PROTECTING PHARMACEUTICAL INVENTIONS IN A *KSR* WORLD

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I. INTRODUCTION

The pharmaceutical sciences and their related disciplines present unique problems for the patent practitioner, the inventor, and the Patent Examiner when determining how, if, and when patent protection is warranted. By statutory design, the Patent Office determines whether a claimed invention is patentable, which includes an inquiry into whether the subject matter of the claims presented to it are new, nonobvious, and useful.[1] Drawing the line between what is or is not obvious for inventions in the pharmaceutical sciences art has always been challenging because there are a finite number of elements, recurring groups, or substituents in complex molecules; structural similarities within classes of compounds; and an ability of chemists and biochemists to undertake systematic experiments in order to modify known compounds.[2] In an era where

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[1] 35 U.S.C. §§ 101–103 (2006). Other standards for patentability are outlined in 35 U.S.C. § 112, including that the application complies with the requirements of written description, enablement and best mode. 35 U.S.C. § 112 (2006). However, those standards revolve around the adequacy of a disclosure and not the patentability of the invention itself.

[2] Eli Lilly & Co. v. Zenith Goldline Pharms., Inc., No. IP 99-38-C H/K, 2001 U.S. Dist. LEXIS 18361, at *14 (S.D. Ind. Oct. 12, 2001) ("Chemical compounds present special issues

many pharmaceutical companies' pipelines are drying up and the public is increasingly demanding more entry by generic companies, understanding the rubric under which the patentability of pharmaceutical compounds are evaluated has never been more critical.

In the framework of this increased pressure and focus on pharmaceutical companies and patents, the U.S. Supreme Court's decision in *KSR International Co. v. Teleflex Inc.*,[3] which was not decided in the context of pharmaceuticals, notified the patent bar and the scientific community of what some have described as a new standard for patentability: an invention may be obvious and thus unpatentable even absent an explicit suggestion either to create such an invention or to combine elements from other known products or processes.[4] This standard raises the bar for patentability and will likely have a more profound effect in the pharmaceutical and chemical arts than in any others because in these arts any one patent may be worth hundreds of millions or even billions of dollars. In order to appreciate the ramifications of *KSR* for these arts, this article summarizes: (Part II) *KSR International Co. v. Teleflex Inc.*; (Part III) the application of that decision as implemented by the Court of Appeals for the Federal Circuit (CAFC) [5] and trial courts with respect to patent claims that are directed to pharmaceutical inventions; and (Part IV) issues for patent holders, competitors of patents holders, inventors and patent practitioners to consider as they try to obtain, to protect and to use their potentially lucrative patent rights in these arts.

II. *KSR INTERNATIONAL CO. V. TELEFLEX INC.*

The Supreme Court in *KSR* revisited the issue of nonobviousness, which it had previously discussed at length forty-one years earlier in the seminal case

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of obviousness because of the limited number of elements, recurring groups or substituents in complex molecules, the structural similarities within classes of related compounds, and the ability of chemists to undertake systematic experiments modifying known compounds."); *see also* Sanofi-Synthelabo v. Apotex, Inc., 492 F. Supp. 2d 353, 389 (S.D.N.Y. 2007) ("Where the claimed invention is a chemical compound, the 'compound and all of its properties are inseparable; they are one and the same thing.'") (quoting *In re* Papesch, 315 F.2d 381, 391 (C.C.P.A. 1963)).

3 550 U.S. 398 (2007).

4 *Id.* at 419 ("[O]bviousness analysis cannot be confirmed by a formalistic conception of the words teaching, suggestion, and motivation, or by overemphasis on the importance of published articles and the explicit content of issued patents.").

5 The CAFC has jurisdiction over all appeals from cases that were filed as patent matters. 28 U.S.C. §§ 1295(a), 1338(a) (2006).

Graham v. John Deere Co.[6] *Graham* established a four-part analytic framework for determining whether an invention is obvious.

Under this framework, one must: (1) determine the scope and the content of the prior art; (2) determine the differences between the prior art and the claims at issue; (3) determine the level of ordinary skill in the art; and (4) consider any secondary considerations of nonobviousness, which include but are not limited to "commercial success, long felt but unsolved needs, [and] failures of others . . . ."[7]

The Supreme Court has yet to overrule *Graham*, but prior to 2007, and in order to apply the obviousness standard, the CAFC developed the well-known "'teaching, suggestion, or motivation test' (TSM test), under which a patent claim is only proved obvious if 'some motivation or suggestion to combine the prior art teachings' can be found in the prior art, the nature of the problem, or the knowledge of a person having ordinary skill in the art."[8] *KSR* criticized this test and the CAFC for setting the standard for nonobviousness too low.[9]

Appreciating the ramifications of its opinion, the Supreme Court provided a number of critical guideposts for the CAFC, the lower courts, and the Patent Office to follow when conducting an obvious analysis:

> 1) a patent for a combination that only unites old elements with no change in their respective functions withdraws what is already known in the field of its monopoly and diminishes what is available to the public—therefore "[t]he combination of fa-

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6 383 U.S. 1 (1966). The obviousness bar is codified in 35 U.S.C. § 103(a), which provides:

> A patent may not be obtained though the invention is not identically disclosed or described as set for in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

35 U.S.C. § 103(a) (2006).

7 *Graham*, 383 U.S. at 17–18.

8 *KSR*, 550 U.S. at 407 (quoting Al-Site Corp. v. VSI Int'l, Inc., 174 F.3d 1308, 1323–24 (Fed. Cir. 1999)).

9 *Id.* at 415 ("We begin by rejecting the rigid approach of the Court of Appeals. Throughout this Court's engagement with the question of obviousness, our cases have set forth an expansive and flexible approach inconsistent with the way the Court of Appeals applied its TSM test here.").

miliar elements according to known methods is likely to be obvious when it does no more than yield predictable results";[10]

2) "[w]hen a work is available in one field of endeavor, design incentives and other market forces can prompt variations of it, either in the same field or a different one";[11]

3) "it will be necessary for a court 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 by the patent at issue";[12]

4) although the analysis of obviousness or nonobviousness should be explicit, "the analysis need not seek out precise teachings directed to the specific subject matter of the challenged claim, for a court can take account of the inferences and creative steps that a person of ordinary skill in the art would employ";[13]

5) "[i]n determining whether the subject matter of a patent claim is obvious, neither the particular motivation nor the avowed purpose of the patentee controls. . . . One of the ways in which a patent's subject matter can be proved obvious is by noting that there existed at the time of invention a known problem for which there was an obvious solution encompassed by the patent's claims" ;[14]

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10 *Id.* at 416.

11 *Id.* at 417.

12 *Id.* at 418.

13 *Id.*

14 KSR Int'l Co. v. Teleflex Inc., 550 U.S. 398, 419–420 (2007). Thus, the Patent Office and the courts should not look solely to the problem that the patent applicant or patentee was trying to solve. Instead, "any need or problem known in the field of endeavor at the time of invention and addressed by the patent can provide a reason for combining the elements in the manner claimed." *Id.* at 420.

6) a person of ordinary skill would not be limited to considering only those elements of the prior art designed to solve the same problem;[15] and

7) "[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" and thus an invention may be obvious to try.[16]

III. THE RECENT APPLICATION OF THE NONOBVIOUSNESS STANDARD TO PHARMACEUTICAL INVENTIONS

In the short time that has passed since *KSR*, the CAFC and the lower courts have struggled to apply *KSR* to pharmaceutical inventions.[17] Below the authors discuss these applications, as well as certain pre-*KSR* cases to highlight the current state of the law with respect to the four basic types of pharmaceutical inventions that are directed to compositions: (A) selection of a chemical species from within a genus; (B) developing new active chemical compounds; (C) new formulations, including processing techniques; and (D) compounds derived from known racemate mixtures.[18]

A. Selection of Species

One type of pharmaceutical composition patent involves patents that are based on the inventive selection of a molecular species from a known genus. For example, prior art disclosures may have indentified common elements of

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15 *Id.* at 420.

16 *Id.* at 421. Recently in *Bayer Schering Pharma AG v. Barr Laboratories, Inc.*, 575 F.3d 1341 (Fed. Cir. 2009), the CAFC elaborated on two classes of inventions that were not obvious to try: (1) "an invention would not have been obvious to try when the inventor would have had to try all possibilities in a field unreduced by direction of the prior art"; and (2) "an invention is not obvious to try where vague prior art does not guide an inventor toward a particular solution." *Id.* at 1347.

17 *See, e.g.*, Roche Palo Alto L.L.C. v. Ranbaxy Labs. Ltd., No. 06-2003, 2009 U.S. Dist. LEXIS 90804, at *138 (D.N.J. Sept. 30, 2009) ("The Federal Circuit has distinguished *KSR*, from the facts presented in cases involving pharmaceutical compounds"); Altana Pharma AG v. Teva Pharms. U.S.A., Inc., 532 F. Supp. 2d 666, 676 n.18 (D.N.J. 2007) (expressing uncertainty as to whether the lead compound requirement survived *KSR*).

18 There are also inventions directed to new and nonobvious methods of using compounds and methods of making compounds, each of which can be of immense value to pharmaceutical companies. However, those types of inventions are beyond the scope of the present article.

many molecules while referencing one or more "R" groups to designate any number of substituents that might fill those groups.[19] Thus, the structural formula may define a genus of compounds that number in the hundreds, thousands, or even millions, while an individual molecule may define a species.[20] Other prior art references may list large numbers of compounds that are not necessarily united by a structural relationship.

In general, as the genus grows larger, the selection of a species becomes less obvious. Additionally, when one can show unexpected results and/or the prior art leads one away from a particular species, the patent holder may have an easier time showing nonobviousness.

When issuing a rejection based on obviousness, the United States Patent and Trademark Office (USPTO) often speaks of the selection of a compound as part of routine optimization of a variable.[21] However, one must keep in mind that selection is not the same as optimization, and a number of pre-*KSR* cases have held that when a parameter to be optimized is not recognized as a "result-effective variable," a rejection or invalidation of a claim as being obvious under the doctrine of routine optimization is not proper.[22]

The viability of the holdings of these cases will likely face certain challenges because at least one of these cases also explicitly stated that it relied on the position that "obvious to try is not the standard of 35 USC 103 [sic]."[23] Because *KSR* called into question a blanket prohibition of the issuance of rejections under an obvious to try standard, one would expect that soon an applicant or a litigant will ask for clarification of this "result-effective variable" doctrine.

How the courts will treat selection cases going forward where a claimed species compound that is encompassed by a prior art disclosed genus remains to be seen. The USPTO guidelines still direct the Examiner to consider whether

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19 *See, e.g.*, U.S. Patent No. 5,886,175 (filed Dec. 8, 1994) (assigned to American Cyanamid Company).

20 *Id.*

21 *See generally* U.S. PAT. & TRADEMARK OFFICE, DEP'T OF COM., MANUAL OF PATENT EXAMINING PROCEDURE § 2144.08–.09 (8th ed., 7th rev. 2008) [hereinafter M.P.E.P.].

22 *See In re* Yates, 663 F.2d 1054, 1056 (C.C.P.A. 1981) (declining to recognize "degree of conversion" as a result-effective variable in a process for oxidizing an olefin to an unsaturated aldehyde); *In re* Antonie, 559 F.2d 618, 620 (C.C.P.A. 1977) (determining that "treatment capacity" is not a result-effective variable of "tank volume" in a wastewater treatment device); *Ex parte* Posa, No. 2004-0146, 2002 Pat. App. LEXIS 233, at *7 (B.P.A.I. Nov. 14, 2002) (finding no evidentiary basis to conclude that the size of the projection is recognized in the art as a variable that is result-effective, and declining to sustain rejections under 35 U.S.C. § 103(a) (2006)).

23 *Yates*, 663 F.2d at 1057. The authors are unaware of any reported case that addresses the issue of results-effective variables in the context of a substituent or a molecule.

the prior teaching provides any motivation to produce what is now being claimed.[24] This consideration requires looking at predictability in the particular art, the properties of the species as compared to those taught for the prior genus, and the closeness in structure of the claimed species to typical or preferred species taught in the prior generic disclosure.[25]

One recent pre-*KSR* case may provide a snapshot of what lies ahead. In *Pfizer, Inc. v. Apotex, Inc.*,[26] Pfizer's patent covering its blockbuster blood pressure drug, amlodipine besylate (Norvasc®), was found invalid for being obvious in view of a prior art patent that disclosed amlodipine but did not expressly disclose the besylate salt form of amlodipine.[27] In rejecting Pfizer's argument that "obvious to try" is not the standard for patentability, the CAFC noted that in this case there were not "'numerous parameters' to try. Rather, the only parameter to be varied is the anion with which to make the amlodipine acid addition salt."[28] In holding Pfizer's patent obvious, the CAFC found that the prior art pointed to only fifty-three different anions known to make pharmaceutically acceptable amlodipine salts, and one of ordinary skill in the art could have narrowed the fifty-three different anions down to an even smaller group to produce the besylate salt.[29] The fact that there were few species in the genus of pharmaceutically acceptable salts appeared to make it obvious to pick one from the fifty-three salt species.[30]

More recently in *Purdue Pharma Products L.P. v. Par Pharmaceutical, Inc.*,[31] the patent holder sued an ANDA holder over its extended release tramadol hydrochloride pain relief medication, a generic version of Ultram®, ER.[32] The asserted patent claims related to controlled release oral formulations of tramadol suitable for dosing every 24 hours.[33] The cited reference described "various controlled release oral dosage formulations, disclosing morphine, hydromorphone, and acetaminophen in specific examples, but broadly claim[ed] that

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24 Examination Guidelines for Determining Obviousness Under 35 U.S.C. 103 in View of the Supreme Court Decision in *KSR International Co. v. Teleflex Inc.*, 72 Fed. Reg. 57,526, 57,534 (Oct. 10, 2007).

25 *See generally* M.P.E.P. § 2144.08.

26 480 F.3d 1348 (Fed. Cir. 2007).

27 *Id.* at 1361, 1371.

28 *Id.* at 1366.

29 *Id.*

30 *Id.* at 1366–68.

31 642 F. Supp. 2d 329 (D. Del. 2009).

32 *Id.* at 332.

33 *Id.* at 340.

any 'systematically active therapeutic agent[s]' may be used."[34] The patent holder tried to emphasize the "scores" of analgesics and combinations in the cited reference.[35] However, the court focused on the small number of opioid analgesics, fourteen, and emphasized: "Plaintiffs fail to recognize that a prior art reference's inclusion of a claimed active agent in an undifferentiated list does not necessarily remove the reference from consideration as invaliditing."[36] From there, the court considered to what degree the evidence of record made tramadol a likely or unlikely candidate, and emphasized the patent holder's own recognition during the relevant time period that it would be a preferable compound, and was obvious.[37]

An example of a recent selection case that resulted in a finding of nonobviousness over the prior art is *Alcon, Inc. v. Teva Pharmaceuticals, U.S.A. Inc.*[38] In *Alcon*, the Defendant sought to market a generic version of the antibacterial drug Vigamox®.[39] Vigamox is a topical ophthalmic solution containing moxifloxacin hydrochloride.[40]

Moxifloxacin was known prior to the Alcon's microbiologist's work with it and Bayer entering into Phase II trials.[41] Alcon's scientist learned of Bayer's in vitro data at a conference in Toronto, Canada.[42] Alcon ultimately obtained a patent directed to a topical ophthalmic pharmaceutical composition comprising moxifloxacin.[43] Despite the disclosure of moxifloxacin in the literature the court held "the record indicates anything but a finite number of identified, predictable solutions."[44] The court pointed to the years spent by the inventor looking for a compound, and the number of compounds tried as evidence of nonobviousness.[45] Most notably the court contrasted the issue of the predictabil-

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34 *Id.* at 369.

35 *Id.*

36 *Id.*

37 *Purdue Pharma*, 642 F. Supp. 2d at 370–71.

38 No. 06-234-SLR, 2009 U.S. Dist. LEXIS 97757 (D. Del. Oct. 19, 2009).

39 *Id.* at *1.

40 *Id.* at *1–2.

41 *Id.* at *7–8.

42 *Id.* at *11.

43 *Id.* at *13–14. The sole independent claim read "A topical ophthalmic pharmaceutical composition comprising moxifloxacin or a pharmaceutically useful hydrate or salt thereof in a concentration of 0.1 to 1.0 wt % and pharmaceutically acceptable vehicle therefore." *Id.* at *14.

44 Alcon, Inc. v. Teva Pharms. U.S.A. Inc., No. 06-234-SLR, 2009 U.S. Dist. LEXIS 97757, at *43–44 (D. Del. Oct. 19, 2009).

45 *Id.* at *44.

ity of the properties of the claimed composition, which the court agreed were predictable, with "whether the prior art motivated a person of ordinary skill to even select moxifloxacin for use in a topical ophthalmic composition."[46] From there the court pointed to Bayer's evidence that moxifloxacin was eight times less active than ciprofloxacin against Pseudomonas, a type of bacteria.[47] This was evidence of a teaching away by the prior art, as well as "[t]he uncertain toxicity status of moxifloxacin," which weighed "against its development into a topical ophthalmic treatment."[48]

B. New Chemical Compounds

Many pharmaceutical inventions are based on newly developed chemical compounds. These compounds may be completely novel, or homologs or isomers of known compounds.[49] Thus, when considering the patentability of these compounds, the USPTO and the courts must ask whether these compounds are close enough to the prior art chemical compounds to give one skilled in the relevant art "motivation to make close relatives[, including] homologs, analogs, isomers, etc."[50]

The inquiry begins with a focus on known chemical structures, because, as the CAFC has explicitly noted: "[f]or chemical compounds, the structure of the compound and its properties are inseparable considerations in the obviousness determination."[51] Accordingly, inventions related to new active chemical compounds involve two threshold issues: (1) whether the selection of the lead

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46 *Id.* at *45.

47 *Id.* at *47.

48 *Id.* at *47–48.

49 *See* Takeda Chem. Indus., Ltd. v. Alphapharm Pty., Ltd., 492 F.3d 1350, 1356 (Fed. Cir. 2007); *see also* M.P.E.P. § 2144.09.

50 Sanofi-Synthelabo v. Apotex, Inc., 492 F. Supp. 2d 353, 389 (S.D.N.Y. 2007).

51 Sanofi-Synthelabo v. Apotex, Inc., 550 F.3d 1075, 1086 (Fed. Cir. 2008); *see also* Yamanouchi Pharm. Co. v. Danbury Pharmacal, Inc., 231 F.3d 1339, 1343 (Fed. Cir. 2000) ("For a chemical compound, a prima facie case of obviousness requires 'structural similarity between claimed and prior art subject matter . . . where the prior art gives reason or motivation to make the claimed compositions.'" (quoting *In re* Dillon, 919 F.2d 688, 692 (Fed. Cir. 1990))); Eli Lilly & Co. v. Zenith Goldline Pharms., No. IP 99-38-C H/K, 2001 U.S. Dist. LEXIS 18361, at *16–17 (S.D. Ind. Oct. 29, 2001) ("Obviousness cannot be determined by chemical structure alone. As applied to chemical compounds, 'a compound and all of its properties are inseparable.'" (quoting *In re Dillon*, 919 F.2d at 697)).

compound is suggested by the prior art; and (2) whether the modifications to the lead compound are predictable.[52]

1. Selection of the Lead Compound(s)

As a general matter, courts have continued to recognize that structural similarity between claimed and prior art subject matter creates a prima facie case of obviousness.[53] Structural similarity alone, however, will not necessarily render a claim invalid, and when considering issues of structural similarity, even in a *KSR* world, courts tend to ask whether the structurally similar compound was a lead candidate.[54]

Lead candidates are those compounds that are the most promising to modify.[55] There may be more than one such compound, and in those cases a court may consider whether a particular lead compound was a logical choice.[56] Thus, a lead compound is a compound that is a promising starting point; however, the closest structure is not necessarily the lead compound.[57]

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52 *See* Altana Pharma AG v. Teva Pharms. U.S.A., Inc., 566 F.3d. 999, 1007 (Fed. Cir. 2009) ("to establish a prima facie case of obviousness in cases involving new chemical compounds, the accused infringer must identify some reason that would have led a chemist to modify a known compound in a particular manner."); *Eli Lilly*, 2001 U.S. Dist. LEXIS 18361, at *24 ("The party claiming obviousness must show that the prior art provided a reasonable expectation that the particular modification of a prior compound would produce a new compound with the desired properties.").

53 *Sanofi-Synthelabo*, 550 F.3d at 1086; Takeda Chem. Indus., Ltd. v. Alphapharm Pty., Ltd., 492 F.3d 1350, 1356 (Fed. Cir. 2007); Altana Pharma AG v. Teva Pharm. U.S.A., Inc., 532 F. Supp. 2d 666, 675 (D.N.J. 2007); Novartis Pharm. Corp. v. Teva Pharm. USA, Inc., No. 05-CV-1887, 2007 U.S. Dist. LEXIS 65792, at *14 (D.N.J. Sept. 6, 2007) ("Takeda . . . reaffirmed the test for *prima facie* obviousness of structurally similar compounds . . . .").

54 *See Novartis*, 2007 U.S. Dist. LEXIS 65792, at *17 (noting that the *Takeda* court considered "whether a person of ordinary skill in the art would select a compound as a lead").

55 *Altana*, 532 F. Supp. 2d at 676 n.18. The *Altana* court contemplated whether the consideration of the presence of a lead compound was appropriate under *KSR* or whether consideration of known compounds was the proper rubric:

> To the extent that the lead compound requirement did not survive *KSR*, the Federal Circuit made clear in *Takeda* that at the very least, to prevail on an obviousness claim, the defendant must show that there was a "reason that would have lead a chemist to modify a *known ompound* [sic] in a particular manner to establish prima facie obviousness of a new chemical compound."

Id. at 676 n.18 (quoting *Takeda*, 493 F.3d at 1357).

56 *Id.* at 676.

57 *See, e.g.*, *Takeda*, 492 F.3d at 1357, 1358. In *Takeda*, a prior art patent disclosed a set of fifty-four compounds, including the compound that the parties agreed was the closest prior art compound. *Id.* That reference did not disclose experimental data of test results for any of

Approximately one year after *KSR*, in *Ortho-McNeil Pharmaceutical, Inc. v. Mylan Laboratories, Inc.*,[58] the CAFC confronted the issue of whether the design of a FBPase inhibitor would have been obvious.[59] The defendant, drawing on the pronouncement in *KSR*, argued that "'when 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.'"[60] The defendant asserted this argument to show that the development of the blockbuster drug topiramate would have been obvious.[61]

The CAFC focused on the issue of whether there was a "finite, and in the context of the art, small or easily traversed, number of options."[62] Weighing against a finding of obviousness, the CAFC noted that: (1) the evidence showed that a person would not start with the compound with which the inventors started; (2) it was not obvious to select the exact route that produced the claimed intermediate; and (3) it would not have been obvious to stop at that intermediate and to test its properties.[63] The CAFC acknowledged the Supreme Court's admonishment against the TSM test, yet still held that "a flexible TSM test remains the primary guarantor against a non-statutory hindsight analysis."[64]

Following *McNeil*, one may expect that to harmonize developments in the CAFC and lower courts with the language of *KSR*, an inquiry into obvious-

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those fifty-four compounds. *Id.* at 1357. The prosecution history, however, disclosed test data for nine compounds, including the closest prior art compound. *Id.* Yet there was no suggestion that those nine compounds were the best performing compounds. *Id.* A second prior art reference disclosed the same closest prior art compound, but it did not deem that compound to be the most favorable in terms of toxicity and activity. *Id.* at 1358. Instead, it suggested not using that compound because it caused considerable increases in body weight and brown fat weight. *Id.* A third prior art reference specifically claimed the closest prior art compound. *Id.* The lower court looked at the prior art in total, and the court emphasized, as the lead compound, the reference that taught away from the closest compound. *Id.* The CAFC held that *KSR* did not dictate a reversal because the closest structural compound was not obvious to try given the negative properties for that compound. *Id.* at 1359.

58 520 F.3d 1358 (Fed. Cir. 2008).

59 *Id.* at 1364.

60 *Id.* (quoting KSR Int'l Co. v. Teleflex Inc., 550 U.S. 398, 421 (2007)).

61 *Id.*

62 *Id.*

63 *Id.*; s*ee also* Eli Lilly & Co. v. Teva Pharms. U.S.A., Inc., 1:06-cv-1017-SEB-JMS, 2009 U.S. Dist. LEXIS 87763, 95–96 (S.D. Ind. Sept. 23, 2009) (finding claims to raloxifene to treat postmenopausal women were not obvious when prior art suggested unsuitability for this purpose).

64 Ortho-McNeil Pharm., Inc. v. Mylan Labs., Inc., 520 F.3d 1358, 1364 (Fed. Cir. 2008).

ness will evolve from an initial focus on what a lead compound consists of to a focus on what constitutes a reasonable set of starting points and whether they are small and finite. As noted above, *KSR* contains explicit language about applying the obviousness standard when there are a finite number of compounds to consider.

When *KSR* was first decided, patentees and patent practitioners saw it as a sword for the Patent Office and generic pharmaceuticals to use in challenging the obviousness of a patent. Under the guidance of the CAFC, however, this has become a shield. In *Eisai Co. v. Dr. Reddy's Laboratories, Ltd.*,[65] the CAFC explicitly stated: "In *KSR*, the Supreme Court noted that an invention may have been obvious 'when there was . . . a design need or market pressure to solve a problem and there were . . . a finite number of identified, predictable solutions.'"[66] From *KSR* the CAFC was able to infer that the Supreme Court relied on three assumptions about the prior art landscape:

> First, *KSR* assumes a starting reference point or points in the art, prior to the time of invention, from which a skilled artisan might identify a problem and pursue potential solutions. Second, *KSR* presupposes that the record up to the time of invention would give some reasons, available within the knowledge of one of skill in the art, to make particular modifications to achieve the claimed compound. Third, the Supreme Court's analysis in *KSR* presumes that the record before the time of invention would supply some reasons for narrowing the prior art universe to a "finite number of identified, predictable solutions."[67]

Relying on its earlier precedent in *Ortho-McNeil*, the CAFC emphasized that an "'easily traversed, small and finite number of alternatives . . . might support an inference of obviousness.'"[68] However, the CAFC also was able to distinguish the chemical arts, which includes pharmaceuticals, because they have long been recognized as unpredictable, explicitly stating: "*KSR's* focus on these 'identified, predictable solutions' may present a difficult hurdle because potential solutions are less likely to be genuinely predictable."[69]

These cases demonstrate that, although a relatively short time has passed since the decision in *KSR*, one can already see the tension between the CAFC and the Supreme Court in applying the obviousness standard when selecting a starting compound.

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65 533 F.3d 1353 (Fed. Cir. 2008).

66 *Id.* at 1359 (quoting KSR Int'l Co. v. Teleflex Inc., 550 U.S. 398, 421 (2007)).

67 *Id.* (quoting *KSR*, 550 U.S. at 421) (citations omitted).

68 *Id.* (quoting *Ortho-McNeil*, 520 F.3d at 1364).

69 *Id.*

2. Modification of Substituent(s)[70]

Once there is a lead compound or a finite set of potential compounds, one may consider the structural similarity to the claimed compound, and whether the modification(s) to a known compound would have been obvious. Historically, courts have considered a number of factors when determining whether a compound is obvious based on the disclosure of a structurally similar compound. These factors include, but are not limited to, the level of activity, absence of dangerous side effects, ability to be taken orally, duration of action, absence of toxicity, and a safe therapeutic ratio.[71] However, many of those cases rested on the presumption that concluding a compound was obvious to try was insufficient to establish obviousness under 35 U.S.C. § 103.[72] Because *KSR* arguably undermined this premise, one should expect a new body of case law to develop that describes under what circumstances molecules with modifications are sufficiently obvious to try that they become obvious under § 103. However, for a challenger to a pharmaceutical patent, the failure to identify a sufficient suggestion for moving a substituent group can still prove to be fatal.[73] The CAFC has made this explicit, even though the retention of this standard may, at first blush, seem at odds with the holding in *KSR*.

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70 A related line of cases are the "pro-drug" cases. A pro-drug is a composition that itself does not have chemical activity, but instead is converted into an active ingredient in the body. One recent pro-drug case is *Novartis Pharm. Co. v. Teva Pharm., Inc.*, No. 05-CV-1887, 2007 U.S. Dist. LEXIS 65792 (D.N.J. Sept. 6, 2007). At issue was whether the pro-drug famciclovir (commercially sold as Famvir®) was obvious in view of the known active ingredient into which it metabolized, penciclovir. This started with the inquiry into whether penciclovir was an obvious lead compound. *Id.* at *15–18. The court concluded that there were only a few compounds that would function as lead compounds, as antiviral agents, and that penciclovir was one of them. *Id.* at *17. Though one of the known problems with penciclovir was its bioavailability, the court held that there was a primary reference that taught that to improve bioavailability, one should try to modify it into a pro-drug and create an oral version. *Id.* at 20–21. Finally, the court addressed whether it would have been obvious to modify penciclovir to create the pro-drug famciclovir. *Id.* at *22–23. The reference that suggested creating pro-drugs also proposed using 6-deoxy and ester modifications on similar base drugs. *Id.* at *21–24. Because of the strength of this art, the District Court denied the plaintiff's request for a preliminary injunction. *Id.* at *45.

71 Eli Lilly v. Zenith Goldline Pharm., Inc., No. IP 99-38-C H/K, 2001 U.S. Dist. LEXIS 18361, at *26–27 (S.D. Ind. Oct. 12, 2001).

72 *See, e.g.*, *id.* at *24–25.

73 *See, e.g.*, Takeda Pharm. Co. v. Teva Pharm. U.S.A., Inc., 542 F. Supp. 2d 342, 359 (D. Del. 2008) ("In short, Teva has not identified a sufficient suggestion in the art for moving the 2,2,2-trifluoroethoxy group to the pyridine ring.").

In *Takeda Chemical Industries, Ltd. v. Alphapharm Pty., Ltd.*,[74] the CAFC was asked to confront the issues of both when selection of the closest compound is obvious, and when certain modifications of that closest compound are obvious.[75] In that case, the CAFC paid homage to *KSR* and then repeated what it described as its "well-established" law regarding a prima facie case of obviousness, setting forth two requirements: (1) there must be "'structural similarity between claimed and prior art subject matter, proved by combining references or otherwise, where the prior art gives reason or motivation to make the claimed compositions, creates a prima facie case of obviousness'";[76] and (2) there must be "a showing of 'adequate support in the prior art' for the change in structure."[77]

The CAFC explained that "a known compound may suggest its homolog, analog or isomer because such compounds 'often have similar properties and therefore chemists of ordinary skill would contemplate making them in order to try to obtain compounds with improved properties.'"[78] The court reasoned that "in order to find a prima facie case of unpatentability in such instances, a showing that the 'prior art would have suggested making the specific molecular modifications necessary to achieve the claimed invention' was also required."[79] Depending on what it means to suggest making a specific modification, this line of reasoning may be viewed as contrary to the very admonishments that the Supreme Court gave with respect to setting the nonobvious bar too low. Yet the CAFC concluded that its test was consistent with the legal principles enunciated in *KSR*, and emphasized that "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."[80]

In *Takeda*, the parties agreed as to what the closest prior art was, and the infringer asserted that two modifications were obvious: (1) homologation, which would have required replacing a methyl group with an ethyl group; and

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74 492 F.3d 1350 (Fed. Cir. 2007).

75 The patent at issue claimed four different ethyl substituted pyridyl rings. *Id.* at 1353–54. The prior art that the generic alleged was invalidating was a methyl substituted pyridyl ring. *Id.* at 1354.

76 *Id.* at 1356 (quoting *In re* Dillon, 919 F.2d 688, 692 (Fed. Cir. 1990)).

77 *Id.* (citing *In re* Grabiak, 769 F.2d 729, 731–32 (Fed. Cir. 1985)) (internal quotation marks omitted).

78 *Id.* (quoting *In re* Deuel, 51 F.3d 1552, 1558 (Fed. Cir. 1995)).

79 *Id.*

80 Takeda Chem. Indus., Ltd. v. Alphapharm Pty., Ltd., 492 F.3d 1350, 1357 (Fed. Cir. 2007).

(2) ring-walking, which would have resulted in moving the ethyl substituent to another position on the ring.[81] It is important to note that although the parties agreed what the closest structural compound was, they disputed whether it would have been obvious to select the lead compound.[82]

The CAFC affirmed a finding of nonobviousness and limited the potential breadth of *KSR* by holding that the prior art merely "disclosed a broad selection of compounds any one of which could have been selected as a lead compound for further investigation."[83] The court also found that "the closest prior art compound . . . exhibited negative properties that would have directed one of ordinary skill in the art away from that compound," and therefore it was not obvious to try.[84] Accordingly, the CAFC affirmed three conclusions: (1) the closest prior art compound was not obvious to try; (2) nothing in the prior art provided a reasonable expectation that adding a methyl group to the closest prior art compound would reduce toxicity; and (3) there was no reasonable expectation of success that changing the positions of a substituent on a pyridyl ring would result in beneficial properties discovered.[85] Thus, under *Takeda* a patent applicant or patent holder should, if possible, emphasize the lack of predictability among homologs and isomers with respect to as many properties of those compounds as possible.

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81 *Id.* at 1357. As one would expect, courts have historically been reluctant to invalidate claims to molecules that differ from prior art compound with respect to more than one substituent. *See, e.g.*, Yamanouchi Pharm. Co. v. Danbury Pharmacal, Inc., 231 F.3d 1339, 1344–45 (Fed. Cir. 2000). The *Yamanouchi* court stated:

> Danbury did not show sufficient motivation for one of ordinary skill in the art at the time of invention to take any one of the following steps . . . (2) combining the polar tail from example 44 with the substituted heterocycle from tiotidine, and (3) substituting the carbamoyl (CONH[2]) group in the intermediate compound with the sulfamoyl group (SO[2]NH[2]) to create famotidine.

Id.

82 *Takeda*, 492 F.3d at 1357 n.3.

83 *Id.* at 1359.

84 *Id.*

85 *Id.* at 1360–61. The United States District Court for the District of New Jersey applied *Takeda* in *Pfizer Inc. v. Ivax Pharm., Inc.*, No. 07-CV-00174, 2008 U.S. Dist. LEXIS 99719, at *1 (D.N.J. Dec. 10, 2008). In denying a motion for summary judgment based on alleged obviousness, the court noted that Pfizer raised the following issues: (1) the cited references did not suggest anything about the selectivity of the compounds that the patents-in-suit claimed; (2) the prior art did not disclose the structural features of the claims; (3) there was no showing that the prior art would have suggested making the specific molecular modifications that were necessary to achieve the claimed invention; (4) the prior art did not suggest considering certain stereochemical factors; and (5) there were secondary considerations of nonobviousness. *Id.* at *30–31.

In *Eisai*, the CAFC confronted the issue of whether three prior art references rendered the claims to raberprazole, a drug used to treat ulcers, obvious.[86] The court in *Eisai* emphasized that when claims are directed to chemical compounds, the third *Graham* factor is often the most important because the case for obviousness frequently turns on structural similarities and differences between the claimed compounds and the prior art.[87]

The claims at issue were directed to raberprazole. However, three prior art references disclosed lansoprazole, omeprazole and the treatment of ulcers using lansoprazole.[88] Lansoprazole and raberprazole differ structurally: in lansoprazole, at the 4-position on the pyridine ring, there is a trifluorethoxy substituent (OCH_2CF_3), whereas in raberprazole there is a methoxypropoxy substituent ($OCH_2CH_2CH_2OCH_3$).[89] One might think this structural difference is minimal, but the trial court in *Eisai* found that: (1) although lansoprazole was the closest structural compound, there was a difference between anti-ulcer and gastric acid inhibition; and (2) the prior art taught that the fluorinated substituent of lansoprazole is at best a special path to achieving lipophilicity.[90] The CAFC, affirming the trial court's finding, then emphasized that there was "no discernible reason for a skilled artisan to begin with lansoprazole only to drop the very feature, the fluorinated substituent, that gave this advantageous property" and held that there were insufficient grounds on which to invalidate the patent under 35 U.S.C. § 103.[91] Thus, again the CAFC refrained from applying *KSR* too broadly.[92] Importantly, although the analysis began with a consideration of issues of structure, to buttress its holding, the court also focused on the secondary consideration of nonobviousness including commercial success.[93]

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86 Eisai Co. v. Dr. Reddy's Labs., Ltd., 533 F.3d 1353, 1355 (Fed. Cir. 2008).

87 *Id.* at 1356–57.

88 *Id.* at 1357.

89 *Id.*

90 *Id.* at 1358.

91 *Id.* at 1358, 1359.

92 Coincidentally, lansoprazole, which is the active ingredient in Prevacid, often referred to as a proton pump inhibitor, was itself the subject of patent litigation. Takeda Pharm. Co. v. Teva Pharm. U.S.A. Inc., 542 F. Supp. 2d 342, 345 (D. Del. 2008). In *Takeda*, Teva tried to invalidate claims to lansoprazole and a pharmaceutical composition containing a benzimidazole compound in combination with a basic inorganic salt that was formulated and coated. *Id.* at 357. The court agreed with Teva's identification of the lead compound and Teva's identification of the four areas on the compound on which to focus for modification. *Id.* However, there were three different substituents between the prior art and lansoprazole, and the court concluded that each move was "not insubstantial." *Id*. at 359. Consequently, the court did not find the claims obvious. *Id.*

93 *Takeda*, 542 F. Supp. 2d at 359.

Two district court cases help to define the analytic framework used to determine whether a claim to a structure that is similar to another structure is obvious.

First, in *Proctor & Gamble Co. v. Teva Pharmaceuticals U.S.A., Inc.*,[94] P&G sued Teva to prevent it from marketing a generic version of risedronate sodium.[95] Teva contended that the structural similarities between risedronate and the prior art compound, 2-pyr EHDP, rendered the relevant claims obvious.[96] These compounds are each bisphosphonates that contain a head portion consisting of a hydroxyl group and a tail portion consisting of a pyridine ring; however, they are isomers.[97] Because they are isomers, the only structural difference between the two molecules is the point of attachment of the pyridyl group to the linking carbon.[98] However, the court noted the dissimilar subject matter claimed in the patent at issue and the prior art patent and the following additional differences between the molecules: charge distribution, polarity and hydrogen bonding, as well as the different subject matter claimed in the patent at issue and the prior art patent.[99]

The *Proctor & Gamble* court first considered whether there was any reason to focus on 2-pyr EHDP as a lead compound.[100] The court concluded that while no specific claims in the prior art were directed to the purported lead compound, there were claims that were directed to dissimilar compounds.[101]

Second, *Daiichi Sankyo Co. Ltd. v. Mylan Pharmaceuticals, Inc.*,[102] which involved olmesartan medoxomil, the active ingredient in Benicair® HCT and Azor®, highlights the importance of having evidence of teaching away from

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94 536 F. Supp. 2d 476 (D. Del. 2008).

95 *Id.* at 478–79. The compound used by Teva may be described by the name 2-(3-pyridy1)-1-hydroxyethane diphosphonic acid. *Id.* at 479.

96 *Id.* at 479–80 (noting that Teva alleged invalidity under both 35 U.S.C. § 103 and the doctrine of obviousness-type double patenting).

97 *Id.* at 493.

98 *Id.* (stating that in 2-pyr EHDP, the linking group is attached to the pyridyl group at the 2 position, while in 3-pyr EHDP it is attached at the 3 position).

99 *Id.* The court's notation of these additional factors is somewhat disingenuous since it is rare that compounds of different structures with the potential for hydrogen bonding will not differ with respect to that factor.

100 Proctor & Gamble Co. v. Teva Pharms. U.S.A., Inc., 536 F. Supp. 2d 476, 495 (D. Del. 2008).

101 *Id.* (observing also that one claim did list a compound that could be used as an intermediate compound to produce the lead compound, but one compound of the eight examples was not enough to find obviousness of the claimed lead compound).

102 Nos. 06-3462, 07-3039, and 08-2752, 2009 U.S. Dist. LEXIS 67978 (D.N.J. July 30, 2009).

a claimed invention.[103] As with many inventions in the pharmaceutical sciences, the chemical backbone was known.[104] However, the parties disagreed as to whether the prior art taught away from the use of a hydrophilic group at the 4-position of the imidazole ring.[105] The CAFC concluded that "[t]he prior art evidences more than a general preference for the use of a lipophilic substituent at the 4-position, clearly discouraging a person of ordinary skill from using a hydrophilic group at this position."[106] Thus, the identification of prior art that teaches away from the properties of a selected substituent may suggest that the inclusion of that substituent is not obvious.[107]

By contrast, a third case, *Altana Pharma AG v. Teva Pharmceuticals U.S.A., Inc.*,[108] provides an example of the type of evidence that would suggest a particular modification to make the compound obvious.[109] The compound at issue and the closest prior art differed by the presence of a methoxy group at the 3-position of the pyridine ring in the claimed compound and the presence of a methyl group at that position in the prior art compound.[110] The prior art also taught that in order to design an effective proton pump inhibitor, the compound should have a pKa of 4.[111] Further, the prior art taught various chemical groups including methyl and methoxy groups at the 3-position of the pyridine ring; also that the pKa of the methyl group is 5 at this position, while the pKa of methoxy at this position is 5.[112] The trial court deemed that at the preliminary injunction stage of the case, this prior art was sufficient to provide a preliminary showing that the claim was obvious.[113]

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103 *Id.* at *2–3, *21–22 (D.N.J. July 30, 2009) ("When the prior art 'teaches away' from a particular combination of known elements, the successful combination of those elements is less likely to be obvious.")

104 *Id.* at *20–21. In this case the backbone was an imidazole ring with a biphenyl tetrazole at the 1-position and a straight chain alkyl at the 2-position. *Id.*

105 *Id.* at *22.

106 *Id.* at *22–23.

107 *Id.* at *48 ("When the prior art teaches a preference for substituents with opposite properties, the invention at issue is not obvious.").

108 532 F. Supp. 2d 660 (D.N.J. 2007).

109 *Id.* at 676.

110 *Id.*

111 *Id.* at 678.

112 *Id.* at 679.

113 *Id.*

C. New Formulations and Processing Techniques

In addition to the selection of chemical species and new molecules, the PTO awards patents for pharmaceutical inventions based on new formulations and new processing techniques. However, even in the pharmaceutical industry, there are many techniques that are well known in the art such as micronizing and enteric coatings to increase bioavailability.[114] The USPTO has deemed the application of these types of techniques obvious to try and, thus, has used them as the basis for a finding of obviousness.

Pfizer, Inc. v. Apotex, Inc.,[115] which was decided a few weeks before *KSR*, provides an example of challenges that a patent applicant and patentee face when claims are directed to new formulations.[116] As discussed above, Pfizer's patent was directed to amlodipine besylate, which was commercially known as Norvasc®.[117] The prior art patent did not expressly disclose the besylate salt, benzene sulphanate anion, salts formed from benzene sulphuric acid, or sulphuric acids in general, all of which would be used to make amlodipine besylate.[118]

Among the arguments advanced by Pfizer was that the closest prior art salt ion was structurally different from that of the claimed compound.[119] However, Apotex stole this argument and persuaded the CAFC to find that given the problems with the prior art salt, one of ordinary skill would have looked to a structurally different salt.[120] The CAFC also pointed to a number of other factors that would have led a person of ordinary skill in the art to consider benzene sulphanate, including: (1) acid strength; (2) solubility; (3) a prior art disclosure that aryl sulphuric acids considerably increase the solubility of pharmaceuticals that contain one or more basically reacting nitrogen atoms; (4) prior art refer-

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114 Bioavailability is a measure of how much drug will get absorbed into the blood. Micronization is a technique used in pharmaceutical sciences to reduce the drug's particle size so it has better absorption characteristics. Enteric coating is another technique used in pharmaceutical sciences where a tablet is coated to trigger it to be absorbed in the small intestine, thus avoiding the harsh acids of the stomach.

115 488 F.3d 1377 (Fed. Cir. 2007).

116 *Id*. at 1378 (denying petition for rehearing after *KSR* was decided).

117 Pfizer, Inc. v. Apotex, Inc., 480 F.3d 1348, 1352 (Fed. Cir. 2007). Amlodipine was part of the prior art. *Id.* at 1353. In fact, it was claimed in a prior patent that was filed by Pfizer and that patent stated that pharmaceutical acceptable salts of amlodipine are those formed from acids that form non-toxic acids in addition to salts containing pharmaceutically acceptable anions. *Id.*

118 *Id.* at 1361.

119 *Id.* at 1362.

120 *Id.*

ences that specifically identify besylate salt as the preferred salt form; and (5) an acid addition salt derived from benzene sulphonate that has "excellent pharmacokinetic properties . . . and improved stability."[121] The court concluded that the selection of the salt was obvious, even if there were a possibility that some salts might not work.[122]

In *Bayer Schering Pharma AG v. Barr Laboratories, Inc.*,[123] Barr sought to market a generic version of Bayer's patented oral contraceptive formulation containing micronized drospirenone/ethinyl estradiol that was not enteric coated. Bayer sued Barr, asserting that Barr's micronized formulation infringed Bayer's patent. During the litigation, Barr argued that micronizing a drug to obtain better absorption characteristics would have been obvious to one of ordinary skill in the art. Bayer countered Barr's argument by asserting that drospirenone is a drug that is susceptible to degradation by the harsh acids of the stomach, and therefore it would not have been obvious to micronize the drug without placing an enteric coating on the drug. In finding Bayer's patent invalid, the District Court relied on *KSR*, holding that it would have been obvious to a person of ordinary skill in the art, when having a finite number of methods for delivering oral contraceptives to choose from, to utilize micronized tablets without an enteric coating to test the bioavailability of drospirenone.[124]

In the more recent case of *King Pharmaceuticals, Inc. v. Eon Labs, Inc.*,[125] the District Court for the Eastern District of New York issued an order invalidating two of King's patents relating to Skelaxin® (metaxalone), a blockbuster muscle relaxant. The patents at issue claimed methods of increasing oral bioavailability of metaxalone by administering the drug with food. Although many of King's patent claims were found invalid in view of anticipating prior art, the court applied the *KSR* obviousness standard to claims directed to administering 400 mg of metaxalone four times day with food.

In holding the claims obvious, the court considered the wide range of means that a person of ordinary skill in the field would utilize at the time to obtain the increased bioavailability by administering the drug with food and emphasized that "the proper question to ask in an obviousness analysis is whether a person of ordinary skill in the art, 'facing the wide range of needs created by developments in the field of endeavor, would have seen a benefit to' combining

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121 *Id.* at 1363.

122 *Id.* at 1366.

123 No. 05-cv-2308 (PGS), 2008 U.S. Dist. LEXIS 15917 (D.N.J. March 3, 2008), *aff'd*, 575 F.3d 1341 (Fed. Cir. 2009).

124 *Id.* at *109–10.

125 593 F. Supp. 2d 501 (E.D.N.Y. 2009).

the claimed prior art steps."[126] The court then framed the issue as "whether a person of such skill, confronted with [a reference's] teaching to take one 400 mg tablet of metaxalone four times daily and [a second reference's] suggestion to take metaxalone with food, would have seen a benefit to administering a 400 mg tablet of metaxalone at mealtimes."[127] The court concluded that the answer is yes.[128]

The trend since the *KSR* decision appears that, at least initially, claims for enhancing bioavailability by processing techniques or changing how the pharmaceutical is taken would be viewed as obvious particularly if they utilize known techniques or methods to administer the pharmaceutical. However, in the more recent case of *Roche Palo Alto LLC v. Ranbaxy Laboratories Limited*,[129] the court held that claims directed to the crystalline form of valganciclovir HCl (which corresponds to Roche's antiviral drug Valcyte®) were not obvious over the prior art of record.[130] In not finding that the claims were obvious, the court noted: (1) "the prior art either did not discuss the crystallinity of any compound, or when it did, it was about the crystallinity of a completely different compound"; and (2) the defendant "offered very little evidence to rebut Roche's assertion that valganciclovir HCl in crystalline form is non-obvious and difficult to produce . . . ."[131]

Similarly, in *Unigene Laboratories, Inc. v. Apotex, Inc.*,[132] the court denied a motion for summary judgment in which the defendant deemed the claim at issue obvious because the prior art allegedly taught each of the five components of the claimed nasal calcitonin formulation.[133] The defendant started with the position that one would be motivated to make a composition comparable to the Novartis' Miacalcin® product, which has the same active ingredient calcitonin in the same amount.[134] The defendant then asserted that it would have been obvious to replace other components in Novartis' formulation with the claimed

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126 *Id.* at 511 (citing KSR Int'l Co. v. Teleflex Inc., 550 U.S. 398, 424 (2007)).

127 *Id.*

128 *Id.*

129 No. 06-2003, 2009 U.S. Dist. LEXIS 90804 (D.N.J. Sept. 30, 2009).

130 *Id.* at *4–5.

131 *Id.* at *139.

132 06 CV. 5571 (RPP), 2009 U.S. Dist. LEXIS 78051 (S.D.N.Y. Aug. 31, 2009).

133 *Id.* at *22–23, *46–47. The claim reads "a liquid pharmaceutical composition comprising about 2,200 MRC units of salmon calcitonin, about 20 mM citric acid, about 0.2% phenylethyl alcohol, about .5% benzyl alcohol, and about .1% polyoxyethylene (20) sorbitan monooolaeate." *Id.* at 6.

134 *Id.* at *24.

component.[135] However, the court emphasized that "a patent comprised of multiple elements, like the one here, 'is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art.'"[136] The court further emphasized, "an invention will likely be obvious when it elicits predictable results."[137] The court then determined that the claim was not obvious because the defendant failed to show that the inclusion of the inactive ingredients would generate the result obtained by the claimed formulation when combined with the active ingredient.[138]

D. Purified Isomers from Mixtures

The last types of patent claims to consider are those claims that are directed to isomers that are purified when the racemate is known. In *Aventis Pharma Deustchland GMBH v. Lupin LTD*,[139] the CAFC addressed "whether the 5(S) stereoisomer of ramipril, in a form substantially free of other isomers would have been obvious over the prior art . . . ."[140] Thus, unlike in *Takeda*, the issue was not whether modifications of known structures were obvious, but whether purifying a mixture of known compounds to contain a particular isomer is obvious. Embracing *KSR*, the CAFC noted that although in order to establish that the claims at issue were obvious it would be necessary to "articulate[] reasoning with some rational underpinning to support the legal conclusion of obviousness," there need not be an explicit teaching to purify the 5(S) stereoisomer from a mixture in which it was the active ingredient.[141]

The *Aventis* court provided the following touch points with respect to claims that implicate purification of known mixtures: (1) a purified compound is not always prima facie obvious over the mixture; but (2):

> If it is known that some desirable property of a mixture derives in whole or in part from a particular one of its components, or if the prior art would provide a person of ordinary skill in the art with reason to believe that this is so, the pu-

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135 *Id.* at *26.

136 *Id.* at *26 n.12

137 *Id.* at *26–27 & n.12 (quoting KSR Int'l Co. v. Teleflex Inc., 550 U.S. 398, 418 (2007)).

138 Unigene Labs., Inc. v. Apotex, Inc., 06 CV. 5571 (RPP), 2009 U.S. Dist. LEXIS 78051, at *27–44 (S.D.N.Y. Aug. 31, 2009).

139 499 F.3d 1293 (Fed. Cir. 2007).

140 *Id.* at 1300. The patent purportedly covered Altace®.

141 *Id.* at 1301 (quoting *KSR*, 550 U.S. at 418 (2007)) (internal quotation marks omitted).

> rified compound is prima facie obvious over the mixture even without an explicit teaching that the ingredient should be concentrated or purified.[142]

It held that based on the evidence before the district court, the finding of obviousness was correct.[143]

However, the *Aventis* decision did not usher in an era of presumption that all isolated isomers are obvious over their racemates. In *Sanofi-Synthelabo v. Apotex Inc.*,[144] Apotex challenged the validity of the patent directed to clopidogrel bisulfate, which is more commonly known as Plavix®.[145] The experts for both sides agreed that it would not have been predictable whether for these enantiomers, any differences would have been weak, moderate, or strong with respect to levels of stereoselectivtiy or the different levels of therapeutic activity and toxicity.[146] The experts also agreed "that weak stereoselectivity of biological properties is more common than strong stereoselectivity, . . . that absolute stereoselectivity is rare[,]" and activity and toxicity were more likely to be positively correlated than negatively correlated.[147] These facts, as well as a few others on which the CAFC commented,[148] caused it to affirm the district court, em-

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142 *Id.*

143 *Id.* at 1303. The court also emphasized:

> Ordinarily, one expects a concentrated or purified ingredient to retain the same properties it exhibited in a mixture, and for those properties to be amplified when the ingredient is concentrated or purified; isolation of interesting compounds is a mainstay of the chemist's art. If it is known how to perform such an isolation, doing so "is likely the product not of innovation but of ordinary skill and common sense."

Id. at 1302 (quoting KSR Int'l Co. v. Teleflex Inc., 550 U.S. 398, 402–03 (2007)). The patentee tried to show unexpected results, but the patentee made the mistake of comparison over its isomers and not the prior art known mixture. *Id.*

144 550 F.3d 1075 (Fed. Cir. 2008).

145 *Id.* at 1078. Apotex argued that the following facts were known: (1) the racemate of the claimed composition; (2) that the racemate is composed of enantiomers; (3) the fact that enantiomers can have different levels of biologic activity; and (4) there were well-known chemical techniques for separating enantiomers. *Id.* at 1083.

146 *Id.* at 1087.

147 *Id.*

148 The generic's expert admitted that one could not predict therapeutic activity and toxicity properties without separating and testing the enantiomers. *Id.* Additionally, there was evidence that when compounds are administered through metabolism within the body, the metabolic processes often return the enantiomers to their racemic state. *Id.* Further, there was evidence that among the ten known processes for separating enantiomers each would have required experimentation to determine whether they could have been successful. *Id.* at 1087–89.

phasizing that the unpredictably of the enantiomer referred to the properties of the molecule.[149]

IV. THOUGHTS FOR THOSE IN THE TRENCHES

In light of the *KSR* decision and looking at the recent trends, pharmaceutical inventions in particular, are likely to face many more obviousness rejections and challenges to validity. In order to stave off these rejections and challenges, patent applicants and patent holders may be required to devote additional resources. This reality may become particularly noticeable in this industry because the level of ordinary skill is higher than in other disciplines and any one patent can be worth so much. However, there are a number of approaches that prudent patent practitioners and litigants can pursue in the trenches to lay the foundation to address issues of obviousness.

First, when selecting lead compounds to develop, particularly where there is a very broad genus described in the prior art, inventors and pharmaceutical companies should if possible consider claiming progressively narrower groups of species or intermediates of that broad genus, making groupings based on what the prior art does not describe. They should also emphasize or make apparent that selecting that particular group of species or intermediates as a starting compound to develop was not suggested by the prior art or even that the prior art taught away from it. Further, they should also develop the record with respect to the unpredictability of modifications. This of course must be balanced against enablement issues, and as with any patent application, claims of appropriate scope should be pursued. These strategies would appear to lead claims that are determined to be nonobvious and would be consistent with the ruling of *Sanofi-Synthelabo*.

Second, to improve chances of establishing nonobviousness or reducing attacks during litigation, it will be prudent to get the inventors involved early in

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[149] *Id.* at 1090; *see also* Eli Lilly & Co. v. Zenith Goldline Pharm., Inc., No. IP 99-38-C H/K, 2001 U.S. Dist. LEXIS 18361 (S.D. Ind. Oct. 12, 2001). In *Eli Lilly* the court stated:

> In deciding obviousness under § 103(a), the focus is not on the ability of chemists to imagine a compound, nor on their ability to synthesize a molecule to order, but on whether the prior art provided apparent reason or motivation to take the steps that led to synthesis of the new compound. The unpredictable nature of chemical reactions is especially pronounced, of course, when dealing with medicinal chemistry, where the biological effects of chemical reactions may be exceedingly difficult to predict from the chemical structure of a compound.

Eli Lilly, 2001 U.S. Dist. LEXIS 18361, at *15.

the prosecution and retain their involvement so that the difficulties in developing the invention and devising a nonobvious solution to the problem are clearly captured early on in the prosecution by the patent practitioner.

Third, it may become increasingly important to be able to show unexpected or superior results. If possible they should be included in the specification. However, because this is not always possible, one should also be prepared to expend resources on declarations that support conclusions of unpredictability. The showing of these types of results can establish that an invention goes beyond a combination of known elements yielding predictable results, and it can be used to counter an "obvious to try" argument presented by the U.S. Patent Office or an adverse party to destroy patentability. This approach would seem most fruitful for the bioavailability and isomer type pharmaceutical patent applications, where many of the processing techniques and methods of administering pharmaceuticals have been known for years and there are a finite number of substituents from which to choose. By focusing on unexpected or superior results as compared to the prior art, one should be able to refute arguments that the inventor(s) merely combined known elements. Of course as with any invention, inventor laboratory notebooks and experimental data should be diligently kept to facilitate submission during prosecution.[150]

Fourth, practitioners can still, if applicable, argue that the prior art cited by the Examiner is non-analogous. For art to be analogous, it must be in the field of the inventor's endeavor or reasonably pertinent to the problem facing the inventor to be solved.[151] *KSR* did not eliminate this line of argument, where the practitioner can argue that the prior art is taken from outside the same field of the inventor and solves a different problem than the inventor tried to solve.[152] Additionally, often when an Examiner looks to non-analogous art, she also uses hindsight reconstruction. Accordingly, the practitioner should also be wary of those types of rejections as well.

Fifth, the *Graham* factors dealing with secondary considerations of nonobviousness, including commercial success, also remain intact after the decision in *KSR*.[153] Pharmaceutical companies should thus be prepared to emphasize the unpredictability of the prior art and the unexpected advantages of the new pharmaceutical compared to other products available at the time and point

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150 They are also of value when trying to establish a date of conception should that ever become an issue.

151 KSR Int'l. Co. v. Teleflex Inc., 550 U.S. 398, 411 (2007).

152 *Id.* at 420.

153 *Id.* at 426.

to the commercial success of their product as evidence of secondary considerations of nonobviousness.

Finally, the practitioner should also consider avoiding extensive background sections characterizing the state of the prior art and stating problems in the art that the inventor is trying to solve when drafting patent applications. These statements will undoubtedly be used against the patentee during litigation as well as by examiners during prosecution. Extensive background sections may enable courts and the USPTO to point to an inventor's own words as evidence that the level of ordinary skill in the art is high and so is their "common sense" thus bolstering a finding of obviousness.

V. CONCLUSION

Given the trend of cases in the pharmaceutical field since *KSR*, patent practitioners should consider revisiting their patent strategy accordingly. To overcome obviousness rejections in this era, inventors and pharmaceutical companies should consider laying the foundation to show that their selected or starting compounds are not apparent from the teaching of the prior art. They also should be prepared to rely more heavily on unexpected results and secondary considerations of nonobviousness, and to provide comparative test results to show unexpected properties of the invention or provide other scientific and technical evidence to show unpredictability. Nevertheless, pharmaceutical companies with truly inventive selections, new compounds, new formulations, or new isolations that are not obvious, will if contained in a properly drafted patent application, survive and be able to increase the value of the pharmaceutical company.