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OBVIOUS FALLACY: IMPROVING THE STANDARD OF OBVIOUSNESS FOR CHEMICAL COMPOUNDS TO MORE ACCURATELY REFLECT COMMON PRACTICE IN THE ART

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INTRODUCTION

Patent protection for newly discovered chemical compounds is one of the most important priorities for a successful pharmaceutical company. In order to obtain a patent, a chemical compound must be nonobvious at the time of its invention.[2] As compared with obviousness evaluations in chemical cases, application of the law of obviousness to inventions in the electrical and mechanical sciences is fairly straightforward. Obviousness in the chemical arts has been difficult to determine in light of chemistry's inherent unpredictability. The properties of a chemical compound can be dramatically altered with only slight structural changes. Courts have attempted to address this difficulty by further defining the law of chemical obviousness to include subtests relating to structural similarity and motivation to make the claimed composition. However, these tests have failed at simplifying the obviousness test for chemical compounds,

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[2] 35 U.S.C. § 103(a) (2004) ("A patent may not be obtained though the invention is not identically disclosed or described as set forth 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 a whole would have been obvious at the time the invention was made to 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.").

particularly in light of the significant increase in combinatorial chemistry techniques in the pharmaceutical industry. Due to the enormous costs associated with drug research and discovery, the law of obviousness of chemical compounds needs to be further defined to provide pharmaceutical companies with sufficient notice as to whether their newly created compounds will be refused patent protection due to obviousness in view of the prior art.

BACKGROUND

The patent laws were enacted to prevent publicly available information from being confiscated and monopolized.[3] When a patent is obtained, the inventor receives the right to exclude others, and the public obtains the benefit of the disclosure.[4] Three important requirements to obtain a patent on an invention are utility,[5] novelty,[6] and nonobviousness.[7] The novelty and utility requirements can typically be readily satisfied for chemical compound inventions, as an invention only needs to be minimally useful and comparatively minor structural changes can render an invention novel.[8] Consequently, nonobviousness frequently becomes the critical element in ultimately determining chemical patentability.[9]

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[3] *See* 60 AM. JUR. 2D *Patents* § 6 (2009).

[4] 60 AM. JUR. 2D *Patents* § 2 (2009).

[5] *See* 35 U.S.C. § 101 (1952).

[6] *See* 35 U.S.C. § 102 (2002).

[7] *See* 35 U.S.C. § 103 (2004).

[8] ROBERT PATRICK MERGES & JOHN FITZGERALD DUFFY, PATENT LAW AND POLICY: CASES AND MATERIALS 612 (4th ed. 2007).

[9] *Id*.

I. The Law of Obviousness Generally

The law of obviousness is codified in Title 35 of the United States Code ("U.S.C."). Under § 103 (a) of the U.S.C., "patent may not be obtained though the invention is not identically disclosed or described [in the prior art], if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a 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."[10] The nonobviousness requirement can be described as the "nontriviality" condition; in other words, an invention does not deserve patent protection although it may be new and useful if it embodies only a trivial modification of the prior art. Obviousness is a legal question based on fundamental factual determinations.[11]

In order to understand obviousness, it is crucial to define a person of ordinary skill in the art. The Manual of Patent Examining Procedure describes five factors that can be used to determine the level of ordinary skill in the art: (1) the type of problems encountered in the art, (2) prior art solutions to the problems, (3) rapidity with which innovations are made, (4) sophistication of the technology, and (5) the educational level of active workers in the field.[12] The person of ordinary skill in the art is a hypothetical person and does not necessarily embody the level of skill of the inventor himself.[13]

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[10] 35 U.S.C. § 103(a) (2008).

[11] *See* Richardson-Vicks, Inc. v. Upjohn Co., 122 F.3d 1476, 1479 (Fed. Cir. 1997).

[12] MANUAL OF PATENT EXAMINING PROCEDURE § 2141.03 (8th ed. 2001); *See, e.g., In re* GPAC, Inc., 57 F.3d 1573, 1579 (Fed. Cir. 1995); Custom Accessories, Inc. v. Jeffrey-Allan Indus., Inc., 807 F.2d 955, 962 (Fed. Cir. 1986); Envtl. Designs, Ltd. v. Union Oil Co., 713 F.2d 693, 696 (Fed. Cir. 1983).

[13] *See* Cool-Fin Elec. Corp. v. Int'l Elec. Research Corp., 491 F.2d 660, 662 n.7 (9th Cir. 1974).

A. Development of the Law of Obviousness

1. The Graham Factors

The Supreme Court in 1966 set forth several factors that can be used to determine obviousness in view of the prior art.[14] In *Graham v. John Deere Co.*, the Court held a patent on a "Clamp for Vibrating Shank Plows," which included a combination of old mechanical elements designed to absorb shock from plow shanks as they moved through rocky soil in order to prevent damage to the plow, as invalid for obviousness.[15] The Court held that the scope and content of the prior art, the level of ordinary skill in the art, the differences between the claimed invention and the prior art, and objective evidence of nonobviousness should be used to determine nonobviousness.[16] Objective evidence of nonobviousness may include commercial success, long-felt but unresolved needs, and the failure of others.[17] However, the Court emphasized that the obviousness inquiry is clearly fact-specific and an analysis including all of these factors was not determinative.[18]

Although *Graham* provided additional considerations to determine nonobviousness, it did not construct bright-line rules for the nonobviousness requirement. Accordingly, an invention does not need to be completely predicted by prior art to be considered obvious.[19] In fact, the

[14] *See* Graham v. John Deere Co. of Kansas City, 383 U.S. 1, 17 (1966) (holding that objective evidence of nonobviousness can be used to determine nonobviousness).

[15] *Id.* at 18.

[16] *Id.* at 17.

[17] *Id.*

[18] *Id.*

[19] *In re* O'Farrell, 853 F.2d 894, 903 (Fed. Cir. 1988) (stating that obviousness does not involve absolute predictability but only a reasonable probability of success).

Federal Circuit in *In re O'Farrell* noted that "[o]bviousness does not require absolute predictability of success."[20] Obviousness only requires a reasonable expectation of success.[21]

2. The Teaching, Suggestion or Motivation Test

In order to examine whether there was a reasonable expectation of success with regard to a particular invention, courts have applied the Teaching, Suggestion, or Motivation test ("TSM test").[22] A teaching, suggestion, or motivation means there was some reason or suggestion to combine known elements in the prior art to form the claimed invention.[23] In *In re Kahn,* the Court of Appeals explained that an analysis of the TSM test involves examining the combined teachings, knowledge of one of ordinary skill in the art, and the nature of the problem to be solved as a whole.[24] By looking at these factors together, the court can determine what would have been suggested to those of ordinary skill in the art at the time that the invention was made.[25] Additionally, the teaching, suggestion, or motivation does not need to be found explicitly in the prior art, but it may be inferred by looking at the prior art as a whole.[26]

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[20] *O'Farrell*, 853 F.2d at 903.

[21] *Id.*

[22] Winner Int'l Royalty Corp. v. Wang, 202 F.3d. 1340, 1348 (Fed. Cir. 2000) (noting that the teaching, suggestion, or motivation test attempts to locate some reason that would have motivated one skilled in the art to modify the prior art to create the new invention). However, the teaching, suggestion, or motivation test was changed in *KSR* (*see infra* note 67).

[23] *Winner Int'l Royalty Corp.*, 202 F.3d. at 1348.

[24] *See In re* Kahn, 441 F.3d 977 (Fed. Cir. 2006).

[25] *Id.* at 986 (holding that the teaching, suggestion, or motivation to modify the prior art may be inferred from viewing the prior art as a whole).

[26] *Id.*

3. Teaching Away

Although an invention merely combines known elements, a patentee may overcome an assertion of obviousness by showing that the prior art teaches away from combining the known elements.[27] In *United States v. Adams*, the Supreme Court held that a patent for a water activated battery, which operated on an open circuit comprising two electrodes, one of magnesium and one of cuprous chloride, was nonobvious even though it simply combined previously known elements in the prior art.[28] The Court emphasized that a person of ordinary skill in the art would have thought that the batteries, which operated on an open circuit and heated in normal use, were not practical. And, water activated batteries were successful only when combined with electrolytes detrimental to the use of magnesium.[29] These accepted principles would have strongly discouraged the person of ordinary skill in the art from attempting to create this particular battery.[30] Therefore, the discovery of a successful means of combining known elements is more likely to be considered nonobvious when the prior art teaches away from their combination.[31]

[27] United States v. Adams, 383 U.S. 39, 51 (1966) (indicating that when the prior art teaches away from combining known elements, the resulting combination is more likely to be nonobvious).

[28] *Id.* at 42, 48.

[29] *Id.* at 51-52.

[30] *Id.* at 52.

[31] *Id.*

4. Unexpected Results

An inventor may also demonstrate that an invention which merely combines known elements in the prior art is nonobvious by providing evidence of "unexpected results."[32] According to *In re Soni*, an inventor may "show that the claimed invention exhibits some superior property or advantage that a person of ordinary skill in the relevant art would have found surprising or unexpected."[33] Therefore, an invention may be held to be nonobvious if the inventor can show that the invention exhibits properties that would have been unanticipated at the time of invention by a person with ordinary skill in the art.[34] Unexpected results must be established with factual data; a mere contention or conclusory statement that the invention exhibits unanticipated and superior properties is not enough to overcome a finding of obviousness.[35]

II. Obviousness of Chemical Compounds

A. Obviousness Pre-KSR

The above-described principles apply generally to obviousness determinations. However, it is complicated to establish obviousness in the chemical arts due to chemistry's intrinsic unpredictability. In many circumstances, a small and seemingly insignificant change in a chemical structure may generate a compound with remarkably different properties. The Graham factors and the TSM test have proved insufficient at providing a workable formula for

[32] *In re* Soni, 54 F.3d 746, 750 (Fed. Cir. 1995) (holding that evidence of "unexpected results" may provide evidence that an invention is nonobvious).

[33] *Id.*

[34] *Id.*

[35] *Id.* at 752.

determining chemical obviousness. Accordingly, courts have attempted to normalize the obviousness standard for chemical compounds by further delineating the requirements. Some of the earliest precedent regarding the obviousness of chemical compounds derives from two early seminal cases: *In re Hass* and *Application of Henze*.[36] The resulting principle of law derived from these two cases is conventionally known as the Hass-Henze Doctrine.[37]

1. The Hass-Henze Doctrine

In re Hass involved an appeal to the Court of Customs and Patent Appeals, predicated on the Board of Patent Appeals' rejection of Hass' patent application.[38] In his patent application, Hass claimed a genus of compounds which included a homologue,[39] 2–nitro–2–pentene, of a compound previously disclosed in the prior art.[40] The Board rejected Hass' claims because there was no critical difference between the properties of the prior art compound and Hass' claimed homologue.[41] Hass argued that it was not necessary to establish any material difference in the properties of the claimed homologue and the prior art compound because the claimed homologue

[36] *In re* Hass, 141 F.2d 122 (C.C.P.A. 1944); *Application of* Henze, 181 F.2d 196 (C.C.P.A. 1950).

[37] *See* Helmuth C. Wegner, *Prima Facie Obviousness of Chemical Compounds*, 6 AIPLA Q. J. 271 (1978) (discussing the evolution of the Hass-Henze doctrine, which was named after *In re* Hass and the *Application of* Henze).

[38] *Hass*, 141 F.2d at 122.

[39] "The term homologue is used to describe a compound belonging to a series of compounds differing from each other by a repeating unit, such as a methylene group, a peptide residue, etc." International Union of Pure and Applied Chemists, *Glossary of Terms Used in Medicinal Chemistry* (1998), *available at* http://www.chem.qmul.ac.uk/iupac/medchem/ah.html#a9 (last visited Jan. 15, 2009).

[40] *Hass*, 141 F.2d at 122-23 (holding that novelty alone does not cause a chemical compound to be patentable over the prior art).

[41] *Id.* at 123.

was novel.[42] The court disagreed with Hass' argument because novelty alone, without non-obviousness, does not render a compound patentable over the prior art.[43] A person skilled in the art would have been motivated to make the claimed homologue since:

> It is well understood by chemists that the members of a homologous series of chemical compounds possess the same principal characteristics; that generally the chemical and physical properties of the individual members vary gradually from member to member; and that knowledge of the properties and chemical behavior of one of the members of the series suggests to the chemist the properties and chemical behavior of the other members of the series.[44]

Consequently, the decision of the board was accordingly affirmed.[45]

A few years later, the Court of Customs and Patent Appeals decided the *Henze* case on similar grounds. The Board of Patent Appeals held that Henze's claimed compound, 5–isopropoxymethyl–5–phenylhydrantoin, was obvious in view of prior art containing the homologue, 5–ethoxymethyl–5–phenylhydratoin.[46] The prior art stated that 5–ethoxymethyl–5–phenylhydratoin caused convulsions at moderate doses, and the range between an effectual and lethal dose was too narrow for 5–ethoxymethyl–5–phenylhydratoin to be commercially viable.[47] Conversely, the compound 5–isopropoxymethyl–5–phenylhydrantoin was shown to have been

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[42] *Hass*, 141 F.2d at 123.

[43] *Id.* at 125.

[44] *Id.* (*citing* Holeman & Walker, Textbook of Organic Chemistry, 5th ed., 1920. 41-42; Paul Karrer, Organic Chemistry, 1938, 23).

[45] *Id.* at 126.

[46] *Henze*, 181 F.2d at 198 (holding that an invention must show that a prior art did not have the same properties as the claimed compound).

[47] *Id.* at 200.

successful as an anticonvulsant with low toxicity.[48] Henze's 5–isopropoxymethyl–5–phenylhydrantoin was rejected as obvious in view of the prior art containing 5–ethoxymethyl–5–phenylhydratoin, even though the prior art made no mention of 5–ethoxymethyl–5–phenylhydratoin's anticonvulsant properties at any level other at moderate levels.[49]

The court held that Henze failed to show that 5–isopropoxymethyl–5–phenylhydrantoin possessed unexpected and advantageous properties not found in the prior art compound 5–ethoxymethyl–5–phenylhydratoin.[50] Henze attempted to assert that it would be sufficient to prove that 5–isopropoxymethyl–5–phenylhydrantoin had properties which were not known to be properties possessed by 5–ethoxymethyl–5–phenylhydratoin.[51] The court rejected this rationale, stating that Henze made no showing that 5–ethoxymethyl–5–phenylhydratoin would not exhibit similar anticonvulsant properties under the same dosage conditions.[52] It was necessary that Henze prove that the prior art compound does not exhibit the same properties of the claimed compound under the same conditions.[53] Again, the assumption underlying this decision is that a chemist skilled in the art would know that homologues typically possess similar properties, and the applicant has the burden of showing that a homologue possesses unexpected properties which make it patentable over the prior art.[54] Essentially, the *Hass-Henze Doctrine* indicates that if an

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[48] *Henze*, 181 F.2d at 200.

[49] *Id.*

[50] *Id.* at 201.

[51] *Id.* at 200.

[52] *Id.* at 202.

[53] *Henze*, 181 F.2d at 202.

[54] *Id.* at 201.

examiner finds a compound in the prior art that is close enough to the claimed compound such that it would motivate a person skilled in the art to make the claimed compound (e.g., a homologue), then the claimed compound is assumed to be obvious unless evidence is provided which shows that the claimed compound possessed unexpected properties.[55]

2. Structural Similarity

The *Hass-Henze Doctrine* was considered good law until *Henze* was explicitly overruled in *Application of Stemniski*. In *Stemniski*, the Court held that an inventor does not need to prove that a prior art homologue to the claimed compound with no disclosed utility possesses properties that are materially different from the claimed compound at issue in order to render the claimed compound patentable over the prior art.[56] Although this portion of the *Henze* decision was overruled, courts continued to use a "structural similarity" test to address the issue of obviousness as shown in *In re Dillon*.[57] In this case, the Court of Appeals held that obviousness could be shown by "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."[58] An obviousness rejection based on structural similarity and function means that there was sufficient motivation for a person of ordinary skill in the art to create the

[55] Harold C. Wegner, POST-KSR CHEMICAL OBVIOUSNESS IN LIGHT OF PFIZER V. APOTEX 8 (2007), *available at* http://www.patenthawk.com/blog_docs/070613_PostKSRChemical Obviousness.pdf (last visited Jan. 14, 2009).

[56] *Application of* Stemniski, 444 F.2d 581, 587 (C.C.P.A. 1971).

[57] *In re* Dillon, 919 F.2d 688 (Fed. Cir. 1990) (noting that a compound may be rejected as obvious in view of the prior art if the claimed compound is structurally similar to the prior art compound and there was motivation to modify the prior art to achieve the claimed compound).

[58] *Id.* at 692.

new compound with the expectation that the new compound would exhibit properties similar to that of a prior art compound because of their structurally similarity.[59]

3. Unexpected Properties

Courts also continued to recognize that obviousness based on structural similarity between a new compound and a prior art compound may be overcome by a showing that the new compound exhibited unexpected properties.[60] In *Application of Papesch*, the inventor claimed a family of compounds which included the compound 2,4,6-triethylpyrazolo(4,3-d)-4,5,6,7-tetrahydropyrimidine-5,7-dione.[61] It was undisputed that this compound was obvious due to structural similarity in light of a prior art compound 2,4,6-trimethylpyrazolo(4,3-d)-4,5,6,7-tetrahydropyrimidine-5,7-dione, since these two compounds differ only in that the prior art compound has three methyl groups where the claimed compound has three ethyl groups.[62] However, the inventor provided test results that demonstrated that the claimed triethyl compound was an active anti-inflammatory agent, whereas the prior art trimethyl compound did not exhibit any anti-inflammatory properties.[63] A close similarity in structure alone does not render a compound obvious.[64] The Court held that the properties of compounds may and should be taken

[59] *Dillon*, 919 F.2d at 692

[60] *Application of* Papesch, 315 F.2d 381 (C.C.P.A. 1963) (stating that a compound may not be held obvious if the inventor can provide evidence that the claimed compound possessed unexpected properties).

[61] *Id.*

[62] *Id.*

[63] *Id.* at 383.

[64] *Id.* at 391.

into account when analyzing obviousness.[65] A compound's structure and its physical, chemical, and biological properties cannot be separated; thus, when proving obviousness, a chemical compound must be considered as a whole.[66]

B. Flexible Teaching, Suggestion, or Motivation Test in *KSR*

In 2007, the Supreme Court made a decision that would significantly affect the obviousness standard for all inventions in *KSR Int'l Co. v. Teleflex, Inc.* *KSR* concerned a patent for an "Adjustable Pedal Assembly with Electric Throttle Control" which was licensed to Teleflex.[67] The claimed invention included an electronic sensor placed on the pivot point of an adjustable accelerator pedal.[68] The sensor detected the position of the pedal and sent this information to a computer which controlled the amount of fuel injected into the engine.[69] Teleflex claimed that KSR infringed the patent when KSR developed an adjustable mechanical pedal with a modular sensor for Ford Motor Company.[70] KSR argued that the Teleflex patent was obvious in light of the relevant prior art.[71] The District Court granted summary judgment for KSR because there was little difference between the prior art and the claimed invention.[72]

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[65] *Papesch*, 315 F.2d at 391.

[66] *Id.*

[67] KSR Int'l Co. v. Teleflex, Inc., 550 U.S. 398, 399 (2007) (holding that the "teaching, suggestion, or motivation" (TSM) test should be flexibly applied, not as "rigid and mandatory formulas").

[68] *Id.* at 399.

[69] *Id.* at 398.

[70] *Id.* at 399.

[71] *Id.*

[72] *KSR*, 550 U.S. at 399-400.

Additionally, the District Court found that the relevant prior art satisfied the Teaching Suggestion or Motivation (TSM) test, and the claimed invention would have been obvious to a person of ordinary skill in the art.[73] The Court of Appeals reversed the district court's decision, stating that the district court did not apply the TSM test strictly enough.[74] The Court of appeals noted that "the District Court's recourse to the nature of the problem to be solved was insufficient because, unless the prior art references addressed the precise problem that the patentee was trying to solve, the problem would not motivate an inventor to look at those references."[75]

The Supreme Court reversed the decision of the Court of Appeals, agreeing with the District Court that the claimed invention would have been obvious to one of ordinary skill in the art.[76] The Supreme Court stated that the Court of Appeals applied the TSM test too rigidly, and criticized the Court of Appeals for indicating the District Court had not applied the TSM test strictly enough.[77] The Supreme Court disapproved of the Court of Appeal's assertion that the prior art must necessarily include a discussion of the exact problem the invention was created to address.[78] The Court of Appeals thought the District Court incorrectly stated that the nature of the problem to be solved satisfied the TSM test.[79] The Court of Appeals indicated that unless the

[73] *KSR*, 550 U.S. at 399-400.

[74] *Id.*

[75] *Id.*

[76] *Id.*

[77] *Id.* at 415.

[78] *KSR*, 550 U.S. at 420.

[79] *Id.* at 400.

prior art references addressed the specific problem that the inventor was attempting to solve, the inventor would not be motivated to consider those references.[80] The Supreme Court disagreed, stating "[w]e 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."[81]

In deciding the *KSR* case, the Supreme Court did not substantially change the TSM test. In fact, the Supreme Court commended the introduction of the TSM test into the obviousness inquiry. The Supreme Court noted, "[w]hen it first established the requirement of demonstrating a teaching, suggestion, or motivation to combine known elements in order to show that the combination is obvious, the Court of Customs and Patent Appeals captured a helpful insight."[82] The Supreme Court repeatedly cautioned against the use of a rigid, pedantic application of the TSM test that the Court of Appeals recommended.[83] The Supreme Court noted:

> Helpful insights, however, need not become rigid and mandatory formulas; and when it is so applied, the TSM test is incompatible with our precedents. The obviousness analysis cannot be confined 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. The diversity of inventive pursuits and of modern technology counsels against limiting the analysis in this way.[84]

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[80] *KSR*, 550 U.S. at 400.

[81] *Id.* at 415.

[82] *Id.* at 418.

[83] *Id.* at 419.

[84] *Id.*

C. Obviousness of Chemical Compounds Post-*KSR*

As a result of *KSR*, determining the obviousness of chemical compounds became increasingly uncertain. It has been speculated that the flexible TSM test supported by the Court in *KSR* would strengthen the ability of generic drug companies to challenge the validity of some pharmaceutical patents.[85] Although many pharmaceutical patents held by major drug companies involve the invention of innovative new drug compounds, many patents simply cover the homologues, salts, metabolites, or new formulas of prior art compounds including time-release capsules, new combinations of old drugs, and larger doses which can be taken less frequently.[86] These patents are a critical part of the innovation companies' strategy for prohibiting generic drug companies from making minor changes to the innovative new patented drugs and claiming them as their own.[87] It has been argued that *KSR*'s flexible TSM test will easily allow generic drug companies to prove that the homologues, salts, metabolites, and new formulas would have been obvious at the time they were made.[88]

In addition to the problem of easing the way for generic drug companies to prove that patented compounds were obvious, it has been argued that *KSR* essentially changed the long-standing rigid approach of evaluating the obviousness of chemical compounds to a new flexible approach inconsistent with the prior case law. Under the so-called "old rigid approach," patent examiners would be required to find structural similarity between the claimed compound and a

[85] Rebecca Eisenberg, *Pharma's Nonobvious Problem*, 12 LEWIS & CLARK L. REV. 375, 377 (2008).

[86] *Id.*

[87] *Id.*

[88] *Id.*

prior art compound.[89] This approach frequently allowed claimed compounds which are not structurally similar to the prior art to automatically be considered nonobvious, even if there may have been some motivation in the prior art to make the claimed compound.[90] For example, in the case of *In re Deuel*, the Court of Appeals indicated that a DNA sequence encoding a polypeptide was nonobvious over prior art which disclosed a partial amino acid sequence.[91] Even though the prior art provided sufficient motivation for a person skilled in the art to clone the DNA sequence, the partial amino acid sequence was not "structurally similar" to the claimed DNA sequence.[92] Ultimately, the court held that the DNA sequence was nonobvious.[93] In the absence of a rigid formula of structural similarity, the Court of Appeals would have been able to find the DNA sequence obvious since there was explicit motivation to make the partial amino acid sequence in the prior art. Therefore, it has been argued that the flexible TSM formula articulated in *KSR* is a deviation from prior precedent.

On the other hand, it has been suggested that the *KSR* decision did not substantially change the obviousness inquiry with regard to chemical compounds.[94] It is contended that by

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[89] Eisenberg, *supra* note 85.

[90] *Id.*

[91] *In re* Deuel, 51 F.3d 1552, 1556 (Fed. Cir. 1995) (holding that motivation to combine the prior art does not render a compound obvious without structural similarity. If the case had been decided using the flexible teaching, suggestion, or motivation test in *KSR*, the court may have reached a different result given that the structural similarity test need not be rigidly applied).

[92] *Id.* at 1557.

[93] *Id.* at 1559.

[94] *See generally* Jonathan M. Spenner, *Obvious-to-Try: Obviousness of Chemical Enantiomers in View of the Pre- and Post-KSR Analysis*, 90 J. PAT. & TRADEMARK OFF. SOC'Y 475 (2008) (arguing that the *KSR* decision may have been a mere anomaly).

rejecting the Court of Appeals' rigid application of the TSM test, the Supreme Court was simply instructing the Court of Appeals to follow its own precedent.[95] Prior to *KSR*, a flexible TSM test was employed to determine the obviousness of chemical compounds.[96] For example, in the case of *Forest Labs., Inc. v. Ivax Pharms., Inc.*, the Court of Appeals held that a claimed enantiomer[97] was nonobvious over the disclosure of the racemic mixture[98] found in the prior art.[99] The Court held that an inventor would not have been motivated to attempt a difficult racemate separation rather than simply try to discover a new compound and the claimed enantiomer was nonobvious.[100] Consequently, the Court failed to make the rigid assumption that enantiomers which were separated from the racemic mixture were obvious over the prior art.[101]

D. *Eisai v. Dr. Reddy's*: Active Site Substitution is "Per Se" Nonobvious

There were clearly conflicting opinions regarding the affects of *KSR* on the obviousness in pharmaceutical cases. In 2008, however, the Court of Appeals had a chance to directly

[95] Spenner, *supra* note 94, at 514.

[96] *Id.*

[97] Enantiomers are molecules having "the same conductivity but differ[ing] in the arrangement of atoms in space . . . that are nonsuperposable mirror images of each other." ERIC V. ANSLYN & DENNIS A. DOUGHERTY, MODERN PHYSICAL ORGANIC CHEMISTRY 299 (John Murdzek ed., University Science 2006).

[98] A racemic mixture is "a 50:50 mixture of enantiomers." ANSLYN & DOUGHERTY, *supra* note 97, at 300.

[99] *See* Forest Labs., Inc. v. Ivax Pharms., Inc., 501 F.3d 1263, 1265-66 (Fed. Cir. 2007) (noting that enantiomers separated from a racemic mixture known in the art are not necessarily obvious).

[100] *Id.* at 1267.

[101] *Id.*

address this question in *Eisai Co. Ltd. v. Dr. Reddy's Labs., Ltd.*[102] Eisai had a patent ("the '552 Patent") on rabeprazole, the active ingredient in Aciphex, shown to be an effective drug for treating ulcers.[103] In order to be able to manufacture a generic version of Aciphex before the end of the patent term, Dr. Reddy's Laboratories ("Dr. Reddy's") and Teva Pharmaceuticals ("Teva") filed Abbreviated New Drug Applications ("ANDA") under the Hatch-Waxman Act.[104] As a result, Eisai filed suit against Dr. Reddy's and Teva for patent infringement since the filing of an ANDA is a legally recognized form of patent infringement.[105] At the trial court, Dr. Reddy's and Teva were found to infringe the '522 Patent, and they appealed the court's judgment.[106] Specifically, Teva asserted that the '552 Patent was invalid for obviousness over a European patent and a United States patent ("the '431 Patent") claiming, as well as an article describing, the ulcer-treating compound lansoprazole.[107]

The chemical formulas of lansoprazole (R-OCH_2CF_3) and rabeprazole (R-$OCH_2CH_2CH_2OCH_3$), where the R-core structure is identical in both molecules, differ only in one substituent group, the trifluoroethoxy substituent (-OCH_2CF_3) for lansoprazole compared to the methoxypropoxy substituent (-$OCH_2CH_2CH_2OCH_3$) for rabeprazole.[108] Lansoprazole was

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[102] *See* Eisai Co. Ltd. v. Dr. Reddy's Labs., Ltd., 533 F.3d 1353, 1362 (Fed. Cir. 2008) (holding that the claimed compound was nonobvious in view of the prior art because the claimed compound was modified at the particular substituent which activated the prior art compound).

[103] *Id.* at 1356.

[104] *Id.*

[105] *Id.* (*citing* Glaxo Group Ltd. v. Apotex, Inc., 376 F.3d 1339, 1344 (Fed. Cir. 2004)).

[106] *Id.* at 1356.

[107] *Eisai*, 533 F.3d at 1356-57.

[108] *Id.* at 1357.

known to possess qualities, including a low molecular weight and lipophilicity, which a person skilled in the art of drug discovery would recognize as positive characteristics for a potential drug candidate.[109] Additionally, lansoprazole was determined to be twenty times more effective than another compound of similar structure, omeprazole, in treating ulcers.[110]

Clearly concerned about the affect of *KSR* on the determination of obviousness of chemical compounds, the Court explained:

> The Supreme Court's analysis in *KSR* thus relies on several 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." In *Ortho-McNeil Pharmaceutical, Inc. v. Mylan Laboratories, Inc*., 520 F.3d 1358, 1364 (Fed. Cir. 2008), this court further explained that this "easily traversed, small and finite number of alternatives . . . might support an inference of obviousness." 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.[111]

The Court noted that the *KSR* decision did not significantly change the obviousness inquiry with respect to chemical compounds.[112]

The Court began its obvious inquiry by identifying lansoprazole as the lead compound

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[109] *Eisai*, 533 F.3d at 1358.

[110] *Id.*

[111] *Id.* at 1359.

[112] *Id.* at 1358.

since the data presented indicated that lansoprazole would make a good starting candidate for anti-ulcer drugs.[113] The Court then attempted to discover some motivation in the prior art for a person skilled in the art to modify lansoprazole to achieve rabeprazole.[114] The prior art European patent containing lansoprazole indicated that lansoprazole's fluorinated substituent gave the compound its increased lipophilicity, which made it a particularly favorable drug candidate.[115] Additionally, Teva's expert witness at trial provided testimony that fluorinated-substituted groups increase lipophilicity.[116] The Court pointed out that lansoprazole's advantageous property, namely its increased lipophilicity, could be attributed to the fluorinated substituent.[117] Consequently, the Court reasoned that a person skilled in the chemical arts would not have considered the elimination or alteration of the same substituent group which gave lansoprazole its beneficial properties to be an identifiable, predictable solution.[118] Although lansoprazole and rabeprazole were structurally similar, the trial court's determination of nonobviousness was affirmed on appeal due to the lack of motivation for a person skilled in the art to modify lansoprazole at the activating substituent group.[119]

III. Compounds Modified at the Active Site Should Be Considered "Ad Hoc"

While it is certainly debatable whether the Court of Appeals in *Eisai* reached the correct

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[113] *Eisai*, 533 F.3d at 1358.

[114] *Id.*

[115] *Id.*

[116] *Id.*

[117] *Id.*

[118] *Eisai*, 533 F.3d at 1358.

[119] *Id.*

conclusion regarding the obviousness of rabeprazole in view of lansoprazole, its reasoning for the ultimate conclusion of nonobviousness is troublesome. The Court indicated that there was no evidence in the record that would motivate a person skilled in the chemical arts to modify the fluorinated substituent group of lansoprazole when that exact group gave the compound its superior properties in comparison to other compounds with the same core structure. Essentially, the argument suggested that chemists skilled in the art, after realizing the effectiveness of a compound following the successful addition of a particular substituent group in a given location, would not further attempt to modify that compound at the same location to improve its efficacy. The logical conclusion which flows from that argument is that a novel compound which is known to possess favorable properties as a drug candidate for a specific human condition will never be obvious in view of a structurally similar prior art compound used for treating that same condition if the novel compound was synthesized solely by altering the activating substituent site. In other words, altering a compound at the location of the particular activating substituent can never be obvious. This represents a fundamental misconception of the drug discovery process. The danger underlying the *Eisai* decision is not the ultimate conclusion of nonobviousness but rather the reasoning behind that decision.

Although chemists regularly synthesize a drug candidate compound with a core structure not previously known to possess therapeutic properties, they will often begin with a core structure which is known to successfully treat a given condition and then subsequently alter the substituent groups.[120] By altering the substituent groups of a compound selected for

[120] *See* ALFRED BURGER, A GUIDE TO THE CHEMICAL BASIS OF DRUG DESIGN, 15 (Wiley-Interscience, Inc. 1983) ("The pattern of accidental or semiplanned drug discovery followed by systematic variation of the 'lead' has been repeated time and again."); 1 C.J. CAVALLITO, MEDICINAL CHEMISTRY 233 (Alfred Burger ed., Wiley-Interscience, Inc. 1957) ("New drug discovery may be considered broadly in terms of two kinds of investigational activities,

experimentation due to some desirable properties, chemists strive to increase the efficacy and decrease the toxicity of the compound.[121] Even if the addition of a particular substituent group increased the therapeutic properties of the compound, chemists will frequently replace this group with other substituent groups which can be reasonably expected to possess the similar or increased advantageous properties at the exact same location. In order to determine what types of substituent groups would be expected to possess the same advantageous properties, chemists will look at structure-activity relationships.[122] Chemists may substitute substituent groups possessing many of the same properties, such as molecular weight, polarity, stereochemical arrangement, and reactivity, since similar substituent groups would likely behave with comparable biological activity.[123] Chemists skilled in the art thoughtfully select particular substituent groups expected to produce a similar or enhanced resulting efficacy to substitute at

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'exploration' and 'exploitation' of leads . . . the latter [involves] the assessment, improvement, and extension of the lead. It is largely in the latter area that rational approaches to drug design have been productive."); *Id*. at 236 ("In molecules with a variety of potential bonding interacting moieties it is useful, when possible, to eliminate individual bonding components sequentially and observe the effects on activity.").

[121] BURGER, *supra* note 120, at 86 ("The purpose of molecular modification is usually to seek subtle changes in the compound that should not alter some properties but change others in order to improve potency, selectivity, duration of action, and reduce toxicity").

[122] *See generally* G. A. Patani & E. J. LaVoie, *Bioisosterism: A Rational Approach in Drug Design*, 96 CHEM. REV. 3147-76 (1996).

[123] BURGER, *supra* note 120, at 86 ("Bioisosteric replacement is the principal guide followed by medicinal chemists in developing analogs of a 'lead' compound . . . [t]he parameters being changed are molecular size, steric shape (bond angles, hybridization), electron distribution, lipid solubility (= hydrophobicity), water solubility, the pKa, the chemical reactivity to cell components and metabolizing enzymes, and the capacity to undergo hydrogen bonding (receptor interactions). [If similar properties predominate], the overall properties of the two compounds may be adequately similar.").

the activating site.[124]

Many examples illustrate this strategy, including research performed on paclitaxel.[125] In its naturally-occurring form, paclitaxel can be used as an anticancer drug.[126] Even after years of its successful use in chemotherapy treatments, researchers continued to modify the peripheral substituent groups which gave paclitaxel its advantageous properties in an effort to improve its efficacy and decrease its toxicity.[127] Although paclitaxel was already known to work for its intended purpose, researchers continued to attempt to improve its effectiveness by modifying its substituent groups.[128]

Another example which illustrates how chemists modify substituent groups on a core molecule to achieve new or enhanced properties involves a group of statins, which are cholesterol-lowering drugs.[129] One of these statins, Mevacor, is a naturally occurring compound which can be isolated from the bacterium *Aspergillius terreus*.[130] Researchers attached one

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[124] *See* 1 ALFRED BURGER, MEDICINAL CHEMISTRY 72-73 (Alfred Burger ed., Wiley-Interscience, Inc. 1957) ("The search for structural analogs for 'lead' compounds . . . can be rationalized by gradually substituting one atom or group of atoms in the parents compound for another with a similar electronic and steric configuration.").

[125] *See generally* W.S. Fang & X.T. Liang, *Recent Progress in Structure Activity Relationship and Mechanistic Studies of Taxol Analogues*, 5 MINI REVIEWS IN MEDICINAL CHEMISTRY 1 (2005).

[126] *Id.*

[127] *Id.*

[128] This is not to suggest that any substituent group substituted at an activating site would necessarily be obvious to one skilled in the art.

[129] Rebecca M. Wilson & Samuel J. Danishefsky, *Small Molecule Natural Products in the Discovery of Therapeutic Agents: The Synthesis Connection*, 71 J. ORG. CHEM. 8329, 8332 (2006).

[130] *Id.*

additional methyl group to Mevacor, which produced the new separately patentable molecule Zocor.[131] Another statin, compactin, is also a naturally occurring compound isolated from the bacterium *Penicillium brevicompactin*.[132] By adding a hydroxyl group to compactin and opening the ring on the core, chemists synthesized the new compound Pravachol, which was subsequently patented by Bristol-Myers Squib.[133] In both of these situations, the two pairs of molecules differed from each other by one substituent group while the core remained the same.

In addition to these specific examples, it is crucial to note that it is common practice for chemists to begin with a known compound and modify the substituent groups when synthesizing new compounds. For example, researchers at Hoffman-La Roche, Inc. fabricated a collection of forty-five benzodiazepines.[134] In order to create this collection, the researchers maintained the core benzodiazepine structure and varied the substituent groups.[135] Then, the newly created compounds were tested for acute toxicities and screened for sedative, muscle-relaxant, taming, and anticonvulsant effects.[136] Two patented drugs resulted from such molecular modification programs focused on benzodiazepines: flurazapem and nitrazepam, both used to treat insomnia.[137] This case presents a clear model of the general practice in the chemical arts of

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[131] Wilson & Danishefsky, *supra* note 129.

[132] *Id.*

[133] *Id. See generally* Bristol-Myers Squib, *Pravachol*, www.pravachol.com (last visited Feb. 28, 2009).

[134] *See* L. H. Sternbach, et al., *Quinazolines and 1,4-Benzodiazepines. XXV. Structure-Activity Relationships of Aminoalkyl-Substituted 1,4-Benzodiazepin-2-ones*, 8 J. MED. CHEM. 815 (1965).

[135] *Id.*

[136] *Id.* at 819.

[137] BURGER, *supra* note 120, at 133.

modifying substituent groups on the core of a compound in order to synthesize a new compound.

One of the best classic examples of the use of molecular modification of known compounds to arrive at potentially useful therapeutic agents involves the sulfanilamides.[138] The antihyperglycemic and diuretic properties of known sulfanilamides prompted investigators to create and test over two thousand analogs.[139] One product of the research was the discovery of acetazolamide, which has been proven clinically useful for treating glaucoma.[140] Therefore, since the obviousness determination would depend on the particular substituent substitution made as shown in the previous examples, it is clear that an ad hoc analysis of a claimed compound in view of the prior art is necessary to more accurately determine the obviousness standard for chemical compounds. In sum, the emphasis should be placed on what substitution was made, not the location of such substitution on the compound.

IV. Proposed Two-Part Test for Obviousness of Chemical Compounds

In order to improve the standard of obviousness for chemical compounds to more accurately reflect synthesis techniques in the art, the following two-part test should be employed: (1) was the particular substitution obvious to a person skilled in the art?; and (2) if so, did the compound exhibit unexpected results?

A. Whether the Particular Substitution Was Obvious to One Skilled in the Art

I propose that a factual inquiry into what specific substitution was made and the reasoning for that specific substitution at the activating site would be required to ultimately determine if a novel compound is truly nonobvious. For example, a substitution involving two

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[138] BURGER, *supra* note 120, at 80.

[139] *Id.*

[140] *Id.*

substituents with similar polarity and molecular weight would more likely be held obvious compared to the substitution of a strong polar substituent for a nonpolar substituent. There is no evidence that the *Eisai* court even considered whether lansprazole's trifluoroethoxy substituent (-OCH_2CF_3) and rabeprazole's methoxypropoxy substituent (-$OCH_2CH_2CH_2OCH_3$) would be expected to possess similar properties and, consequently, cause similar or enhanced antiulcer capabilities.[141] Following this type of inquiry, the *Eisai* court would have been better equipped to determine rabeprazole's potential obviousness.

B. Whether There Were Unexpected Results

Even if a particular substitution may have been considered obvious to one of ordinary skill in the art, an appropriate standard for determining the obviousness of chemical compounds must include a consideration of unexpected results. The doctrine of unexpected results has long been a part of the obviousness inquiry. In *In re May*, the invention encompassed the acid addition salts of certain levo and alpha-levo isomers of N-methyl benzomorphan.[142] May attempted to rebut the presumption of obviousness by showing that claimed compounds possessed pain-relieving properties similar to morphine, but they did not have the adverse side effects of morphine, for example, addictiveness.[143] The court determined that the nonaddictive property of the N-methyl benzomorphans would have been totally unexpected to a person skilled in the art.[144] Due to this unexpected property, the court held that the N-methyl benzomorphans

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[141] *See generally Eisai*, 533 F.3d 1353.

[142] *In re* May, 574 F.2d 1082, 1084 (C.C.P.A. 1978) (stating that evidence of unexpected properties may refute a determination of obviousness).

[143] *Id.*

[144] *Id.* at 1092.

would not have been obvious to one skilled in the art.[145]

Accordingly, the standard for determining obviousness of chemical compounds should also allow for a compound which was synthesized by obvious substitutions to a prior art compound to be patented when there is a showing of unexpected results. Pharmaceutical companies should not be barred from patenting a compound with clearly new or significantly enhanced therapeutic properties simply because an obvious substitution was made to the prior art compound.[146]

C. Proposed Two-Part Test Would Lead to Increased Efficiency

By employing a test of chemical obviousness which allows a fact-specific inquiry into the particular substitution and reasoning, the standard of obviousness for a novel chemical compound would become more practicable. Chemists skilled in the art are capable of predicting, within the limits of chemistry's uncertainty, whether certain substituent groups substituted on a core molecule could reasonably lead to expected results. This would result in a more efficient allocation of monetary resources, because chemists would spend more time and money pursuing the development of compounds which are less likely to be held obvious. The expansion of drug development involving compounds, which would be nonobvious under my proposed standard, would potentially lead to the discovery of truly innovative, not merely trivially different, drugs.

Additionally, a more clearly defined obviousness standard for chemical compounds would allow pharmaceutical companies to pursue the most economically viable, potential drug candidates. In 2004, United States pharmaceutical companies alone spent approximately $98

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[145] *May*, 574 F.2d at 1093.

[146] ALFRED BURGER, MEDICINAL CHEMISTRY 64 (Alfred Burger ed., Wiley-Interscience, Inc. 1957) ("An added bonus of molecular modification may be the discovery of an unrelated pharmacological side effect that could be of interest in another context.").

billion on drug research and development; this represents approximately 0.85 percent of the United States gross domestic product (GDP).[147] This enormous amount of money spent on drug research should be spent striving to attack new and unsolved problems in medicinal chemistry rather than making minimal changes to compounds which have already been shown to work for a specified purpose. The Constitution of the United States gives Congress the power to "promote the progress of science and useful arts, by securing for limited times to authors and inventors the exclusive right to their respective writings and discoveries."[148] The most important word in this clause is progress. By more efficiently allocating the money spent on pursuing drug research, the United States could be at the forefront of progressive drug exploration, targeting key diseases like cancer, AIDS, autism, and many others.

In addition, the widespread use of combinatorial chemistry[149] significantly increases the discovery rate of new chemical compounds that can be reasonably synthesized and tested for pharmacological activity. Combinatorial chemistry is relatively new methodology developed by chemists to decrease the time and monetary costs required to produce effective new drug compounds. Chemists use combinatorial chemistry to generate a library of molecules that can be examined resourcefully at the same time. Through creating increasingly diverse chemical

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[147] Samuel C. Silverstein, M.D., *What does economic research tell us about the economic benefits of investments in medical and health research and training?* 2 (2005), *available at* http://www.asbmb.org/uploadedFiles/Advocacy/Economic%20Benefits%20of%20Research%20Investments%20(Silverstein,%20SC).pdf (last visited Jan. 16, 2009).

[148] U.S. CONST. art 1, § 8, cl. 8.

[149] For a detailed description of combinatorial chemistry techniques, *see* E. V. Gordeeva et al., *COMPASS program – An Original Semi-Empirical Approach to Computer-Assisted Synthesis*, 48 TETRAHEDRON 3789 (1992); X. D. Xiang et al., *A Combinatorial Approach to Materials Discovery*, 268 SCIENCE 1738 (1995); Miklos Feher & Jonathan M. Schmidt, *Property Distribution: Differences Between Drugs, Natural Products, and Molecules from Combinatorial Chemistry*, 43 J. CHEM. INF. COMPUT. SCI. 218 (2003).

compound libraries, pharmaceutical companies can enhance the probability of identifying novel compounds with important medicinal and economic value. With these techniques, the patent office and the courts should anticipate an increase in the number of chemical compound patents whose ultimate patentability will depend on the nonobviousness requirement. Therefore, a more well-defined and accurate obviousness standard for chemical compounds based on actual practice in the art will decrease the burden placed on patent examiners and the court system who are frequently left to toil with a vague and impracticable chemical obviousness standard.

CONCLUSION

The law of obviousness has been constantly evolving since its statutory enactment in 1952. While this law has been an effective tool in eliminating trivial improvements on inventions in the electrical and mechanical sciences, the law of obviousness has failed to provide the chemical arts with a clear standard to determine whether chemical compounds will be held obvious in view of the prior art.

The current standard for assessing the obviousness of a chemical compound has two parts: (1) identification of a prior art compound with a structure similar to the claimed compound and (2) motivation for a person skilled in the art to modify the prior art compound to achieve the claimed compound. *KSR*, which struck down the rigid TSM test employed by the Court of Appeals, raised questions as to whether it would be essentially the same or easier for generic drug companies to show that patented chemical compounds would have been obvious at the time of their discovery. When the Court of Appeals had the chance to specifically address this issue in the *Eisai* case, the court failed to more clearly delineate the obviousness standard for chemical compounds. Additionally, the Court's reasoning for holding the claimed compound in *Eisai* to be nonobvious is inconsistent with generally accepted drug discovery principles. An

inquiry into the motivation for making a substituent substation on the core of a molecule known to have therapeutic properties must necessarily include an investigation of the particular substitution made and the reason for that substitution, not merely an analysis of the location of that substitution on the compound's core.

Chemistry is an intrinsically volatile art; consequently, an unambiguous obviousness standard has been difficult to outline. The *Eisai* court's decision has set the stage for trivial substitutions to known compounds to be held nonobvious. Due to the enormous amount of money spent on pharmaceutical research and development in the United States, the development of a more well-defined obviousness standard is necessary to allow pharmaceutical companies to put the most time and money into economically practical areas to promote the progress of the human society.