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REPORT

PATENTS

The authors argue that the ''sea change'' in decisions on obviousness after the U.S. Supreme Court's *KSR* ruling did not occur, at least with respect to chemical compound patent challenges.

Was the Concern That *KSR* Was a Game-Changer Justified? Not for Chemical Cases Before the Federal Circuit

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In the immediate aftermath of the U.S. Supreme Court's ruling in *KSR v. Teleflex*,[1] many thought there would be major changes in how courts analyze obviousness. Subsequent case law in the U.S. Court of Appeals for the Federal Circuit shows that, at least for chemical patent litigation, *KSR* did not significantly alter the validity analysis. The touchstone continues to be ''predictability.''

In litigation, courts recognize that unlike the mechanical arts, combinations and modifications of chemicals often produce unpredictable results, like drastic increases in potency or the ability to treat unrelated diseases. A showing of unpredictability (or unexpected results) was a linchpin to preserving validity in chemical patent litigation pre-*KSR*, and that continues to be the case post-*KSR*.

KSR did not significantly change the factors considered when assessing obviousness under Section 103 of the Patent Act, 35 U.S.C. § 103. Instead, a review of Federal Circuit case law shows that *KSR* only rejected a

[1] *KSR International Co. v. Teleflex Inc.*, 550 U.S. 398, 82 USPQ2d 1385 (2007) (5 PLIR 487, 5/11/07).

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rigid application of the Federal Circuit's ''teaching, suggestion, or motivation'' test (TSM) and reconfirmed that the Supreme Court's *Graham* factors[2] set out the appropriate framework for determining obviousness.[3] These Supreme Court enunciated factors were the basis for proper validity analysis prior to *KSR*, and remain so today.

KSR's impact on chemical cases can be analyzed in two groups: (1) chemical compound patents (including enantiomer patent cases); and (2) formulation or composition patents (including combination patents).

Compound Patents

The Federal Circuit reviewed several chemical compound patents in the wake of *KSR*. While heeding *KSR*'s instruction to avoid a rigid application of the TSM test, the Federal Circuit recognized that the unpredictable nature of the chemical arts impacts the obviousness analysis.

Both pre-*KSR* and post-*KSR*, obviousness inquiries in chemical compound cases tend to identify a ''lead compound.'' A ''lead compound'' is a short-hand way of referring to the closest prior art—again, a long accepted approach to analyzing validity. Post-*KSR* nonobvious rulings are primarily based on the lack of a prior art-based reason to either (1) select a specific lead compound (or compounds) or (2) modify the lead compound resulting in the claimed compound. Not surprisingly, these rationales supported decisions upholding validity pre-*KSR* as well. For example, in *Takeda v. Alphapharm*,[4] the Federal Circuit confirmed that *KSR* does not prevent use of the TSM test, as long as the test is not rigidly applied. In the chemical arts, ''normally a *prima facie* case of obviousness is based upon structural similarity, *i.e.*, an established structural relationship between a prior art compound and the claimed compound.'' But a *prima facie* case also requires ''a showing that the prior art would have suggested making the specific molecular modifications necessary to achieve the claimed invention.''[5]

Whether or not referred to as a ''teaching, suggestion or motivation'' test, the law pre-*KSR* and post-*KSR* requires a reason (in the prior art) for making the modification. Thus, in *Takeda*, the court affirmed nonobviousness of a compound, the antidiabetic drug pioglitazone (ACTOS), that was structurally similar to a prior art compound (compound b) because there was no motivation—no reason—for a skilled person to select compound b as the lead compound, and nothing to suggest—no reason for—making the molecular modifications necessary to achieve the claimed compound. In fact, the court noted that prior art taught away from selecting compound b as the lead compound because it had toxic properties. The court's analysis in *Takeda* focused on predictability as understood by persons skilled in the art and the reasons available in the prior art for making changes to the prior art to arrive at the invention. In short, the court used the same basic approach to address obviousness.

In *Ortho-McNeil v. Mylan*[6] the court highlighted the need to consider the predictability of the art in question when making an obviousness determination, and the unexpected nature of the chemical arts as opposed to the mechanical apparatus of *KSR*. The court pointed out that the *KSR* obviousness standard presumes a finite and, in the context of the art, small or easily traversed number of options. But in *Ortho-McNeil*, the court found that although the compound topiramate (Topamax) was structurally similar to prior art compounds, the patent at issue was not obvious because it taught a different use of the compound to treat an unrelated disease. The use of the compound to treat an unrelated disease was considered nonobvious, since ''. . . the ordinary artisan in this field would have had to . . . stop at that intermediate and test it for properties far afield from the purpose for the development in the first place (epilepsy rather than diabetes).''[7]

The court emphasized that a flexible application of the TSM test as contemplated by *KSR* assists the obviousness analysis by preventing inappropriate use of hindsight. The district court opinion was rendered before *KSR*, but the Federal Circuit found that there was no rigid application by the district court of the evidentiary requirements for obviousness and affirmed, confirming that *KSR* did not drastically alter the validity inquiry.

In *Eisai v. Dr. Reddy's*,[8] the Federal Circuit again acknowledged that unpredictability may well differentiate the chemical arts from the facts of *KSR*: ''To the extent an art is unpredictable, as the chemical arts often are, *KSR*'s focus on these 'identified, predictable solutions' may present a difficult hurdle because potential solutions are less likely to be genuinely predictable.''[9] In *Eisai*, the court affirmed summary judgment that a patent claiming rabeprazole (Aciphex), a proton pump inhibitor, was not an obvious modification of a prior art compound. Again, predictability was key: there was no discernible reason for a skilled artisan to modify the ''lead'' prior art compound in a way that eliminated an element to which the compound's advantageous treatment property had been ascribed.

In *Procter & Gamble v. Teva*,[10] the Federal Circuit affirmed the district court's decision that the patent claiming risedronate (Actonel) was valid. The court recognized the need to evaluate whether at the time of the invention, a skilled person had a reason to attempt to make the compound, and a reasonable expectation of success in doing so. Teva (the patent challenger) did not establish sufficient motivation (a reason) for a skilled person to synthesize and test the compound, or that there was a reasonable expectation of success. Relying on *Eisai*, the Federal Circuit once again explained

[2] *Graham v. John Deere Co. of Kansas City*, 383 U.S. 1, 148 USPQ 459 (1966). These factors include the scope and content of the prior art, the differences between the prior art and the claims at issue, the level of ordinary skill in the art, and objective evidence of nonobviousness.

[3] *KSR*, 550 U.S. at 406-407.

[4] *Takeda Chemical Industries Ltd. v. Alphapharm Pty. Ltd.*, 492 F.3d 1350, 83 USPQ2d 1169 (Fed. Cir. 2007)(5 PLIR 713, 7/13/07).

[5] *Id.* at 1356.

[6] *Ortho-McNeil Pharmaceutical Inc. v. Mylan Laboratories Inc.*, 520 F.3d 1358, 86 USPQ2d 1196 (Fed. Cir. 2008) (6 PLIR 384, 4/4/08).

[7] *Id.* at 1364.

[8] *Eisai Co. v. Dr. Reddy's Laboratories Ltd.*, 533 F.3d 1353, 87 USPQ2d 1452 (Fed. Cir. 2008) (6 PLIR 845, 7/25/08).

[9] *Id.* at 1359.

[10] *Procter & Gamble Co. v. Teva Pharmaceuticals USA Inc.*, 566 F.3d 989, 90 USPQ2d 1947 (Fed. Cir. 2009) (7 PLIR 581, 5/22/09).

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that *KSR*'s focus on ''identified, predictable'' solutions may present a difficult hurdle because solutions in the chemical field are less likely to be predictable.[11]

As would be expected, patent challengers succeed where sufficient evidence is presented to demonstrate reasons supported by prior art to modify the closest prior art to engulf the claimed compound. For example, in *Altana v. Teva*,[12] the Federal Circuit affirmed a district court's denial of Altana's motion for a preliminary injunction, ruling that Teva succeeded in raising a substantial question of obviousness of the patent directed to pantoprazole (Protonix). Teva (the patent challenger) identified a lead compound (the closest prior art) and then showed that there was motivation to modify that compound to obtain pantoprazole. The court found that Altana's own earlier patent identified a promising lead compound and that prior art provided a reason and method to lower the compound's pKa to improve stability. The court noted that the prior art does not have to point to a single lead compound since that would give rise to a rigid test similar to the TSM test rejected in *KSR*. These facts supported a strong showing that a reason existed to modify the prior art to encompass the claims (even if the prior art reason for modifying differed from the inventive reason for making changes).

Of course, the burden of showing a substantial question of obviousness at the preliminary injunction stage is lower than the burden of showing clear and convincing evidence of invalidity at trial. After trial in *Altana*, a jury returned a verdict in favor of the patentee. The jury found that a skilled person did not have a reason or motivation to select either of two potential lead compounds, modify it to obtain pantoprazole, or have a reasonable expectation of success.[13] The court denied a motion for a judgment as a matter of law, stating that defendants failed to establish a *prima facie* case of obviousness.[14]

Enantiomer Patents

Stereoisomers are compounds that contain the same constituent atoms and the same bonds between atoms, but have different spatial arrangements. An ''enantiomer'' is one of two stereoisomers that are mirror images of each other and are nonsuperimposable, generally explained by comparing the right and left hands. A ''racemic mixture'' or ''racemate'' contains equal amounts of both enantiomers. Because an enantiomer may sometimes make up a portion of a prior art racemic mixture, alleged infringers invariably argue that separating and testing the enantiomers would be obvious to a skilled person. The Federal Circuit cases pre-*KSR* and post-*KSR*, however, highlight consideration of time-tested factors when deciding the obviousness question: unpredictable and unexpected properties of the enantiomer over the racemate, and the ability to make the claimed enantiomers. Comparing the post-*KSR* Federal Circuit decisions—*Forest*, *Aventis* and *Sanofi*—helps illustrate how the court analyzes these types of chemical cases, upholding validity in two cases while invalidating the patent in the third.

In *Forest v. Ivax*,[15] the Federal Circuit affirmed the district court's pre-*KSR* decision maintaining validity for a patent relating to a substantially pure (+)-enantiomer of citalopram, used in the antidepressant drug Lexapro. Ivax argued that (+)-citalopram was obvious in light of racemic citalopram and descriptions of various techniques available to separate isomers from their racemates. Also, Ivax argued there was an expectation in the art that one enantiomer would be more potent than the other and therefore a reason existed for a skilled person to isolate the enantiomers. Forest argued that the difficulty of separating the enantiomers and the unexpected properties of the (+)-enantiomer (twice the potency of the racemate) supported nonobviousness.

The district court concluded that a skilled person would have been motivated to make a new compound rather than undertake the unpredictable task of separating the enantiomers, and would have no reasonable expectation of success. The court also found that none of the prior art references described the reactions claimed by the patent. The Federal Circuit agreed that the claims were not invalid, holding that the district court properly applied the *Graham* factors. The Federal Circuit opinion issued five months after, but did not cite, *KSR*.

In *Aventis v. Lupin*,[16] the Federal Circuit reversed the district court and invalidated a patent directed to the blood pressure medication ramipril (Altace). The Federal Circuit found that the prior art showed the immediate precursor of ramipril, its active stereoisomers, and how to isolate them, making a patent covering the similar active stereoisomers of ramipril obvious. Ramipril's structure contains five stereocenters, each of which can be in the ''R'' or ''S'' orientation. There was a prior art composition that included only the all-S (SSSSS) and SSSSR stereoisomers of ramipril (in other words the prior art was not free of all other isomers as required by the claims). It was also known in the prior art that the all-S (SSS) stereoisomer of a related ACE inhibitor was 700 times more potent than the SSR stereoisomer. The court found this would have led a skilled person to expect that the all-S stereoisomer of ramipril would have a similar effect, noting that post-*KSR*, ''It remains necessary to show some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness, but such reasoning need not seek out precise teachings directed to the specific subject matter of the challenged claim.''[17]

In *Sanofi v. Apotex*,[18] the Federal Circuit considered the obviousness of an enantiomer patent relating to clopidogrel bisulfate (Plavix), used to treat or prevent blood-thrombotic events such as heart attacks and strokes. Unlike in *Aventis*, the court affirmed the district court's finding that the results of the separation of the enantiomers were unpredictable and not obvious. It

[11] *Id.* at 996.

[12] *Altana Pharma AG v. Teva Pharmaceuticals USA Inc.*, 566 F.3d 999, 91 USPQ2d 1018 (Fed. Cir. 2009) (7 PLIR 585, 5/22/09).

[13] No. 04-2355 (JLL) (D.N.J., *jury verdict* April 23, 2010) (8 PLIR 584, 5/7/10).

[14] No. 04-2355 (JLL) (D.N.J. July 15, 2010).

[15] *Forest Laboratories Inc. v. Ivax Pharmaceuticals Inc.*, 501 F.3d 1263, 84 USPQ2d 1099 (Fed. Cir. 2007) (5 PLIR 900, 9/7/07).

[16] *Aventis Pharma Deutschland GmbH v. Lupin Ltd.*, 499 F.3d 1293, 84 USPQ2d 1197 (Fed. Cir. 2007) (5 PLIR 929, 9/14/07).

[17] *Id.* at 1301 (internal quotation marks omitted).

[18] *Sanofi-Synthelabo v. Apotex Inc.*, 550 F.3d 1075, 89 USPQ2d 1370 (Fed. Cir. 2008) (6 PLIR 1395, 12/19/08).

was unexpected that one isomer would exhibit the desired characteristics without the negative side effects, while the other isomer had the negative side effects and not the desired activity. In addition, although there were several general methods for separating isomers, achieving the separation for the isomer in question required significant efforts because it was not known in advance which process would work. And, nothing in the prior art directed a skilled person to form the specific claimed salt of the enantiomer.

The court rejected Apotex's argument that separating the enantiomers and determining their properties was obvious and covered by *KSR*'s determination that a combination of familiar elements is likely to be obvious when it yields predictable results. The court emphasized that, unlike the *KSR* mechanical device, *Sanofi* did not concern a ''combination of familiar elements.''[19]

Formulation Patents

When considering formulation patents, the Federal Circuit again focused on the unpredictability of the chemical arts, and whether the prior art narrows the range of solutions to a finite and limited number that could be systematically tried.

In *Abbott v. Sandoz*,[20] the Federal Circuit considered patents relating to extended release clarithromycin formulations, marketed as Biaxin XL. Sandoz alleged the two patents at issue were obvious in view of certain references. Sandoz asserted that *KSR* significantly changed the obviousness analysis and that the district court did not give proper recognition to the changes when it granted Abbott's motion for a preliminary injunction pre-*KSR*.[21]

The Federal Circuit affirmed the preliminary injunction in part because the patentee established a likelihood of success in demonstrating nonobviousness. The court noted that the art was unpredictable, and the prior art did not narrow the range of solutions to a finite number that made it obvious to combine the references. The Federal Circuit emphasized that the obviousness inquiry should consider the nature of the science or technology at issue and that each case must be decided based on the characteristics and state of the particular field of technology.

In contrast to *Abbott*, in *Bayer v. Barr*,[22] the Federal Circuit found that the prior art narrowed the list of possible solutions to a finite number and upheld a district court's obviousness ruling on a patent relating to drospirenone (Yasmin), an oral contraceptive. The court found there was a limited number of possible formulations and that it would have been obvious to deliver the micronized drug via a normal pill.

Bayer argued before the USPTO that micronizing a drug improved its absorption, but led to increased isomerization in the stomach, which taught away from delivering the drug using a normal pill as opposed to an enteric coated pill. Enteric coated pills, however, reduce the drug's bioavailability and create patient-to-patient variation in the onset of therapeutic response to the drug. The district court held that under *KSR* it would have been obvious to a person of skill in the art to try a normal pill formulation. The Federal Circuit agreed, pointing out that a skilled person would be faced with two options for formulating the product: an enteric coated pill and a normal pill.[23] Judge Pauline Newman dissented from the opinion, stating that it was not obvious for persons of ordinary skill in the art to try a formulation that contravened conventional knowledge in the field and was not deemed reasonably likely to succeed.[24] The unanswered question here is whether there were other options or unsuccessful attempts to use formulations that would lead a person of ordinary skill away from using the ''normal pill formulation,'' making its choice less predictable.

In *Purdue v. Par*,[25] the Federal Circuit, in a nonprecedential opinion, affirmed the district court's ruling that patents relating to controlled-release tramadol formulations (Ultram ER) were invalid for obviousness. The court rejected Purdue's argument that a skilled person would not have selected tramadol for use in a once-daily formulation in view of a prior art patent listing tramadol as one of fourteen compounds for use in a controlled-release formulation to provide effective blood levels for a 24-hour period. The court agreed with the district court that the prior art patent and available knowledge would have led a skilled person to the claimed formulation through routine experimentation. The court did not discuss any evidence that would teach away from using tramadol in the formulation, and was not convinced by Purdue's secondary considerations of nonobviousness. The Federal Circuit did not cite *KSR* in its opinion, but did consider the *Graham* factors.

Combination Patents

Recent Federal Circuit and district court cases relating to combination patents recognize *KSR*, but it is likely that the outcome of the cases would have been the same prior to *KSR*. In *KSR* the Supreme Court affirmed its ''earlier instructions concerning the need for caution in granting a patent based on the combination of elements found in the prior art.'' The court explained that the combination of familiar elements according to known methods is likely obvious when it only yields predictable results.[26] Thus, once again, before and after *KSR*, the main question with chemical combination patents remains whether the combination of known elements produces an unexpected effect. Any other approach would eviscerate the large body of case law acknowledging that the mere fact that each element in a combination was known in the prior art does not by itself invalidate a patent.[27]

In *Ortho-McNeil v. Teva*,[28] the Federal Circuit considered the validity of a reissued patent directed to a combination of tramadol and acetaminophen for use in pre-

[19] *Id.* at 1090.

[20] *Abbott Laboratories v. Sandoz Inc.*, 544 F.3d 1341, 89 USPQ2d 1161 (Fed. Cir. 2008) (6 PLIR 1231, 10/31/08).

[21] The district court's original opinion issued before *KSR*. The court then requested additional briefing and argument and issued another opinion discussing *KSR*.

[22] *Bayer Schering Pharma AG v. Barr Laboratories Inc.*, 575 F.3d 1341, 91 USPQ2d 1569 (Fed. Cir. 2009) (7 PLIR 937, 8/14/09).

[23] *Id.* at 1350.

[24] *Id.* at 1350-1351.

[25] *Purdue Pharma Products LP v. Par Pharmaceuticals Inc.*, No. 2009-1553 (Fed. Cir. June 3, 2010) (8 PLIR 743, 6/11/10).

[26] *KSR*, 550 U.S. at 415-416.

[27] *Id.* at 418.

[28] *Ortho-McNeil Pharmaceutical Inc. v. Teva Pharmaceuticals Industries Ltd.*, 344 Fed. Appx. 595, 93 USPQ2d 1125 (Fed. Cir. 2009) (7 PLIR 1025, 9/11/09).

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scription pain relief, sold under the name Ultracet. The court reversed the district court's summary judgment of invalidity of certain claims of the patent, and affirmed judgment of invalidity of one of the claims. In considering validity, the court distanced chemical patents from *KSR* by stating, ''each case must be decided in its particular context, including the characteristics of the science or technology, the nature of the choices available to one skilled in the art, the specificity of the prior art, and the predictability of results in the area of interest.''[29]

The court vacated the district court's summary judgment of invalidity of certain claims of the reissue patent. The court credited expert testimony that prior art that disclosed a combination of tramadol, acetaminophen, and two other ingredients (the Flick patent) did not make the claims at issue obvious because interactions between tramadol and acetaminophen were poorly understood and unpredictable at the time, and it was not obvious what would happen if the two other ingredients were removed from the prior art example. Thus, the court recognized a material fact issue remained to be resolved, making summary judgment inappropriate.[30]

However, the court found a claim that used the term ''comprising'' of tramadol and acetaminophen in a certain ratio obvious in light of Flick because ''comprising'' is an open-ended term that could include the other two materials (which in combination with tramadol and acetaminophen would include all the elements of the prior art). The court further determined that the difference between the ratio in the patent claim and in the prior art was too slight to preserve the claim's validity.[31]

Judge Haldane Robert Mayer dissented, stating that the patent did nothing more than combine two known pain relievers into one tablet and prior art already taught that the two ingredients could be combined for effective pain relief. Mayer explained that one of ordinary skill in the art at the time would have been motivated to remove the two other Flick ingredients because it was suspected they had negative effects, and that it was known that the combination of tramadol with other analgesics showed synergistic effects.[32] The value of the surviving claims remains to be evaluated given this history.

While the Federal Circuit has not had the opportunity to review many chemical combination patents post-*KSR*, recent district court cases shed some light.

In *McNeil PPC v. Perrigo*,[33] the district court, while invalidating the claims at issue, addressed *KSR* at length, highlighting the Supreme Court's approval of the *Graham* factors, the rejection of a rigid TSM test, and the caution against relying on hindsight. The Federal Circuit affirmed without an opinion.[34]

The patent at issue was directed to a combination of aluminum or magnesium hydroxide (an antacid) with famotidine (a histamine H2-receptor antagonist) used in Pepcid Complete. The invention used impermeably coated famotidine, which otherwise degrades in stomach acid and has a bitter taste. Prior art reviewed by the court included references to a solid oral dosage form containing uncoated famotidine and an antacid, a method for coating various drugs (including famotidine) to mask their taste, and a combination of another bitter H2 blocker and an antacid in a chewable tablet.

The plaintiff argued that the claimed coated famotidine degrades more slowly than the uncoated form. The court, however, found the claims obvious because the prior art provided an independent motivation to coat famotidine to mask its bitter taste, regardless of its effects on degradation. Thus, consistent with *KSR* (and pre-*KSR* law), the court considered the teachings in the prior art and what would be obvious avenues of development for a person of ordinary skill in the art.

In *Sanofi-Aventis v. Glenmark*,[35] the district court denied the defendant's motion for summary judgment of invalidity of a combination patent. The patent claims were directed to a combination of an angiotensin-converting enzyme inhibitor (ACE inhibitor) and a calcium antagonist that Sanofi sells under the name Tarka.

The defendants alleged that ACE inhibitors, calcium antagonists, the combination of both, and their respective anti-hypertensive activities were known in the art at the time of the invention. They also pointed to the Tarka label which read ''the antihypertensive effect of the combination is approximately additive to the individual components'' to show that the combination did not produce unexpected results. The plaintiffs argued that it was not known how the two interacted and worked together to regulate blood pressure and that the duration and efficacy of Tarka is superior to the closest prior art combination.

The court denied summary judgment of invalidity recognizing the existence of questions of fact regarding the independent and collective properties of the compounds. The court also acknowledged that fact questions existed regarding the scope of prior art disclosure, including whether prior art disclosing short term reduction of blood pressure made the use of the combination for the treatment of hypertension obvious.

The defendants subsequently received final Food and Drug Administration approval to market their abbreviated new drug application (ANDA) product, and Sanofi sought a preliminary injunction and temporary restraining order. In its decision, the court discussed *KSR*'s rejection of a rigid application of the TSM test, reviewed the cited prior art, and applied the *Graham* factors. The court denied the request for a preliminary injunction, finding that the patentee did not meet its burden of proof.[36] It remains to be seen how the court will ultimately rule on the merits of the case, but the court's reliance on the *Graham* factors confirms that the validity analysis of chemical combination patents was not altered by *KSR*.

Conclusion

As can be seen from the post-*KSR* Federal Circuit cases and district court cases, the validity inquiry applied by courts in chemical/pharmaceutical patent liti-

[29] *Id.* at 598.
[30] *Id*. at 598-599.
[31] *Id*. at 599-601.
[32] *Id*. at 601-603.
[33] *McNeil-PPC Inc. v. Perrigo Co.*, 516 F. Supp. 2d 238 (S.D.N.Y. 2007) (5 PLIR 613, 6/15/07).
[34] 274 Fed.Appx. 899 (Fed. Cir. 2008).
[35] *Sanofi-Aventis Deutschland GmbH v. Glenmark Pharmaceuticals Inc. USA*, No. 07-CV-5855(DMC), 2010 WL 715402 (D.N.J. Feb. 19, 2010) (8 PLIR 775, 6/18/10).
[36] *Sanofi-Aventis Deutschland GmbH v. Glenmark Pharmaceuticals Inc. USA*, No. 07-CV-5855 (DMC), 2010 WL 2428561 (D.N.J. June 9, 2010) (8 PLIR 775, 6/18/10).

gation has remained largely the same. *KSR*'s warning against the rigid application of the TSM test supports a flexible inquiry. The validity inquiry balances the number of potential solutions, the innovative steps used to create the patented product, and what was obvious to a skilled person at the time. A review of post-*KSR* case law demonstrates that commentators who foresaw a ''sea-change'' in how cases would be analyzed appears to have been wrong at least with respect to chemical cases.

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