Obviousness Of Enantiomers After KSR

Law360, New York (March 26, 2009) -- The full impact on different technological areas of the Supreme Court's decision in KSR Int'l Co. v. Teleflex Inc. ("KSR") has yet to be felt.[1]

The KSR court rejected the Federal Circuit's "rigid approach" to obviousness in favor of a more "expansive and flexible" approach where "[i]f a person of ordinary skill can implement a predictable variation, § 103 likely bars its patentability."[2]

While KSR involved a patent claim directed to a mechanical invention, its reasoning will likely have wide-ranging impact in those technical areas where patentability depends on what may be regarded as small or incremental differences from the prior art.

In the pharmaceutical area, for example, an obviousness challenge to a claimed compound is typically based on similarities between its chemical structure and structures of prior art compounds, which can easily and incorrectly be characterized as obvious.

One of the promising areas for research and development of new drugs is based on the purification of "enantiomers" — two mirror image versions of a chemical compound having a left-handed and a right-handed variety — from their "racemate," which is an equal mixture of the compound's left-handed and right-handed forms.

Enantiomers have nearly identical physical properties but may have divergent pharmacological properties, while racemates typically share the pharmacological characteristics of each individual enantiomer. Thus, a purified enantiomer may well have improved therapeutic possibilities in comparison with its racemate.

Because it is superficially easy to claim that the separation of enantiomers from a prior art racemate is (at the least) obvious to attempt, a legal standard which makes it easier to establish obviousness may have important implications for the pharmaceutical industry.

Pharmaceutical companies may be reluctant to pursue promising research on enantiomers of a known racemate if they are not able to obtain patent protection for the product.

Accordingly, understanding the strength of patents for enantiomers in the post-KSR world is important both for companies seeking to develop and patent such compounds, as well as for companies that may be contemplating challenges to such patents.

To date, the Federal Circuit has decided three post-KSR decisions relating to the obviousness of enantiomers over prior art racemates.

In each decision the court focused on the specific facts of each situation, concluding that two of the enantiomeric products were nonobvious over their racemates.
While the relatively small number of decisions makes it difficult to generalize, these early decisions suggest that the Federal Circuit, in appropriate cases, will still place considerable weight on the unpredictability of pharmaceutical research and will decline to find such patents obvious.

The cases further suggest that the analysis will be highly dependent on the particular purification techniques required to achieve the separation of enantiomers.

**Forest Labs Inc. v. Ivax Pharm. Inc.[3]**

Decided about five months after the KSR decision, Forest Labs v. Ivax (“Forest”) involved a patent dispute over a substantially pure enantiomer of citalopram, a therapeutically valuable antidepressant disclosed in the prior art in racemate form.

Ivax argued that the desired enantiomerically pure citalopram (“(+)-citalopram”) was obvious in light of the prior art disclosure of racemic citalopram in combination with publicly available descriptions of general purification techniques used to separate enantiomers from their racemates.[4]

Conversely, Forest argued that (+)-citalopram was not obvious in light of its racemate because the resolution of this racemate was itself non-obvious.[5]

Forest further argued that the (+)-citalopram displayed unexpected benefits over the racemate in that it held all of the therapeutic value (i.e. the other enantiomer had no therapeutic effect).[6]

The Federal Circuit upheld the district court’s pre-KSR decision, holding that enantiomerically pure citalopram was not obvious over the racemate.

The court cited to the district court’s factual findings that separating enantiomers using the purification techniques available to persons of ordinary skill in the art (“POSITA”) at the time of the invention were difficult and unpredictable, and therefore not obvious.[7]

Further, the court cited to several unsuccessful attempts by research scientists, with arguably higher levels of skill than POSITA, to isolate the desired (+)-citalopram over the course of several years, and cited to the unexpected benefit that one enantiomer contained all of the therapeutic value.[8]

This case indicates the importance of the particular purification techniques used, and their availability at the time the patent was filed.

Here, the enantiomer was deemed non-obvious over its racemate primarily because the known purification methods available at the time of the invention to resolve the racemate, circa 1989, were themselves non-obvious. Interestingly, the court did not cite to KSR in rendering this decision.

**Aventis Pharma Ltd. v. Lupin Ltd.[9]**

Only one week after deciding Forest, the Federal Circuit decided Aventis Pharma v. Lupin (“Aventis”), another patent dispute involving an enantiomerically purified pharmaceutical product and a previously disclosed racemate.

Aventis involved a patent dispute over ramipril, an enantiomerically pure cardiovascular medication with five chiral centers. Similar to the situation in Forest Labs, the key question before the court was whether the therapeutically valuable pure stereoisomer of ramipril, 5(S) ramipril, was obvious over its prior art racemate.[10]
Reversing the district court’s pre-KSR decision of nonobviousness, the Federal Circuit held 5(S) ramipril obvious over its prior art racemate.

The district court had seen this as a close case and had rendered its decision principally on the absence of clear and convincing evidence showing specific motivation to purify the ramipril racemate.[11]

The Federal Circuit reasoned that “[r]equiring an explicit teaching to purify the 5(S) stereoisomer from a mixture in which it is the active ingredient is precisely the sort of rigid application of the [teaching, suggestion, motivation] (“TSM”) test that was criticized in KSR.”[12]

The therapeutically valuable ramipril racemate contains only two enantiomers and it was known in the art that molecules having close structural relationship to ramipril were more biologically active in the (S) enantiomer form.[13]

Furthermore, the prior art specifically taught that the stereoisomers of ramipril “[could] be separated by conventional chromatographic or fractional crystallization methods.”[14] Therefore the prior art not only motivated POSITA to isolate 5(S) ramipril from its racemate, but specifically taught one how to do so.

The decision in Aventis, like that in Forest Labs, underscores the importance of the specific purification techniques implicated.

The evidentiary record showed that the prior art taught 5(S) ramipril to be the therapeutically valuable enantiomer and that it could likely be attained via conventional purification techniques available to POSITA in the early 1980s.[15]

This is in contrast to Forest Labs, where the court found that POSITA “would generally have been motivated to develop new compounds rather than undertake the difficult and unpredictable task of resolving [racemic citalopram].”[16]

Sanofi-Synthelabo Inc. v. Apotex Inc.[17]

The Federal Circuit’s most recent enantiomer case, Sanofi-Synthelabo v. Apotex (“Sanofi-Synthelabo”), demonstrates that the court perceives unpredictability in pharmaceutical research and development as a factor that may distinguish pharmaceutical patents from simple mechanical device patents in its obviousness analyses.

Apotex argued that enantiomerically pure clopidogrel was obvious because its racemate was disclosed in the prior art as an attractive lead compound.[18]

POSITA would therefore have been encouraged to resolve this racemate using conventional resolution techniques for the purpose of testing the biological activity of the individual enantiomers.[19]

Apotex added that potential regulations requiring the separation of enantiomers for such testing would have also motivated POSITA to resolve the clopidogrel racemate.[20]

Apotex further argued that the effect of any unexpected or unpredictable properties of the enantiomerically pure clopidogrel should be outweighed by the fact that its racemate is composed of two possible enantiomers, either or both of which necessarily possess the overall biological activity of the racemate.[21]

The court affirmed the district court’s holding that enantiomerically pure clopidogrel was nonobvious over its racemate. The court based its decision in large part on the guidance of expert testimony from both parties depicting the unpredictable nature of pharmaceutical research.
Experts testified that it was impossible to predict the degree by which enantiomers would differ in terms of biological activity and toxicity.[22]

Experts further testified that it was rare and unexpected for the biological activity of a racemate to rest solely in one enantiomer, and toxicity in the other, as was the case for clopidogrel.[23]

Citing its Aventis decision, the court stated, “[t]he district court entered extensive findings in this case on the unexpected and unpredictable properties of clopidogrel, and there was no contrary evidence suggesting ... that the stereoselective properties were ‘precisely what one would expect,’ as in Aventis.”[24]

Therefore, the beneficial and unpredictable properties of pure clopidogrel supported the district court’s holding that it was non-obvious over its racemate.

The court was also persuaded by expert testimony supporting the nonobviousness of resolving the clopidogrel racemate using techniques available at the time of the invention.

While at least ten techniques were used to separate enantiomers in 1987, they all required experimentation to determine whether they could be successful for a particular compound.[25]

The court found that there was no “infallible recipe” to achieve separation of enantiomers and it was instead a “paradigm of trial and error.”[26]

Furthermore, clopidogrel was particularly susceptible to racemization (the process of converting back to the racemate), so even if the enantiomers were successfully separated, POSITA could have no expectation that they would remain pure.[27]

Thus the successful resolution of the clopidogrel racemate was unpredictable and non-obvious.

The court considered Apotex’s argument that Sanofi resolved the clopidogrel racemate because of possible future regulatory requirements to do so, thus making the separation obvious, but was not persuaded.

The court determined that although POSITA generally knew that stereoisomers could exhibit different properties, this knowledge did not teach how to separate given enantiomers, or what results may have ensued upon separation.[28]

**Summary**

The Federal Circuit’s post-KSR decisions in Aventis, Forest and Sanofi-Synthelabo show us that while the court has abandoned the rigid application of the TSM test, it has worked to balance this test against the unpredictability of pharmaceutical research.

Thus, pharmaceutical compounds involving enantiomers derived from prior art racemates will continue to be patentable under the proper circumstances.

The court’s opinions indicate that obviousness determinations for enantiomeric products are highly dependent on the predictability of their purification.

Prior art may teach that a given enantiomer is obvious in light of its racemate if its separation is routine and predictable or, alternatively, may teach that an enantiomer is nonobvious if its racemate’s separation is particularly difficult or unpredictable.
It will be interesting to see how future cases are decided as regulations requiring the separation of racemates become more prevalent and available technologies provide easier and more predictable separations.[29]

The Federal Circuit’s opinions also underscore that unpredictable or unexpected advantages will strengthen the case for nonobviousness. This is, again, a fact-dependent determination that is driven by both prior art and expert testimony.

Generally, in the cases to date, the court has found that it is not possible to predict the degree by which the individual enantiomers of a racemate will differ in terms of biological activity, toxicity or other pharmacological properties.

For instance, given the factual record in these cases, it was deemed rare and unexpected for all biological activity of a racemate to reside in one enantiomer.

More generally, the Federal Circuit’s post-KSR enantiomer cases offer indications of how to apply KSR’s fact-driven obvious analysis to pharmaceutical products.

These decisions show that the strict application of the TSM test is no longer valid, as can be seen by the Aventis panel’s reversal of the district court’s non-obviousness holding.

However, this is balanced by the court’s deference to the unpredictability of the pharmaceutical arts. Even in the extreme case of enantiomers with prior art racemates discussed herein, arguments regarding unpredictability in the pharmaceutical sciences may carry significant weight.

--By Monica Bhattacharyya and David Galluzzo, Kasowitz Benson Torres and Friedman LLP

Monica Bhattacharyya is a partner with Kasowitz Benson Torres and Friedman in the firm’s New York office. David Galluzzo is an associate with the firm in the New York office. Prior to practicing law, David was a research scientist at Pfizer Inc.

The opinions expressed are those of the authors and do not necessarily reflect the views of Portfolio Media, publisher of Law360.


[2] 127 S. Ct. 1727, 1740


[4] Id. at 1269.

[5] Id.

[6] Id.

[7] Id.

[8] Id. at 1266, 1269.

[10] Id. at 1300.
[11] Id. at 1301.
[12] Id.
[13] Id. at 1302.
[14] Id.
[15] Id. at 1299-1300.
[16] Forest Labs, 501 F.3d at 1267.
[18] Id. at 27, 28.
[19] Id. at 28.
[20] Id. at 37.
[21] Id. at 28.
[22] Id. at 29.
[23] Id. at 30.
[24] Id. at 37.
[25] Id. at 31.
[26] Id. at 32, 33.
[27] Id. at 30, 32.
[28] Id. at 38.