THE INVENTIVENESS OF ENANTIOMERS

Many of the world's most popular drugs are based on enantiomeric compounds. Edgar Cataxinos and Allen Turner look at the way patent offices award, and courts protect, patents for these inventions.

Most of the world's best-selling pharmaceuticals are enantiomeric compounds. For instance, eight of the world's top 10 best-selling drugs in 2006 had at least one chiral centre, the hallmark of stereochemical activity. These included Lipitor, Plavix, Nexium, Seretide, Zocor, Norvasc, Prevacid and Effexor. In 2005, global sales of these drugs exceeded $48 billion, the bulk of which occurred in the US. Patent protection of such compounds is of paramount importance to the companies that developed these drugs and the generic companies that want to market them.

Previously, synthetically produced pharmaceutical compositions were generally only available as racemic mixtures (50:50 mixtures of enantiomers or stereoisomers). The nearly identical compounds that form these racemic mixtures are identified and separated (or resolved) by modern chemical techniques and the relative pharmacological activities of the stereoisomers are determined. It has been found that some of these nearly identical compounds could have quite different pharmacological activities. At the same time, however, depending on where the chiral centre (or centres) exists in the molecule, it may have little or no effect on the pharmacological activity. These facts have provided the pharmaceutical industry with an opportunity to market (and patent) the purified and active enantiomeric compound, potentially extending the compound's exclusivity.

As stated by Judge Lourie in *Forest Labs v. Ivax Pharm*: "[s]tereoisomers are compounds that contain the same constituent atoms and the same bonding between those atoms but have different spatial arrangements. Enantiomers are stereoisomers that are nonsuperimposable mirror images of one another. Enantiomers accordingly exhibit different optical activity; the enantiomer that rotates a plane of polarized light in the clockwise direction is the (+)-enantiomer; the enantiomer that rotates a plane of polarized light in the counterclockwise direction is the (-)-enantiomer. Enantiomers may also be designated as the S-enantiomer and the R-enantiomer according to a different criterion relating to the location of the chiral centers. A mixture of equal amounts of two enantiomers is called a racemic mixture or a racemate, and separating the two enantiomers from a racemate is referred to as resolving the compound."

In essence, the stereoisomers are mirror images of one another, much like the left hand is to the right. A right hand molecule will not fit into the left hand's 'glove' (the enzyme receptor) and, while one stereoisomer will be pharmacologically active, the other may not have any of the sought-after pharmacological activity at all.

As with any chemical compound, the patentability of a stereoisomer is based upon its utility, novelty and non-obviousness (or inventiveness). As the selected stereoisomer was chosen for its particular pharmacological activity, utility is not generally a problem. With respect to novelty, ever since the case of *In re Williams*, which found that a claim directed to a compound free of its dextrorotatory form did not read on the racemic mixture, properly drafted patent claims have not met serious problems with respect to anticipation.

Before 1953, obviousness was governed by case law such as *In re Merz*. Prior to the enactment of 35 U.S.C. § 103 relating to obviousness, this held that an applicant was "not entitled to a patent on [an] article [that] after being produced has a greater degree of purity than the product produced by former methods", unless the purification results in "properties and characteristics which were different in kind from those of the known product rather than in degree".

The law of obviousness was codified in 35 U.S.C. § 103 and interpreted by the Supreme Court in *Graham v. John Deere Co of Kansas City.* This held that "[u]nder §103, [1] the scope and content of the prior art are to be determined; [2] differences between the prior art and the claims at issue are to be ascertained; and [3] the level of ordinary skill in the pertinent art resolved. Against this background the obviousness or nonobviousness of the subject matter is determined. [4] Such secondary considerations as commercial success, long felt but unsolved needs, failure of others, etc., might be utilized to give light to the circumstances surrounding the origin of the subject matter sought to be patented." The CCPA interpreted cases dealing with enantiomers consistently with *Graham*.

In *KSR Int'l v. Teleflex*, the Supreme Court further elucidated the *Graham* inquiry. To establish obviousness, the prior art itself or "the inferences and creative steps that a person of ordinary skill in the art would [have] employ[ed]" at the time of the invention are to have taught or suggested the claim elements. Additionally, there must have been "a reason that would have prompted a person of ordinary skill in the relevant field to combine the [prior art] elements" in the manner claimed.

"Often, it will be necessary for a [factfinder] to look to interrelated teachings of multiple patents; the effects of demands known to the design community or present in the marketplace; and the background knowledge possessed by a person having ordinary skill in the art, all in order to determine whether there was an apparent reason to combine the known elements in the fashion claimed…." Furthermore, to establish

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obviousness, there must have been a reasonable expectation of success. Of course, hindsight cannot be used.

Even if a *prima facie* case for obviousness is established, *Graham* set forth a broad inquiry and invited those making decisions as to patentability to look at any secondary considerations that would prove instructive. "[A] patent composed of several elements is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art. Although common sense directs one to look with care at a patent application that claims as innovation the combination of two known devices according to their established functions, it can be important to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does. This is so because inventions in most, if not all, instances rely upon building blocks long since uncovered, and claimed discoveries almost of necessity will be combinations of what, in some sense, is already known."

More problematically for those seeking to protect enantiomers, in *KSR*, the court brought into question earlier law holding that "obvious to try" was not the standard of obviousness. Specifically, the court stated "that it might have been obvious to try the combination of [prior art references] was likewise irrelevant, in the [Federal Circuit's] view, because 'obvious to try' has long been held not to constitute obviousness".

The court found the Federal Circuit's reliance on "obvious to try" as an error, explaining that "[t]he same constricted analysis led the [Federal Circuit] to conclude, in error, that a patent claim cannot be proved obvious merely by showing that the combination of elements was 'obvious to try'". The court ultimately concluded that: "[W]hen there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions, a person of

ordinary skill has good reason to pursue the known options within his or her technical grasp. If this leads to the anticipated success, it is likely the product is not of innovation, but of ordinary skill and common sense. In that instance, the fact that a combination was obvious to try might show that it was obvious under § 103."

The importance of *KSR* was not lost on the Federal Circuit. *Aventis Pharma Deutschland v. Lupin* involved the blood pressure medicine ramipril or Altace, an ACE inhibitor. Ramipril has five different chiral centres allowing for 32 different stereoisomers to select from and analyse. The 'SSSSS' form is the active stereoisomer.

After Lupin filed an abbreviated new drug application for ramipril, Aventis and its exclusive licensee, King Pharmaceuticals, sued Lupin for infringement of US Patent 5,061,722 under 35 U.S.C. § 271(e)(2)(A). The district court, applying the law pre-*KSR*, found the '722 patent not invalid for obviousness, and Lupin appealed. The Federal Circuit, applying *KSR*, reversed, finding the '722 patent obvious even though there was no specific teaching in the prior art to separate and purify the SSSSS enantiomer, and there were arguably unexpected results.

However, just a few days earlier, in *Forest Labs v. Ivax Pharm,* the *prima facie* obviousness of a claim to a particular stereoisomer over a racemic mixture was rebutted where the particular stereoisomer (the S enantiomer of escitalopram, (Lexapro)) showed unexpected benefits and the evidence indicated that the isomers would have been difficult for an ordinarily skilled person to separate. In this case, the Federal Circuit found the enantiomers were difficult to separate, and unexpected properties were present. Interestingly, the Federal Circuit never mentioned *KSR* in its obviousness analysis.

In *Sanofi-Synthelabo et al v. Apotex*, the Federal Circuit applying *KSR*'s "obvious to try" standard, found that the enantiomeric separation to form the drug dextrorotatory isomer clopidogrel bisulfate (Plavix) was complex, and the selected enantiomer had the "rare characteristic" of "absolute stereoselectivity", where all of the favourable activity was found in the enantiomer without significant toxicity, and affirmed the trial court, holding that the patent non-obvious.

Similarly in *Ortho-McNeil Pharmaceutical v. Mylan Laboratories* (not specifically involving enantiomer resolution), the Federal Circuit found that the patent claiming the anticonvulsant topiramate (Topomax) was not obvious, while applying *KSR*. Addressing the Supreme Court's "obvious to try" statement, the Federal Circuit observed that although the inventor's "pathway to the invention, of course, seems to follow the logical steps to produce these properties…at the time of invention, the inventor's insights, willingness to confront and overcome obstacles, and yes, even serendipity, cannot be discounted", and found the invention non-obvious.

Although selecting and producing enantiomers and testing them for activity might seem like KSR's choosing from a finite number of predictable solutions with some expectation of success, the courts have been willing to consider secondary considerations, such as unexpected results and difficulty in separating the enantiomers, in coming to the conclusion that an invention is not obvious.

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