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Obviousness of Pharmaceuticals - Patentability Over Known, Structurally Similar Compounds

Ethyl, methyl, butyl…futile – the running joke in grad school. Just try a different substituent until you find an active compound – or not. But while tweaking an alkyl substituent might seem "obvious" in the lab, when it comes to patent protection of small molecules, is it necessarily obvious? When examining a patent application with claims directed to novel chemical compounds, an examiner may reject those claims under 35 U.S.C. § 103 as obvious over structurally similar compounds in the prior art. Likewise, an accused infringer will often allege that the asserted claims to chemical compounds are "obvious" when challenging the validity of a patent. Successfully overcoming a charge of obviousness can be critical where the compound(s) in question are clinical candidates or are already highly successful commercial therapeutics. So how can you defeat those assertions?

Obviousness Before *KSR*

While the concept of obviousness seems intuitive, it is not easily defined. Fortunately, the Supreme Court provided some guidance in the form of a framework that can be used when considering the obviousness of a claim. The seminal case of *Graham v. John Deere Co. of Kansas City*1 counsels that the following factors be considered in any obvious analysis: 1) the scope and content of the prior art, 2) the differences between the claimed subject matter and the prior art, 3) the level of ordinary skill in the art, and 4) any secondary considerations such as commercial success, long-felt but unresolved need, failure of others, etc.

Based on the teachings of *Graham v. John Deere* and other Supreme Court decisions, the Court of Customs and Patent Appeals ("CCPA"), the predecessor to the Federal Circuit, developed its own jurisprudence on the meaning of obviousness. A key test developed by the CCPA was the Teaching, Suggestion or Motivation test ("TSM") for ascertaining whether a combination of known elements was obvious. Under this test, a claim is obvious if there is a teaching, suggestion, or motivation that would cause a person of ordinary skill in the art to combine known elements, or modify a known item in a particular way.

When the Federal Circuit was formed and thereby replaced the CCPA, the Federal Circuit adopted the CCPA's precedents, including the TSM test. But over time, the Federal Circuit's obviousness analysis and application of the TSM test became rigid, drifting away from considering the level of skill in the art and toward focusing on what was explicitly taught or suggested in the cited prior art references. That changed, however, in the wake of the Supreme Court's opinion in *KSR Int'l Co. v. Teleflex Inc.*2

KSR Framework

The patent-in-suit in *KSR*, licensed to Teleflex, was directed towards a position adjustable pedal assembly with an electronic sensor attached to the assembly for use in cars and light trucks. When Teleflex sued KSR for infringement by KSR's adjustable pedal assembly, KSR countered with an attack on the validity of the patent-in-suit, including an argument that the asserted claim of the patent-in-suit was obvious. Applying the teachings of *Graham v. John Deere* and the TSM test, the district court found the asserted claim invalid as obvious and granted summary judgment in favor of KSR. Teleflex appealed, and the Federal Circuit, applying the TSM test, reversed. The Federal Circuit found that the district court had failed to make specific findings as to the understanding or

principle that would have led a skilled person to combine the teachings of the cited references and prepare the claimed pedal assembly and, as such, had not been strict enough in applying the TSM test. In response to KSR's argument to the contrary, the Federal Circuit reiterated its standard that obvious to try is not obvious.

KSR then appealed and the Supreme Court reversed the Federal Circuit. In its decision, the Supreme Court took the Federal Circuit to task for applying a rigid obviousness analysis that failed to fully comport with *Graham v. John Deere* and other Supreme Court case law. In particular, the Supreme Court made clear that an obviousness analysis needs to be expansive and flexible, and that such an approach is inconsistent with the Federal Circuit's practice of rigidly applying the TSM test. However, the Supreme Court did not completely reject the TSM test; rather, it made clear that "there is no necessary inconsistency between the idea underlying the TSM test and the *Graham* analysis."**3** Thus, the TSM test is still a viable test, but it is not to be rigidly applied. Following *KSR*, the TSM analysis no longer requires an express teaching or suggestion in the cited prior art. Instead, the analysis must consider whether a person of ordinary skill could have been motivated by any need or problem and might use familiar items in ways beyond their primary purpose.

In *KSR*, the Supreme Court also made clear that an approach that is obvious to try may, in fact, be obvious. More specifically, where there is a need to solve a problem and there are a "finite number of identified, predictable solutions,"**4** pursuing those known options may indeed be obvious, because common sense would dictate that those options be tried. Indeed, the Supreme Court advised that, as a general principle, rigid rules that deny factfinders the use of common sense are improper and inconsistent with the law.

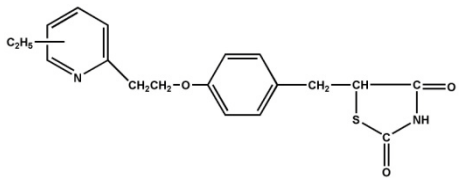
The general consensus is that it is easier to establish obviousness post-*KSR* than it was pre-*KSR*. But how has *KSR*, which was concerned with a rather simple mechanical device, affected the obviousness analysis for chemical inventions? Fortunately, in the approximately four years since the *KSR* case was decided, the Federal Circuit has issued several obviousness opinions, a few of which are discussed below, that provide guidance on conducting an obviousness inquiry in the chemical arts, and that provide insight into defending against an assertion of obviousness.

Structural Obviousness of Pharmaceuticals After *KSR:* Example Federal Circuit Opinions

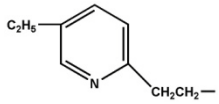
Takeda v. Alphapharm

Following on the heels of *KSR*, the Federal Circuit had an opportunity to address structural obviousness in *Takeda Chem. Indus., Ltd. v. Alphapharm Pty., Ltd*.**5** Alphapharm was sued by Takeda for infringement of U.S. Patent No. 4,687,777 (the "'777 patent") following Alphapharm's Paragraph IV certification in conjunction with its filing of an ANDA to manufacture a generic version of Takeda's Actos® ("pioglitazone"), used to treat Type 2 diabetes. Pioglitazone is a member of a class of drugs for the treatment of diabetes known as thiazolidinediones ("TZDs"), a technology area in which Takeda had been active for decades. In asserting invalidity of the '777 patent, Alphapharm alleged that the claims were obvious in view of "compound b," a prior art TZD compound disclosed in the '777 patent and in earlier Takeda patent applications.

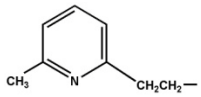
Claim 1 of the '777 patent is directed to a compound of the formula:



The portion of the claimed structure that was at issue is the ethyl-substituted pyridyl ring at the left of the molecule. The ethyl substituent is in the 5-position in pioglitazone:



Compound b, the prior art compound asserted by Alphapharm, contains the same core structure as the claimed formula, but has a methyl at the 6-position of the pyridyl ring:



The district court concluded that there was no motivation in the prior art to select compound b as a lead compound for diabetes therapeutics and that the prior art taught away from its use. Thus, the district court found that Alphapharm had failed to make a *prima facie* case of obviousness. The district court further concluded that even if Alphapharm had established a *prima facie* case of obviousness, it was rebutted by pioglitazone's unexpected nontoxicity. The Federal Circuit affirmed those findings.

On appeal, Alphapharm argued, *inter alia*, that the district court's decision was erroneous on the basis that it had misapplied the law on obviousness, particularly with regard to structurally similar chemical compounds. The Federal Circuit found no error, and noted that even in view of the pronouncement in *KSR* that the TSM test was not to be rigidly or mandatorily applied, "in cases involving new chemical compounds, it remains necessary to identify some reason that would have led a chemist to modify a known compound in a particular manner to establish prima facie obviousness of a new claimed compound."**6**

In its analysis, the Federal Circuit noted the *Graham v. John Deere* factors endorsed in *KSR*, but focused primarily on the first factor: the scope and content of the prior art. More specifically, the Federal Circuit first addressed the matter of selection of compound b as the lead compound,7 and then turned to the choice of the claimed compounds in the '777 patent.

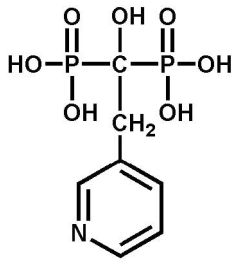
With respect to the lead compound issue, Alphapharm had argued that the prior art (including a statement in the prosecution history of an earlier Takeda application noting that compound b was of particular importance) would have led one of skill in the art to select compound b as a lead compound – and then one of skill in the art would make two obvious types of modifications: homologation (replacing the methyl of compound b with ethyl) and "ring walking" (moving the

substituent to each position on the ring). The Federal Circuit agreed with the district court's finding that Alphapharm's assertions were unfounded.

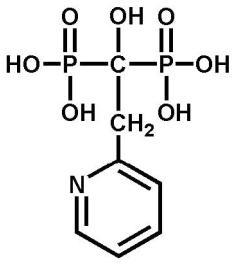
More specifically, the Federal Circuit agreed that while compound b was disclosed in the prior art, and efficacy data provided, it was but one of *many* disclosed compounds, and there was nothing in the prior art to suggest that of the many compounds (most of which lacked data that would permit an assessment of efficacy and safety), compound b was one of the best performing compounds and therefore could be a candidate as a lead compound. Moreover, there was a prior art journal article that singled out compound b as having negative effects, making it an unattractive candidate as a lead compound to one of skill in the art. Those negative effects were, in fact, particularly problematic to those suffering from diabetes. Thus, the Federal Circuit agreed that the journal article taught away from the use of pyridyl compounds, including compound b, in the treatment of diabetes.

The Federal Circuit, having affirmed that Alphapharm had failed to establish a *prima facie* case of obvious, nevertheless addressed the issue of the choice of the claimed compounds in the '777 patent, and concluded that this served as a second basis on which Alphapharm's obviousness argument failed. The Federal Circuit concluded that there was nothing in the prior art that suggested the specific modifications necessary to arrive at the claimed compound of the '777 patent from compound b. In particular, the evidence showed that while homologation and "ring-walking" were routine, one of skill in the art would consider various different substituents, including, for example, halides, in modifying the pyridyl ring. Additionally, prior work with related compounds suggested that homologation would have no tendency to decrease the unwanted side effects, leading one of skill in the art in a different direction. And finally, the journal article found to teach away from the claimed invention also showed unpredictability in the biological activity of various substituents within the TZD class of compounds.

Alphapharm argued, based on prior case law, that there was an expectation that structurally similar compounds would have similar properties, and that expectation had to be rebutted in order to avoid an obviousness determination. The Federal Circuit concluded that Takeda had indeed rebutted that presumption: experimental results showed that pioglitazone exhibited superior properties over compound b, as it was non-toxic, and there was no reasonable expectation that pioglitazone would possess non-toxicity, especially in view of the toxicity of compound b.



Risedronate



Prior Art Compound 2-pyr EHDP

Procter & Gamble v. Teva

The Federal Circuit opined on the obviousness of isomers in *Procter & Gamble Co. v. Teva Pharm., Inc.*8 Teva Pharmaceuticals ("Teva"), looking to sell a generic version of Procter and Gamble's

("P&G") osteoporosis drug, Actonel® ("risedronate"), filed a Paragraph IV certification that included an allegation that the claims of P&G's patent, U.S. Patent No. 5,583,122 (the "'122 patent"), were obvious in light of the disclosure contained in P&G's expired U.S. Patent No. 4,761,406 (the "'406 patent"). P&G then sued Teva for infringement.

In support of its contention that the asserted claims of the '122 patent were invalid, Teva argued that the structural similarity between the prior art compound 2-pyr EHDP (disclosed in the '406 patent) and risedronate rendered the claims of the '122 patent invalid. (The structures of risedronate and 2-pyr EHDP are shown on this page.)

The district court rejected Teva's argument. In finding the claims to risedronate to be non-obvious, the court determined that the '406 patent would not have led a person of ordinary skill in the art to use 2-pyr EHDP as the lead compound. The court also relied on 1) the extremely unpredictable nature of bisphosphonates at the time of the invention, and 2) there being no motivation for a person of ordinary skill in the art to perform the modifications necessary to make risedronate from 2-pyr EHDP. Finally, the court found that secondary considerations of non-obviousness supported its conclusions.

On appeal, the Federal Circuit affirmed. The Federal Circuit started with an identification of the applicable legal standards, noting that the TSM test provided useful insights, so long as it wasn't rigidly applied, and acknowledging *KSR* and its prior decision in *Takeda.* The court further stated that post-*KSR*, an obviousness analysis for a chemical compound generally begins with the reasoned identification of a lead compound. It was noted, however, that a patent owner can refute a *prima facie* case of obviousness by demonstrating a property of the compound that a person of ordinary skill in the art would find surprising or unexpected.

The Federal Circuit began its analysis by noting that even if 2-pyr EHDP was the lead compound (a review the Federal Circuit did not undertake), there was no evidence that a person of ordinary skill would have modified it to make risedronate. The Federal Circuit noted that risedronate and 2-pyr EHDP were isomers, and that structurally similar compounds often have similar properties, which could lead to the requisite motivation to modify the prior art compound. But, there was evidence that each bisphosphonate compound exhibited its own properties and activities and should be considered on its own, and that inferring characteristics and activities from one bisphosphonate to another was dangerous and could be misleading. There was also evidence that P&G prepared and tested the 2-pyr and 4-pyr EHDP isomers along with risedronate and reported that the 4-pyr EHDP was not active in inhibiting bone resorption. Since the bisphosphonate art was unpredictable, as the chemical arts often are, the Court stated that "*KSR*'s focus on [ ] 'identified, predictable solutions' may present a difficult hurdle because potential solutions are less likely to be genuinely predictable."9 The Court, however, agreed with the district court's conclusion that Teva had failed to establish the requisite motivation for a person of ordinary skill in the art to synthesize and test risedronate.

The Federal Circuit also found that there was insufficient evidence showing a person of ordinary skill in the art would have had a "reasonable expectation of success" in synthesizing and testing risedronate.10 The Federal Circuit analyzed the issue by focusing on whether a particular molecular modification would be carried out as a part of routine testing, *i.e.* where "a person of ordinary skill is faced with a 'finite number of identified, predictable solutions' to a problem and pursues 'the known options within his or her technical grasp.'"11 As the Federal Circuit noted, non-routine testing would

be where one of skill in the art could only vary all parameters or try numerous possible choices until the desired result is achieved, because the prior art provides no indication of which parameters are key or which choices are likely to be successful.12 Teva's evidence on this issue was deemed not persuasive, as it failed to establish that the bisphosphonate art was predictable, that the necessary structural modification was routine, or that there was a reasonable expectation of success. Thus, the Federal Circuit held that the district court did not err in finding that Teva had failed to establish a *prima facie* case of obviousness.

Finally, the Federal Circuit addressed secondary considerations of non-obviousness. Actonel® was characterized as "an undisputed commercial success" with aggregate domestic sales of $2.7 billion. The Federal Circuit further considered whether Actonel® satisfied a long-felt but unmet need and agreed that when the application that matured into the '122 patent was filed, the existing treatments for osteoporosis were inadequate. Thus, the Federal Circuit found that it was not clear error for the district court to have found that secondary considerations supported the non-obviousness of the claims.

Sanofi-Synthelabo v. Apotex, Inc.

The Federal Circuit addressed the patentability of an enantiomer in light of the prior disclosure of the racemic compound in *Sanofi-Synthelabo v. Apotex, Inc*.**13** U.S. Patent No. 4,847,265 (the "'265 patent"), assigned to Sanofi-Synthelabo ("Sanofi"), covers the platelet aggregation inhibitor clopidogrel bisulfate (Plavix®). Clopidogrel bisulfate is the dextrorotatory enantiomer of methyl alpha-5(4,5,6,7-tetrahydro(3,2-c)thienopyridyl)(2-chlorophenyl)-acetate and it is used to treat heart attacks and strokes. Apotex, Inc. ("Apotex") filed an ANDA seeking approval for generic Plavix®, and in its Paragraph IV certification alleged that the '265 patent was invalid as obvious because racemic methyl alpha-5(4,5,6,7-tetrahydro(3,2-c)thienopyridyl)(2-chlorophenyl)-acetate was described in two prior art patents owned by Sanofi, U.S. Patent No. 4,529,596 and Canadian Patent No. 1,194,875.

The district court found the '265 patent to be non-obvious. The district court presumed that Apotex had established a *prima facie* case of obviousness based on the prior disclosure of the racemate, statements made in the prior art patents regarding enantiomers, and general knowledge in the art that enantiomers may be separated and may have different biological activities. But, based on the unpredictable and unusual properties of the claimed dextrorotatory enantiomer, the district court found the presumption of obviousness to have been overcome. Specifically, evidence showed that the enantiomers of methyl alpha-5(4,5,6,7-tetrahydro(3,2-c)thienopyridyl)(2-chlorophenyl)-acetate had the rare characteristic of "absolute stereoselectivity," where the dextrorotatory enantiomer provided all of the favorable antiplatelet activity but no significant neurotoxicity, while the levorotatory enantiomer produced no antiplatelet activity but virtually all of the neurotoxicity. Additionally, experts for both Sanofi and Apotex agreed that it while it was known that enantiomers could have different properties, "absolute stereoselectivity" was impossible to predict.

On appeal, Apotex argued that the recognition in the prior art that methyl alpha-5(4,5,6,7-tetrahydro(3,2-c)thienopyridyl)(2-chlorophenyl)-acetate existed as an enantiomeric mixture outweighed any unexpected properties of the separate dextrorotatory enantiomer. Apotex contended that since Sanofi had been developing racemic methyl alpha-5(4,5,6,7-tetrahydro(3,2-c)thienopyridyl)(2-chlorophenyl)-acetate as a drug, it was natural to use it as a lead compound for

further research. Moreover, Apotex argued, it was known that enantiomers may have different properties and that the separation of enantiomers could be achieved through well-known chemical techniques. Thus, Apotex reasoned a person of ordinary skill in the art would have had motivation to separate the enantiomers and a reasonable expectation of success in separating and evaluating the individual enantiomers. However, evidence adduced at trial (including an admission by Apotex's expert) showed that while differing biological properties would be expected for different enantiomers, it was not possible predict the extent or nature of those differences. Thus, the Federal Circuit found there was no clear error in the district court's conclusion of non-obviousness, particularly in view of the evidence that one of skill in the art would not have reasonably predicted that the dextrorotatory enantiomer would provide all of the therapeutically beneficial activity and none of the adverse side effects.

The Federal Circuit also found no clear error in the district court's decision to dismiss Apotex's argument that techniques for separating enantiomers were well known in the art and as such, separated enantiomers were obvious as a matter of law. Before the district court, the evidence indicated that Sanofi had suffered several failures as it tried to separate the enantiomers and that the method Sanofi ultimately used to separate the enantiomers of methyl alpha-5(4,5,6,7-tetrahydro(3,2-c)thienopyridyl)(2-chlorophenyl)-acetate, *i.e.*, diastereomeric salt formation, had previously failed when Sanofi attempted to separate the enantiomers of a compound related to methyl alpha-5(4,5,6,7-tetrahydro(3,2-c)thienopyridyl)(2-chlorophenyl)-acetate. Thus, the Federal Circuit endorsed the district court's conclusion that enantiomeric separation in this particular instance was difficult and unpredictable.

Finally, the Federal Circuit dismissed Apotex's argument that the district court did not adequately follow the Supreme Court's holding in *KSR* that the "combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results."14 Apotex contended that Sanofi simply separated the isomers and identified their properties, and that the properties were those of the racemate, just allocated between the isomers. The Federal Circuit was unpersuaded by this argument, particularly in view of the evidence supporting the district court's finding that the result of the separation of the enantiomers was unpredictable.

Conclusion

Taken together, these cases provide some clear guidance to an applicant or patentee faced with an assertion that its pending or asserted claims are obvious in view of a structurally similar compound in the prior art, which can be summarized as follows:

- Claims directed to homologs, isomers, and enantiomers of, or compounds having structural similarity to, known compounds are not *ipso facto* obvious. However, the presumption that structurally similar compounds would have similar properties must be rebutted.
- In order to establish a *prima facie* case of obviousness of a new compound, a reason must be identified as to why one of skill in the art would have been led to modify a known compound in the particular manner necessary to arrive at the new compound. More specifically, there must also be a basis for selecting a particular compound – from among other known compounds – as a lead compound to be modified.
- In order to establish a *prima facie* case of obviousness, there must be a reasonable expectation of success in synthesizing and testing the claimed compound; modifications that involve non-routine testing (such as varying all parameters where there is no indication as to

which parameters are key or which choices might lead to success) are not considered to have a reasonable expectation of success.

- Prior art that reveals negative properties of a lead compound, or teaches away from the claimed compounds, can prevent a patent examiner or patent challenger from being able to establish a *prima facie* case of obviousness.
- An assertion of obviousness may be negated where there is nothing in the prior art to suggest the specific modifications made to the lead compound to arrive at the claimed compound.
- A showing of unpredictability among a particular class of compounds can support a non-obviousness argument; the greater the unpredictability, the more likely it is that a new compound will be found non-obvious.
- Even if a *prima facie* case of obviousness can be established, experimental results demonstrating superior, unpredictable, or unusual properties of a claimed compound over the lead compound can rebut a presumption that structurally similar compounds have similar properties and are therefore obvious.
- Secondary considerations, such as commercial success and failure of others, may be helpful in leading to a finding of non-obviousness.

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Endnotes

1. 383 U.S. 1 (1966).
2. 550 U.S. 398 (2007).
3. *Id.* at 1741.
4. *Id.* at 1732.
5. 492 F.3d 1350 (Fed. Cir. 2007).
6. *Id.* at 1357
7. "Lead compound" was – and continues to be – used to refer to "a compound in the prior art that would be most promising to modify in order to improve upon its [] activity and obtain a compound with better activity." *Id.* at 1357.
8. *Procter & Gamble Co. v. Teva Pharm., Inc.* 566 F.3d 989 (Fed. Cir. 2009).
9. *Id.* at 996 (quoting *Eisai Co. Ltd. v. Dr. Reddy's Labs., Ltd.*, 533 F.3d 1353, 1359 (Fed. Cir. 2008)).
10. *Id.*
11. *Id.* (quoting *KSR*, 550 U.S. at 421).
12. *Id.* at 996-997.
13. 550 F.3d 1075 (Fed. Cir. 2008).
14. *KSR v. Teleflex*, 550 U.S. at 416.