. It was agreed that the basic patent (the prior art) did not anticipate the isolated enantiomer. The claimants argued that the claim of the enantiomer patent to the (+)-enantiomer itself is not only for the isolated enantiomer but also for the enantiomer as an unresolved moiety of the racemate. To that extent, it is anticipated by the basic patent that disclosed the racemate (citalopram) and enables it to be made. This raised the question of construction. However, the court held that the patentee was not intending to cover the racemate. For the purpose of deciding the question of anticipation, it was enough to say that the claim would not be construed as including the unresolved part of the racemate [14]. The anticipation challenge on the validity of

an enantiomer patent might fail even when the corresponding basic patent claims explicitly the single enantiomer(s) in addition to the racemate, as in the Plavix enantiomer patent litigation in Canada [11].

According to the recent decision of the Supreme Court of Canada in the Plavix enantiomer patent litigation, if in reading the basic patent, there is no discovery of the special advantages of the enantiomer patent, the basic patent does not anticipate the enantiomer patent and the disclosure requirement to prove anticipation fails. Because the basic patent did not teach these special advantages, the invention of the enantiomer patent was not disclosed and, therefore, was not anticipated [11].

Inventiveness

According to the EPO jurisprudence, to render an inventive step in a selection patent, compounds having a maximum structural resemblance must be compared with one another [9]. To establish inventiveness (nonobviousness), the description in an enantiomer patent should include superior pharmacological and/or pharmaceutical properties of the selected single enantiomer, not only versus the paired enantiomer but also versus the racemate (efficacy, and/or reduced toxicity and/or solubility and other pharmaceutical properties), well above the expected ratio of 2:1 [21]. 'Levofloxacin is not just twice as active as ofloxacin (which might be expected)...' [21]. Indeed, the US Federal Circuit held in the Altace (ramipril) case that the necessary comparison is to the stereoisomer or mixture of stereoisomers that constitute the closest prior art (e.g. racemate, epimers) [22]. For ramipril (Fig. 1), the court held that for the (*S*,*S*,*S*,*S*,*S*)-enantiomer, the comparison should be not to the next most potent (*R*,*R*,*S*,*S*,*S*)-stereoisomer, but to the combination containing only the (*S*,*S*,*S*,*S*,*S*)- and (*S*,*S*,*S*,*S*,*R*)-epimers [22]. The court found that the observed potency varied with the absolute amounts of the (*S*,*S*,*S*,*S*,*S*)-enantiomer in the above combination [22]. The court held that this was not unexpected and, therefore, was obvious [22]. In the antimicrobial levofloxacin patents [EP (UK) 0,206,283; US 5,053,407; and CA 1,304,080] litigations, the unexpected and surprising markedly higher water solubility of the (*S*)-enantiomer (9:1), as compared with the corresponding racemate ofloxacin, was emphasized. The increased aqueous solubility over the racemate, unlike the biological activity, is not an intrinsic property of the (*S*)-enantiomer; it also holds true for the (*R*)-enantiomer. This advantage, in addition to increased antimicrobial activity (2:1) and reduced toxicity, has been highlighted by UK, US and Canadian courts, overcoming prima facie case of obviousness [21,23,24]: 'Only a curmudgeon would say there was no invention here' [21]. In the enantiomer patents of Lipitor (Box 1), a surprising ratio of 10:1 in pharmacological activity of the (3*R*, 5*R*)-enantiomer ((*R*-*R**, *R**)-enantiomer) versus racemate was described. However, in Australia, the enantiomer patent was revoked because the court held that the 10:1 ratio reported in the enantiomer specification was a false suggestion [13]: 'The enantiomer specification cites the Broader Patent as prior art. It was common general knowledge that, on resolution or synthesis to obtain the enantiomers, one of them would likely have an activity of twice that of the racemate. In the ordinary course, that would make a patent claiming the enantiomer not novel or obvious. The enantiomer specification asserts a surprising result. It asserts, by statement and by supporting data, that the enantiomer has an unexpected and surprising level of activity of more than twice that of the racemate. That was a false representation' [13]. Likewise, the Federal Court of Canada rejected unequivocally the reliability of the data supporting the claim of a tenfold advantage for atorvastatin calcium and did not accept the evidence that atorvastatin has unexpected or surprising inhibitory advantage over the racemate [25]. The court held that the patent (CA 2,021,546) was invalid because it did not meet the test for a valid selection [25]. In the UK, the enantiomer patent of atorvastatin calcium [EP (UK) 0,409,281 B1] was invalidated for lack of novelty and obviousness [26].

Challenging the validity of enantiomer patents on the ground of obviousness has been enhanced by the introduction of the 'obvious to try' test, which is accepted as relevant in an obviousness inquiry in the UK [27], Canada [11], US [28] and EPO [29] but not Australia [30]. Quoting the House of Lords, '"obvious to try" has tended to take on a life of its own, as an important weapon in the armoury of those challenging the validity of a patent' [31]. 'Obvious to try' is one factor of a number in the assessment of obviousness [27]. 'In the end the question simply was, "was the invention obvious?" That involves taking into account a number of factors... "Obvious to try" may come into the assessment. It is one factor of a number that should be considered having regard to the context and the nature of the invention' [27]. According to EPO case law, 'the key question ... is whether it was obvious for a skilled person to try the idea outlined above with a reasonable expectation of success' [29]. It is only obvious to try when there is at least a fair expectation of success [21,27,31]. In the landmark KSR decision, the US Supreme Court emphasized the 'obvious to try' inquiry in an obviousness analysis [28]. 'The Court of Appeals conclude[d] ... in error, that a patent claim cannot be proven obvious merely by showing that the combination of elements was obvious to try' [28].

Were chiral switches to single enantiomers 'obvious to try' when Plavix, Lipitor and Lexapro/Cipralex were invented [32]? The strategy of chiral switches was not new [e.g. Norgestreal → Levonorgestreal, (1977), D-penicillamine, L-dopa] [33]. Indeed, it has been accepted since the early 1980s that often, the majority of the biological activity observed for a racemate resides within a single enantiomer. The drug companies developing chiral drugs were well aware at that time of Ariëns' outspoken and effective rediscovery and advocacy of the significance of stereochemistry in therapeutic action and the preference for single-enantiomer drugs over racemic drugs. Ariëns propounded that the neglect of stereochemistry in the study and evaluation of racemic products would lead to the performance of expensive "highly sophisticated scientific nonsense" and to the acceptance of inferior biological products [34]. Ariëns, in fact, predicted in 1986 the strategy of enantiomer patents [35]: 'In the coming years, many patents, also on inferior racemic drugs, are expiring. This may be a good occasion to replace these by "new", "DEXTRO-" or "LAEVO"-products to be announced as twice as active! Free of bulk impurity! No isomeric ballast! Less side effects...! In some cases patent protection may be obtained on the rejuvenated drug' [35]. Many textbooks and papers are consistent in revealing an appreciation by medicinal chemists in 1985 that the stereochemistry of a molecule can play a major part in its pharmacological properties [36]. 'It has been known for many years that despite their similarities, the two enantiomers may bind to different proteins and produce different biological effects.' [14] 'It was generally known that very often the majority of the biological activity observed for a racemate resides within a single enantiomer.' [37] 'Any medicinal chemist ... in 1988 should have appreciated that the enantiomers might well have different activities, that an inactive enantiomer was, at best, ballast but might be toxic or have some other negative effect, that the regulators considered that an investigation of the enantiomer was desirable and that such an investigation might in due course become mandatory. All of these matters provide a clear motive to isolate and test the enantiomers and this would have been well

understood by the notional skilled addressee' [37]. Moreover, in the 1980s, when Plavix, Lipitor and Lexapro/Cipralex were invented, single enantiomers had already been a statistically significant component of approved drugs [38]. Furthermore, in February 1987, FDA Guidelines stated that the sponsor of a new drug containing a chiral center should ideally have obtained the individual potential stereoisomers [39,40]. The Japanese Ministry of Health's 'Requirements for Drug Manufacturing Approval' (paragraph 99) were amended in 1985 to add a sentence stating: 'When the drug concerned is a racemate, it is recommended to investigate the absorption, distribution, metabolism and excretion of each optical isomer' [37]. This, of course, would require resolution of the enantiomers and the administration of each enantiomer separately [39]. Resolutions of racemates into single enantiomers using Pasteur's method of diastereomeric salt formations and other methods in the standard arsenal of stereochemists were also 'obvious to try' in the mid-1980s.

From all of these perspectives, chiral switches to single enantiomers were 'obvious to try', unless there has been a teaching away from this strategy (e.g. in cases of *in vivo* racemization or epimerization). In adopting the strategy of chiral switches, there is at least a fair expectation of success. However, 'obvious to try' chiral switches and enantiomer patents thereof can sometimes be nonobvious. In the recent Plavix and Lexapro patent litigations in Canada and the UK, respectively, the Courts applied the 'obvious to try' test but concluded on the basis of the evidence in each case that the enantiomer patents were not obvious [11,14]. The Supreme Court of Canada accepted that at the relevant time, there was evidence that a skilled person would know that the properties of a racemate and its enantiomers might be different [11]. The Court held, however, that a possibility of finding the invention is not enough. The evidence in the case did not show that the invention was self-evident from the prior art and common general knowledge and, therefore, the 'obvious to try' test was not satisfied [11]. The basic patent did not differentiate between what to select and what to omit on the basis of efficacy and toxicity [11].

In the escitalopram enantiomer patent litigation in the UK [14,37], the claimants' case that the claimed method for the preparation of escitalopram (the diol route) was obvious to try was based upon an expert opinion that there was a 'high expectation that the experiment . . . would work'. The Court rejected this assessment, however, and concluded that the diol route was not obvious [14,37]. By contrast, a Dutch court concluded recently that claim 6, a method for the preparation of escitalopram by converting the corresponding single enantiomer diol into escitalopram by mean of a stereoselective S_N2 reaction (the diol route) lacked inventive step [19]. Very recently, the Federal Court of Justice of Germany (BGH) did not agree with the Dutch Court's assessment, holding that the stereoselective synthesis of escitalopram via the intermediate diol had inventive merit [41]. The BGH validated the escitalopram patent and held that 'the provision of an individual enantiomer of a compound previously only existing as a mixture of enantiomers (racemate) can be based on inventive merit even if the existence of the enantiomers is apparent in an obvious manner from the prior art. Decisive is whether or not there was an obvious manner for the person skilled in the art to obtain the enantiomer on the date of priority' [41] (translated from the original). In general, the courts' considerations of inventiveness of process claims of enantiomer patents pertaining to resolutions and to stereoselective syntheses have not been uniform (Table 1).

Double patenting

It is not surprising that the validities of enantiomer patents have been challenged on the grounds of double patenting, especially when the enantiomers had been explicitly claimed in the basic patent. The general argument is that the doctrine of selection patents enables a patent holder to 'evergreen' an invention. The Supreme Court of Canada held in the Plavix case [11] that although evergreening is a legitimate concern, a general concern about evergreening is not a justification for an attack on the doctrine of selection patents, emphasizing that selection patents encourage improvements by selection because the selection does something better than or different to what was claimed in the genus patent [11]. The court held that the claims of the enantiomer patent (CA 1,336,777) and of the basic patent (CA 1,194,875) were not identical or coterminous [11]. The court also held that there was no basis for a challenge based on 'obviousness' double patenting because the (+)-enantiomer of the racemate relevant to the case had beneficial properties over both the racemate and the (−)-enantiomer; the claim in the enantiomer patent reflected a patentable compound distinct from the compounds in the basic patent [11]. Inventing the single-enantiomer drug as a successor to the racemic drug does not 'extend', 'repatent' or 'evergreen' the basic patent.

Brand-generic enantiomer patent settlement agreements

Enantiomer patent litigations have often been susceptible to out-of-court settlement agreements, in which the brand-name drug company patent holder incentivises its potential generic competitor (an alleged patent infringer), especially first-filers (which might be entitled in the USA to 180 days of marketing co-exclusivity with the patent holder to sell the drug [4]), by paying the generic to abandon the patent challenge and delay entering the market with a lower cost generic product. Agreements with first-filers are particularly attractive because the first-filer can control generic entry. The US Circuit Courts of Appeal held (contrary to the position of the US Federal Trade Commission) that these 'pay-for-delay settlements' (also called 'reverse payments' and 'exclusive payments') do not violate antitrust laws and that settlement agreements are within the exclusionary zone of the patent (in the absence of evidence of fraud before the US Patent and Trademark Office or sham litigation). The mere presence of a patent entitles the patent holder to purchase protection from competition until the patent expiration [42,43]. The worldwide battle between Pfizer and Ranbaxy on the validities of the basic and the enantiomer patents of Lipitor (the mother of all patent challenges) resulted in a settlement agreement resolving substantially all of Ranbaxy's outstanding worldwide Lipitor patents challenges (announced in June 2008). In July 2008, Pfizer and Apotex reached an agreement to settle litigation with respect to certain Lipitor patents in Canada (but not the US Lipitor enantiomer patent). In the USA, the challenge by Apotex of the enantiomer patent of Plavix led in 2006 to two settlement agreements between Sanofi-Sythelabo/Bristol-Myers Squibb and Apotex. These agreements did not get regulatory approval. However, the second agreement gave Apotex assurances that it could launch generic clopidogrel bisulfate in the US with limited damages, which Apotex did ('at risk') with exclusivity for a short period [44]. Subsequently, the courts prevented Apotex from continuing to sell the generic drug [45], and the Plavix enantiomer patent was validated by the US Federal Circuit [46]. AstraZeneca and Ranbaxy Pharmaceutical Industries (a first-filer) reached a settlement agreement on the US Nexium patent litigation in April 2008. According to this agreement, which was accompanied by a manufacturing and distribution agreement, Ranbaxy conceded that all six Nexium patents asserted by AstraZeneca in the patent litigation are valid and enforceable, and Ranbaxy is

allowed to commence sales of a generic version of Nexium from 27 May 2014. AstraZeneca also reached an agreement with Teva Pharmaceuticals and affiliates regarding Nexium US patent litigation. AstraZeneca's Nexium patent infringement litigation against Dr. Reddy's Laboratories remains ongoing.

Concluding remarks

Enantiomer patents[1] are important constituents in the discovery of chiral drugs. The enantiomer patents of the majority of chiral switch drugs have been challenged. The validities of enantiomer patents are not a simple, straightforward matter [49] and should be evaluated on a case-by-case basis. The necessary condition for the validity of enantiomer patents that the novelty of the enantiomers is not destroyed by the description of the racemates is uniformly accepted in the major jurisdictions. The case law of enantiomer patents is rather divided. The novelty of claims to enantiomers in enantiomer patents depends on the particular circumstances, including the disclosure and claims in the respective basic patents. With regard to the inventive step, the results of the cases depend crucially on the facts, arguments and evidence that are presented. A US scholar has noted that the decisions of the Federal Circuit in enantiomer patent cases have been mixed and that it is difficult to find a basis for distinguishing the cases that would provide meaningful guidance in future cases [50]. Nevertheless, the case law of enantiomer patents is crystallizing. A trend in enantiomer patents is emerging, whereby chiral switches, including enantiomer patents, are not 'patent extenders' and patenting the single enantiomer drug does not necessarily constitute extending, repatenting or evergreening. A generalized concern about 'evergreening' is not a justification for an attack on enantiomer patents. A variation on the theme of enantiomer patents is a patent claiming a combination of two single enantiomers developed in chiral switch scenarios (a 'double chiral switch' [47]), such as Vimovo (PN 400), a combination of the proton pump inhibitor (PPI) esomeprazole and the non-steroidal anti-inflammatory drug naproxen (US 6,926,907 B2; CA 2,511,158 A1). The strategy of enantiomer patents is a double-edged sword that serves not only brand-name companies [51] but also generic companies. The ensuing long legal battles of the enantiomer patent challenges serve as an impetus for arriving at out-of-court settlements. The enantiomer and basic patent settlement agreements are major components of the life-cycle management of chiral drugs. Finally, the important role of enantiomer patents in drug discovery today is reflected in the forthcoming 'patent cliff' threat (the wave of major patent expiries looming over the next few years, particularly around 2010–2012) [52], which is dominated by the expiries of enantiomer patents of blockbuster chiral drugs.

[1] Enantiomer patents should not be confused with enantiomeric pair of patents in a chiral switch scenario [2,47]. These paired patents have identical priority dates and claim, respectively, that the (+)-enantiomer and (−)-enantiomer of a drug are superior to the corresponding racemate. Each of the paired patents is *ipso facto* an enantiomer patent. The Paris Court (Tribunal de Grand Instance) held in October 2009 that in such a scenario, the lack of experimental part concerning the activity of the enantiomer [(−)-cetirizine] in the application as filed conducts to the revocation of the patent. The court found that the applicant (Sepracor) did not know which enantiomer was the more effective (or showed less side-effects) or which one of the two enantiomers was more effective (or with less side-effects) than the racemate [48].

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